Single Technology Assessment

Axicabtagene ciloleucel (Yescarta) for the treatment of second or later relapsed/refractory diffuse large B cell lymphoma (DLBCL) and primary mediastinal large B-cell lymphoma (PMBCL)

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PREFACE

Implementation of the National System for the introduction of new technologies in the specialist healthcare system will help ensure that assessment of appropriate new technologies happens in a systematic manner with respect to efficacy and safety, as well as impacts on health and society. The main aim of the new system is described in the National Health and Care Plan 2011-2015 and the White Paper 10 (2012-2013), Good quality - safe services. The regional health authorities, the Norwegian Knowledge Centre for Health Services, the Norwegian Medicines Agency and the Directorate of Health collaborate on tasks related to the establishment and implementation of the new system. Eventually, the National System for the introduction of new technologies in the specialist healthcare system will assist in the rational use of health care resources.

The Norwegian Medicines Agency has been assigned the responsibility to evaluate Single Technology Assessments of individual pharmaceuticals. A Single Technology Assessment is a systematic summary of evidence based on research on efficacy, safety and impact assessment. For pharmaceuticals, this will usually revolve around budgetary consequences or resource allocation. The burden of proof relating to the documentation of efficacy, safety and cost-effectiveness is borne by the MA-holder for the pharmaceutical under review. NoMA can, when necessary, provide guidance to pharmaceutical companies.

NoMA assesses the submitted evidence for all important clinical outcomes, resource use as well as the assumptions made in the analysis presented by the MA-holder and the presented results. NoMA does not perform its own health economic analyses. If required, NoMA may request additional information and perform additional calculations of the costs and cost effectiveness using the submitted model.

NoMA evaluates the relative efficacy and incremental costs in relation to a relevant comparator. NoMA does not assess the benefit risk balance already assessed under the marketing-authorization procedure. Information about this is provided by EMA.

Single Technology Assessment of pharmaceuticals is intended to support sound decision making on potential introductions of new technologies, and prioritization made at the Health Authority level. NoMA has no decision-making authority in this system.

All assessments are published and available to the public (www.legemiddelverket.no).

EXECUTIVE SUMMARY

Rationale
Single technology assessment (STA) of axicabtagene ciloleucel (axi-cel, Yescarta) for the treatment of adult patients with relapsed or refractory (r/r) diffuse large B-cell lymphoma (DLBCL) and r/r primary mediastinal large B cell lymphoma (PMBCL) after two or more lines of systemic therapy. The benefits and risks of axi-cel in r/r DLBCL and r/r PMBCL have been documented through the approval of marketing authorisation. In this STA, NoMA has assessed axi-cel treatment against the prioritisation criteria – the benefit criterion, the resource criterion and the severity criterion – according to the Summary of product characteristics (SmPC) for axi-cel and the request specifications from Ordering Forum (request number ID2017_105: Axicabtagene ciloleucel (Yescarta). Behandling av diffust storcellet B-celle lymfom, primært mediastinalt B-celle lymfom og transformert follikulært lymfom). Request from Ordering Forum can be found at www.nyemetoder.no. NoMAs´s assessment is primarily, but not exclusively, based on the documentation presented by Gilead.

Background
Axi-cel is a CAR-T cell therapy, a novel cancer therapy that involves reprogramming patient's own T cells with a transgene encoding a chimeric antigen receptor (CAR) to identify and eliminate cells that express the cell surface molecule called cluster of differentiation 19 (CD19). The CD19 antigen is exclusively expressed on B cells, including the cancer cells in DLBCL and PMBCL. When axi-cel is given to the patient, the modified T cells attach to and kill the cancer cells, thereby helping to eliminate the cancer cells from the body.

The clinical process starts with leukapheresis, in which the patient's own peripheral blood mononuclear cells containing T cells are collected. The cells are then shipped to a central manufacturing facility that engineers the CAR-T cells using retroviruses to insert the DNA for the chimeric protein into the DNA of the patient's T cells. The newly engineered cells are then frozen and shipped back to the treating institution.

Axi-cel is given as a single intravenous infusion. Before receiving axi-cel, patients are treated with lymphodepleting chemotherapy (fludarabine in combination with cyclophosphamide) to decrease the number of competing T cells.

According to Gilead, the manufacture and release of the axi-cel product usually takes about 3-4 weeks. Some patients require bridging chemotherapy to stabilize the cancer while waiting for the axi-cel infusion. During this waiting period, some patients will die, while others become too sick to tolerate treatment with CAR-T cell therapy. Additionally, the manufacturing process occasionally fails to produce a sufficient number of CAR-T cells required for infusion.

Patient population
In Norway, approximately 20 r/r DLBCL and r/r PMBCL patients are expected to be candidates for treatment with CAR-T cell therapy on a yearly basis.

Severity and shortfall
The prognosis in patients with r/r DLBCL and r/r PMBCL is poor. In Norway, the degree of severity affects whether the costs are considered reasonable relative to the benefit of the treatment. NoMA has

estimated that adult patients with r/r DLBCL have an absolute shortfall of approximately 15-16 Quality Adjusted Life Years (QALYs).

Treatment in the Norwegian setting
Treatment of DLBCL and PMBCL is described in national guidelines from The Norwegian Directorate of Health (1). With current frontline standard of care (R-CHOP, rituximab with cyclophosphamide, doxorubicin, vincristine, and prednisolone), the overall cure rate of adult patients with DLBCL is around 50 – 60%. Patients who relapse will be offered new treatment regimens with chemotherapy followed by high dose chemotherapy and autologous stem cell transplant (HDC-ASCT) in eligible patients after obtaining a new response to second-line therapy. For patients with DLBCL and PMBCL who are refractory to last line or those who have had a second or later relapse, the currently available treatment option is new regimens of chemotherapy combinations with rituximab. Patients with a response to third- or later lines of salvage regimens and who are medically fit can proceed to transplant (ASCT or allogenic SCT).

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

Clinical efficacy
The clinical efficacy and safety of axi-cel was demonstrated in one pivotal phase II study (ZUMA-1) in adult patients with refractory DLBCL and PMBCL. The primary end point was the best objective response rate (ORR) defined as the combined rates of complete response (CR) and partial response (PR), as assessed by the study investigators, reported in the modified intention-to-treat (mITT) population of all the patients who had received axi-cel. Secondary end points included progression free survival (PFS) and overall survival (OS). The ZUMA-1 study is ongoing. At the latest data cutoff date of 11-Aug-2018, the median time from infusion to last follow-up was 27.1 months. Among the 111 patients enrolled in ZUMA-1, 101 patients (91%) received infusion with axi-cel. The reasons for discontinuation prior to axi-cel infusion included: adverse events (n=4), deaths (n=3), non-measurable disease before lymphodepleting chemotherapy (n=2), and manufacturing failure (n=1). The median time from leukapheresis to CAR-T administration was 23 days (range: 15 to 72 days).

Among the 101 patients who received axi-cel (mITT), the best ORR was 83% (58% CR) according to the study investigators assessment (primary endpoint), and 74% (54% CR) according to an independent central review committee assessment. The median PFS was 9.1 months (95% CI: 5.7, not estimable), and the median OS was not estimable. In the intention-to-treat (ITT) analyses of the enrolled patient population (111 patients), the rates of PFS and OS were 46% and 60%, respectively, at 12 months, and 38% and 48% at 24 months. The median PFS was 9.5 months (95% CI: 6.1 to 15.4), and the median OS was 17.4 months (95% CI: 11.6 to not estimable).

The ZUMA-1 trial was designed as a single arm study. Data for the comparator arm are collected from the SCHOLAR-1 trial (2), the largest patient-level pooled retrospective meta-analysis that charactericed response rates and survival of salvage chemotherapy among patients with refractory DLBCL. Gilead has access to patient-level data from SCHOLAR-1, and individuals from SCHOLAR-1 with missing data or with mismatched patient characteristics compared to ZUMA-1 could be excluded from the data set. As a base case, Gilead has submitted SCHOLAR-1 data where patients with post-refractory SCT and ECOG 2-4 were

removed. Gilead has also conducted a Propensity Score (PS)-adjusted analysis of ZUMA-1 versus SCHOLAR-1 in order to estimate the relative efficacy of axi-cel compared to chemotherapy regimens. The PS-adjustment did not result in perfectly aligned patient characteristics between ZUMA-1 and SCHOLAR-1, and it is unclear how these imbalances in patient characteristics affected the results. The median OS was 6.4 months in the PS-adjusted SCHOLAR-1 populations (both mITT and ITT).

Safety

Serious side effects occur in most patients. As the activated CAR-T cells proliferate in the patient and kill tumor B cells, they release inflammatory cytokines. This can cause cytokine release syndrome (CRS) with symptoms like high fevers, low blood pressure, and respiratory distress. Another common and serious side effect is neurotoxicity. The most common signs or symptoms associated with neurologic adverse reactions include encephalopathy, tremor, confusional state, aphasia, and somnolence. Higher-grade CRS and neurotoxicity can be life threatening and requires care in an intensive care unit. Patients should be closely monitored for 10 days after treatment for side effects and are advised to stay close to a specialist hospital for at least 4 weeks after treatment.

Another important adverse event is secondary hypogammaglobulinemia due to B-cell aplasia. Patients with reduced immunoglobulins produced by normal B cells are at risk for infections and 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 most serious and frequently occurring adverse reactions are CRS (93%), encephalopathy (37%), and infections (42%). Grade 3 or higher neutropenia, thrombocytopenia, and anaemia still present at Day 30 or beyond occurred in 26%, 24% and 10% of the treated patients, respectively.

Cost effectiveness

NoMA has assessed the submitted health economic analyses from Gilead. NoMA considers both the ITT population (enrolled patients) and the modified ITT (mITT) population (infused patients) relevant for decision making. NoMA has made the following changes to the Gilead analysis:

- Patients with post-refractory SCT were included in the SCHOLAR-1 dataset, and NoMA's requested PS-adjusted analysis was used to estimate OS.
- OS for axi-cel extrapolated with a spline function with 2 knots constrained by the PFS curve as opposed to Weibull mixture cure model.
- OS for chemotherapy extrapolated with a spline function with 1 knot as opposed to Gompertz single parametric curve.
- Patients that remain progression-free are considered "cured", as opposed to an assumption that both progression-free and progressed patients are "cured" at year 2 post-treatment.
- The modelled mortality rate for long-term survivors on axi-cel has been set equal to the mortality rate as modelled for long-term survivors in SCHOLAR-1, as opposed to general population mortality
- Health state utilities sourced from the CAR-T study JULIET as opposed to ZUMA-1 safety cohort.
- Age adjustment of health state utility values in line with NoMA guidelines
- No reduction in long term quality of life, compared to 5% reduction in Gileads base case.

- Leukapheresis costs 50 845 NOK based on data from Oslo University Hospital, as opposed to 9 728 NOK (source: Helsedirektoratet, 2*DRG 816P).
- Hospitalisation for 14.7 days for comparator treatment (source: clinical expert opinion) as opposed to outpatient treatment.
- Hospitalisation for 21.6 days for axi-cel treatmens (source: ZUMA-1 clinical study report) as opposed to 7 days (source: Gilead assumption).
- Rituximab included in the costs of comparator treatment.
- Hospitalisation and ICU costs derived from Lindemark (3)
- Costs of subsequent SCT (both alloSCT and ASCT) included in the comparator arm
- Terminal care costs 57 820 NOK based on Wang (4), as opposed to 169 371 NOK based on Moger (5)
- IVIG treatment due to B-cell aplasia included.

NoMA has estimated an incremental cost-effectiveness ratio for axi-cel compared to chemotherapy. Multiple important limitations and uncertainties in the analysis were identified and remained.

In NoMA's base case analyses, the additional costs for axi-cel compared to chemotherapy, with public list prices ex. VAT for medicines, are:

- 1.4 million NOK per QALY gained in the ITT population (enrolled patients)
- 1.3 million NOK per QALY gained in the mITT population (infused patients)

The long-term survival of 20% for the comparator arm in the model may be higher than experienced in clinical practice. However, it is not appropriate to compare the ZUMA-1 clinical trial with a historical control which approximates clinical practice. NoMA intended to select those patients from the SCHOLAR-1 data that could have been included in a theoretical ZUMA-1 control arm. In this adjusted SCHOLAR-1 dataset, the proportion of patients who received subsequent SCT and hence the long term survival increased. In scenarioanalyses where 1) subsequent SCTs and ECOG 2-4 were removed from the SCHOLAR-1 data, and 2) only ECOG 2-4 was removed, resulted in ICERs of 0.8 and 1 million NOK per QALY gained, respectively.

Budget impact

NoMA estimated the budget impact of the total healthcare costs for the specialist health services to be around 67 million NOK including VAT in the fifth year after introduction, provided that all eligible adult patients with r/r DLBCL and r/r PMBCL are treated with axi-cel.

NoMA´s overall assessment

NoMA identified multiple important limitations and uncertainties in the analysis that remained. The ZUMA-1 study was a single arm study of small size (101 infused patients), and with a median follow-up time just above 2 years. The study lacks a control arm, and it is therefore not possible to compare outcomes from this trial with outcomes from comparator trials without a high degree of uncertainty. Long-term outcomes - both in terms of efficacy and safety - are currently not known. Thus far, none of the trials for CAR-T therapy have followed patients for a sufficient time to ascertain whether adult patients with r/r DLBCL and r/r PMBCL who have an ongoing response could be considered cured. NoMA considers the estimated gain in overall and quality adjusted survival for axi-cel compared to chemotherapy to be

highly uncertain. Additional follow-up data are needed to evaluate the long-term outcomes with axi-cel and reduce the large amount of uncertainty in the current analysis. New and ongoing studies are expected to report in the coming years, and data from these studies will likely improve decision making.

OPPSUMMERING

Formål
Hurtig metodevurdering av legemiddelet Yescarta (axicabtagene ciloleucel) i henhold til godkjent preparatomtale og bestilling ID2017_105: «Axicabtagene ciloleucel (Yescarta). Behandling av diffust storcellet B-celle lymfom, primært mediastinalt B-celle lymfom og transformert follikulært lymfom». Legemiddelverket har vurdert prioriteringskriteriene knyttet til alvorlighet, nytte og ressursbruk. Vurderingen tar utgangspunkt i dokumentasjon innsendt av Gilead.

Bakgrunn
Yescarta er CAR-T celleterapi, en ny type avansert behandling der legemidlet lages av pasientens egne T-celler. Et nytt gen blir satt inn i T-cellene slik at disse blir i stand til å gjenkjenne og drepe kreftcellene. Det er vanligvis 3-4 uker ventetid mens Yescarta lages. Yescarta gis som infusjon, og er en engangsbehandling. Før infusjonen får pasientene en kur med lymfodepleterende kjemoterapi.

Yescarta er godkjent til behandling av voksne pasienter med residivert eller refraktært diffust storcellet B-cellelymfom (DLBCL) og primært mediastinalt storcellet B-cellelymfom (PMBCL), etter to eller flere linjer med systemisk behandling. Om lag 20 av disse pasientene er aktuelle for behandling med CAR-T celleterapi hvert år i Norge.

Alvorlighet og helsetap
Pasienter med residivert/refraktært DLBCL og PMBCL har dårlig prognose med dagens behandling. Legemiddelverket har beregnet at absolutt prognosetap er ca. 15-16 gode leveår for denne pasientgruppen.

Effekt
Av totalt 111 pasienter som ble inkludert i hovedstudien ZUMA-1, var det 10 pasienter som ikke fikk infusjon med Yescarta, enten fordi Yescarta ikke kunne lages, eller fordi pasientene døde, fikk sykdomsprogresjon eller bivirkninger fra annen behandling i løpet av ventetiden. Av 101 pasienter som fikk infusjon med Yescarta, var det 74 % som fikk respons. Etter to år var sannsynligheten for å være i live ca. 51 % for de pasientene som hadde fått infusjon. Det var ingen kontrollgruppe i studien og oppfølgingstiden er foreløpig relativt kort. Behandlingsalternativet i dag er kjemoterapi kombinert med rituksimab, som hos noen pasienter blir etterfulgt av stamcelletransplantasjon. Vi har ikke pålitelige data for effektforskjellen mellom Yescarta og dagens behandling.

Sikkerhet
De fleste får bivirkninger etter infusjon av Yescarta. En alvorlig og svært vanlig tilstand er cytokinfrigjøringssyndrom (CRS), med symptomer som høy feber, lavt blodtrykk og pustevansker. Nevrologiske bivirkninger er også vanlige, og kan være alvorlig. På grunn av faren for alvorlige bivirkninger må pasienten overvåkes daglig de første 10 dagene etter infusjon, og må oppholde seg i nærheten av sykehuset i minst 4 uker etter behandlingen. Risiko for infeksjoner kan vedvare, og noen pasienter vil trenge immunoglobulinbehandling.

Kostnadseffektivitet
Legemiddelverket har analysert kostnadseffektiviteten i to pasientgrupper: Innrullerte pasienter (alle pasienter i studien, både pasienter som fikk infusjon med Yescarta og pasienter som falt fra i løpet av ventetiden) og Infuserte pasienter (kun pasienter som fikk infusjon med Yescarta). I de analysene Legemiddelverket mener kan være sannsynlige, med dagens maksimalpriser for legemidlene, er merkostnad for Yescarta sammenlignet med kjemoterapi:

- 1,4 millioner NOK per vunnet kvalitetsjusterte leveår (QALY) for innrullerte pasienter (ITT).
- 1,3 millioner NOK per vunnet kvalitetsjusterte leveår (QALY) for infuserte pasienter (mITT).

En langtidsoverlevelse på 20 % I komparatoramen i modellen kan være høyere enn det erfaringer fra klinisk praksis tilsier. Det er imidlertid ikke hensiktsmessig å sammenligne en klinisk studie (ZUMA-1) med en historisk kontroll som ligner klinisk praksis. Legemiddelverket har forsøkt å selektere de pasientene fra SCHOLAR-1 datasettet som kunne vært inkludert i en teoretisk ZUMA-1 kontrollarm. I dette justerte SCHOLAR-1 datasettet, er andelen pasienter som får etterfølgende SCT og overlevelse økt sammenlignet med klinisk praksis. I scenarioanalyser der 1) Etterfølgende SCT og ECOG 2-4 var fjernet fra SCHOLAR-1 data, og 2) Kun ECOG 2-4 var fjernet, resulterte i IKER på hhv. 0,8 og 1 millioner NOK per vunnet QALY.

Analysene har en rekke viktige begresninger og usikkerheter, og resultatene er svært usikre.

Budsjettkonsekvenser
Legemiddelverket har estimert at budsjettvirkningen for sykehusenes totale budsjett vil være om lag 67 millioner NOK per år i år fem, hvis Yescarta innføres til behandling av voksne pasienter med residivert/refraktært DLBCL og PMBCL.

Legemiddelverkets vurdering
Langtidsvirkning av Yescarta – både når det gjelder effekt og sikkerhet – er foreløpig ikke kjent. Så langt har ingen studier av CAR-T celleterapi fulgt pasientene lenge nok til å fastslå om pasienter med vedvarende respons kan anses å være kurerte. Vi har heller ikke pålitelige data for effektforskjellen mellom Yescarta og dagens behandling. Analysene har en rekke viktige begrensninger og usikkerheter.

3-SIDERS SAMMENDRAG

Metode
Hurtig metodevurdering av legemiddelet Yescarta (aksikabtagenciloleucel, axi-cel) til behandling av voksne pasienter med residivert eller refraktært (r/r) diffust storcellet B-cellelymfom (DLBCL) og primært mediastinalt storcellet B-cellelymfom (PMBCL), etter to eller flere systemiske behandlinger. Vurderingen er i henhold til godkjent preparatomtale og bestilling ID2017_105: «Axicabtagene ciloleucel (Yescarta). Behandling av diffust storcellet B-celle lymfom, primært mediastinalt B-celle lymfom og transformert follikulært lymfom». Legemiddelverket har vurdert prioriteringskriteriene knyttet til alvorlighet, nytte og ressursbruk. Vurderingen tar utgangspunkt i dokumentasjon innsendt av Gilead.

Bakgrunn
Axi-cel er CAR-T celleterapi, en ny 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 f.eks. 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.

Axi-cel gis som infusjon, og er en engangsbehandling. Før infusjonen får pasientene en kur med lymfodepleterende kjemoterapi (fludarabin i kombinasjon med syklofosfamid) for å redusere antallet konkurrerende T-celler.

Ifølge Gilead, vil produksjon og frigiving av ferdig axi-cel vanligvis ta 3-4 uker. Noen pasienter vil trenge kjemoterapi for å stabilisere kreftsykdommen mens de venter på infusjon med axi-cel. I denne ventetiden vil noen pasienter dø, mens andre blir for syke til å kunne tolerere behandling med CAR-T celleterapi. I tillegg vil produksjonsprosessen i noen tilfeller ikke lykkes med å lage et tilstrekkelig antall CAR-T celler nødvendig for behandlingen.

Pasientgrunnlag i Norge
Om lag 20 voksne pasienter med r/r DLBCL og r/r PMBCL er aktuelle for behandling med CAR-T celleterapi hvert år i Norge.

Alvorlighet og prognosetap
Pasienter med r/r DLBCL og r/r PMBCL har dårlig prognose med dagens behandling. Alvorlighetsgraden kan påvirke om kostnadene vurderes å stå i rimelig forhold til nytten av behandlingen. Legemiddelverket har beregnet at absolutt prognosetap er ca. 15-16 gode leveår for denne pasientgruppen.

Behandling i norsk klinisk praksis
Behandling av DLBCL og PMBCL er beskrevet i "Nasjonalt handlingsprogram med retningslinjer for diagnostikk behandling og oppfølging av maligne lymfomer" fra Helsedirektoratet (1). I dag blir ca. 50 – 60 % av pasientene kurert ved standard førstelinjebehandling med rituksimab kombinert med syklofosfamid, doksorubicin, vinkristin og prednisolon (R-CHOP). Pasienter med tilbakefall vil få ny behandling med kjemoterapi, etterfulgt av høydose kjemoterapibehandling og autolog stamcelletransplantasjon (ASCT) for de som responderer og som er egnet for slik behandling. For pasienter som er refraktære eller har hatt to eller flere tilbakefall, er dagens behandling ulike kjemoterapi kombinasjoner. Pasienter som får respons på tredjelinje eller senere linjer kjemoterapi, og som har god allmenntilstand, kan få SCT (autolog eller allogen)

Legemiddelverket har valgt kjemoterapi med rituksimab, etterfulgt av SCT hos pasienter som er egnet, som komparator i metodevurderingen.

Effekt
Klinisk effekt og sikkerhet for axi-cel er vist i en åpen, enarmet, fase 2 studie (ZUMA-1) hos voksne pasienter med refraktær DLBCL og PMBCL. Primært endepunkt var beste objektiv responsrate (ORR), som inkluderte komplett respons (CR) og partiell respons (PR), vurdert av utprøver i modifisert intention-to-treat (mITT) populasjon av alle pasienter som fikk axi-cel. Totaloverlevelse (OS) og progresjonsfri overlevelse (PFS) var sekundære endepunkter. ZUMA-1 pågår fortsatt. Ved siste datakutt (11-08-2018) var median oppfølgingstid 27,1 måneder etter infusjon. Av 111 pasienter som ble innrullert i ZUMA-1, fikk 101 (91 %) infusjon med axi-cel. Årsaker til frafall før infusjon var bivirkninger (n=4), død (n=3), ikke-målbar sykdom før lymfodepleterende kjemoterapi (n=2) og at axi-cel ikke kunne produseres (n=1). Median tid fra leukaferese til CAR-T infusjon var 23 dager (fra 15 til 72 dager).

Av de 101 pasientene som fikk axi-cel (mITT), var beste ORR 83 % (CR 58 %) basert på vurdering av utprøver (primært endelpunkt), og 74 % (54 % CR) basert på vurdering av en uavhengig komité. Median PFS var 9,1 måneder (95% KI: 5,7 – ikke oppnådd) og median OS var ikke nådd. I intention-to-treat (ITT) analysen av alle innrullerte pasienter (111 pasienter), var sannsynligheten for PFS og OS henholdsvis 46 % og 60 % ved 12 måneder og 38 % og 48 % ved 24 måneder. Median PFS var 9,5 måneder (95 % KI: 6,1 – 15,4) og median OS var 17,4 måneder (95 % KI: 11,6 – ikke oppnådd).

ZUMA-1 har enkeltarmet studiedesign. Data for komparator er hentet fra studien SCHOLAR-1 (2), den største retrospektive meta-analysen, basert på sammenslåtte individuelle pasientdata, som har rapportert responsrater og overlevelse ved kjemoterapibehandling hos pasienter med refraktært DLBCL. Gilead har tilgang på individuelle pasientdata fra SCHOLAR-1, og pasienter med manglende data eller med pasientkarakteristika som ikke matcher populasjonen i ZUMA-1, kan ekskluderes fra datasettet. Gilead har ekskludert pasienter med etterfølgende SCT og med ECOG 2-4 fra SCHOLAR-1 i innsendt base case. Gilead har også gjort en justert indirekte sammenligning (Propensity Score (PS)-justert analyse) av ZUMA-1 versus SCHOLAR-1. PS-justeringen medførte imidlertid ikke en fullstendig balanse i pasientkarakteristika mellom pasientene i ZUMA-1 og SCHOLAR-1. Det er usikkert hvordan denne ubalansen i pasientkarakteristika påvirker resultatene. Median OS var 6,4 måneder i den PS-justerte SCHOLAR-1 populasjonen (både mITT og ITT).

Sikkerhet
De fleste får bivirkninger etter infusjon av axi-cel. Etter hvert som de aktiverte CAR-T cellene prolifererer i pasienten og dreper kreftceller, vil inflammatoriske cytokiner frisettes. Dette kan forårsake cytokinfrigjøringssyndrom (CRS) med symptomer som høy feber, lavt blodtrykk og pustevansker. En annen vanlig og alvorlig bivirkning er nevrotoksisitet. De vanligste nevrologiske bivirkningenen er encefalopati, skjelvinger, forvirring, afasi og søvnighet. CRS og nevrotoksisitet kan være livstruende og kreve behandling i intensivavdeling på sykehus. Pasientene skal derfor overvåkes daglig de første 10 dagene etter infusjon for tegn og symptomer på alvorlige bivirkninger, og skal informeres om å oppholde seg i nærheten av et kvalifisert behandlingssted i minst 4 uker etter infusjonen.

En annen viktig bivirkning er sekundær hypogammaglobulinemi på grunn av B-celleaplasi. Pasienter med redusert nivå av immunoglobuliner, som produseres av B-celler, har økt risiko for infeksjoner og kan trenge månedlig substitusjonsbehandling med immunoglobuliner intravenøst (IVIG). Varigheten av B-celleaplasi er ikke kjent, men kan vare så lenge axi-cel er tilstede i pasienten.

De mest alvorlige og hyppige bivirkningene er CRS (93 %), encefalopati (37 %) og infeksjoner (42 %). Nøytropeni, trombocytopeni og anemi av grad 3 eller høyere, som fortsatt var tilstede 30 dager etter infusjon, forekom i henholdsvis 26 %, 24 % og 10 % av pasientene.

Kostnadseffektivitet
Legemiddelverket har vurdert innsendt helseøkonomisk analyse fra Gilead, og forutsetninger for denne. Legemiddelverket mener at både ITT populasjonen (innrullerte pasienter) og mITT populasjonen (infuserte pasienter) er relevante for metodevurderingen. Legemiddelverket har gjort følgende endringer i analysene fra Gilead:

- Pasienter som fikk etterfølgende SCT ble beholdt i SCHOLAR-1 datasettet, og PS-justerte analyse ble brukt til å estimere OS.
- OS for axi-cel er ekstrapolert med en spline funksjon med 2 knots begrenset av PFS-kurven, og ikke med en Weibull mixture cure modell.
- OS for kjemoterapi er ekstrapolert med en spline funksjon med 1 knot, og ikke med en Gompertz parametrisk kurve
- Pasienter som forblir progresjonsfrie antas å være «kurert», i motsetning til en antagelse om at både progresjonsfrie og progredierte pasienter er «kurert» 2 år etter infusjon.
- Den modellerte mortalitetsraten til langtidsoverlevere på axi-cel er satt lik modellert mortalitetsrate til langtidsoverlevere i SCHOLAR-1.
- Livskvalitetsvekter for helsetilstandene er basert på data fra CAR-T studien JULIET, og ikke på data fra kohort 3 i ZUMA-1.
- Livskvalitetsvekter er aldersjustert i tråd med Legemiddelverkets retningslinjer
- Ingen reduksjon i langsiktig livskvalitet, sammenlignet med 5% reduksjon i Gileads hovedscenario
- Kostnader for leukaferese satt til 50 845 NOK basert på data fra Oslo Universitetssykehus, og ikke 9 728 NOK (kilde: Helsedirektoratet, 2*DRG 816P)
- Sykehusinnleggelse i 14,7 dager ved komparatorbehandling (kilde: kliniske eksperter), i stedet for komparatorbehandling utenfor sykehus

- Sykehusinnleggelse i 21,6 dager ved axi-cel behandling (kilde: ZUMA-1, klinisk studierapport), og ikke i 7 dager (kilde: Gileads antagelse).
- Kostnad for rituksimab inkludert i komparatorarmen
- Sykehuskostnader, inkl. innleggelse på intensivavdeling, er hentet fra Lindemark (3).
- Kostnader for etterfølgende SCT (alloSCT og ASCT) er inkludert i komparatorarmen.
- Kostnader ved livets sluttfase satt til 57 820 NOK basert på Wang (4), og ikke 169 371 NOK basert på Moger (5).
- IVIG-behandling på grunn av B-celleaplasi er inkludert.

Legemiddelverket har estimert en inkrementell kostnad-effektbrøk for axi-cel sammenlignet med kjemoterapi. Analysene har en rekke viktige begrensninger og usikkerheter. Legemiddelverket anser derfor at estimatene for kostnadseffektivitet er svært usikre. I Legemiddelverkets analyser, med dagens maksimalpriser for legemidlene, er merkostnad for axi-cel sammenlignet med kjemoterapi:

- 1,4 millioner NOK per vunnet kvalitetsjusterte leveår (QALY) for innrullerte pasienter (ITT).
- 1,3 millioner NOK per vunnet kvalitetsjusterte leveår (QALY) for infuserte pasienter (mITT).

En langtidsoverlevelse på 20 % I komparatoramen i modellen kan være høyere enn det erfaringer fra klinisk praksis tilsier. Det er imidlertid ikke hensiktsmessig å sammenligne en klinisk studie (ZUMA-1) med en historisk kontroll som ligner klinisk praksis. Legemiddelverket har forsøkt å selektere de pasientene fra SCHOLAR-1 datasettet som kunne vært inkludert i en teoretisk ZUMA-1 kontrollarm. I dette justerte SCHOLAR-1 datasettet, er andelen pasienter som får etterfølgende SCT og overlevelse økt sammenlignet med klinisk praksis. I scenarioanalyser der 1) Etterfølgende SCT og ECOG 2-4 var fjernet fra SCHOLAR-1 data, og 2) Kun ECOG 2-4 var fjernet, resulterte i IKER på hhv. 0,8 og 1 millioner NOK per vunnet QALY.

Budsjettkonsekvenser
Legemiddelverket har estimert at budsjettvirkningen for sykehusenes totale budsjett vil være om lag 67 millioner NOK per år i år fem, hvis axi-cel innføres til behandling av voksne pasienter med r/r DLBCL og r/r PMBCL.

Legemiddelverkets totalvurdering
Legemiddelverket har identifisert en rekke viktige begrensninger og usikkerheter i analysene. Studien ZUMA-1 har enkeltarmet studiedesign, er relativt liten (111 innrullerte pasienter, 101 infuserte pasienter) og median oppfølgingstid er foreløpig 27,1 måneder. ZUMA-1 mangler kontrollarm, og det er derfor ikke mulig å sammenligne resultater fra denne studien med resultater fra komparatorstudiene uten stor grad av usikkerhet. Langtidsvirkninger – både når det gjelder effekt og bivirkninger – er foreløpig ikke kjent. Så langt har ingen studier av CAR-T celleterapi fulgt pasientene lenge nok til å fastslå om pasienter med vedvarende respons kan anses å være kurerte. Legemiddelverket vurderer at estimert gevinst i totaloverlevelse og kvalitetsjustert overlevelse, for axi-cel sammenlignet med kjemoterapi, er svært usikker.

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LOGG

Bestilling:	ID2017_105: Hurtig metodevurdering gjennomføres ved Statens legemiddelverk for axicabtagene ciloleucel til behandling av diffust storcellet B-celle lymfom, primært mediastinalt B-celle lymfom og transformert follikulært lymfom.
Forslagstiller:	Metodevarsel fra Legemiddelverket
Legemiddelfirma:	Gilead
Preparat:	Yescarta
Virkestoff:	Axicabtagene cilolecleucel
Indikasjon:	Behandling av voksne pasienter med residivert eller refraktær diffust storcellet B-cellelymfom (DLBCL) og primært mediastinalt storcellet B-cellelymfom (PMBCL), etter to eller flere linjer med systemisk behandling.
ATC-nr:	L01X

Prosess

Dokumentasjon bestilt av Legemiddelverket	10.11.2017
Fullstendig dokumentasjon mottatt hos Legemiddelverket	28.06.2018
Klinikere kontaktet for første gang	20.08.2018
LIS/HINAS kontaktet for første gang av Legemiddelverket.	20.08.2018
Legemiddelverket bedt om ytterligere dokumentasjon	05.07.2018: svar mottatt 01.08.18 (27 dager) 17.08.2018: svar mottatt 03.12.2018 (108 dager) 25.01.2019: svar mottatt 15.02.2019 (21 dager) 28.03.2019: svar mottatt 12.04.2019 (15 dager) 24.04.2019: svar mottatt 03.06.2019 (40 dager)
Rapport ferdigstilt:	18.06.2019
Saksbehandlingstid:	Reell saksbehandlingstid 144 dager Total saksbehandlingstid 355 dager hvorav 211 dager i påvente av ytterligere opplysninger fra legemiddelfirma.
Saksutredere:	Ania Urbaniak Einar Andreassen Kirsti Hjelme Maria Elisabeth Kalland Mathyn Vervaart Terry Vrinzen
Kliniske eksperter:	Alexander Fosså (OUS) Bjørn Østenstad (OUS) Fredrik Sund (UNN) Unn Merete Fagerli (St. Olav)

Kliniske eksperter 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. Kliniske eksperter har ikke vært involvert i noen konsensusprosess eller hatt noen «peer-review» funksjon ved utarbeidelse av rapporten.

Glossary

alloSCT	Allogenic Stem Cell Transplantation
AE	Adverse event
ASCT	Autologous Stem Cell Transplantation
Axi-cel	axicabtagene ciloleucel (Yescarta)
CAR	Chimeric Antigen Receptor
CNS	Central Nervous System
CR	Complete Response
CRS	Cytokine Releasing Syndrome
DCO	Data-cut off
DHAP	Dexamethasone, cytarabine, cisplatin
DLBCL	Diffuse large B-cell lymphoma
DoR	Duration of overall response
DRG	Diagnosis Related group
ECOG	Eastern Cooperative Oncology Group
EFS	Event-Free Survival
EMA	European Medicines Agency
EPOCH	etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin
EQ-5D	European Quality of Life-5 Dimensions
ESHAP	Etoposide, methylprednisolone, cytarabine, cisplatin
FACT-Lym	Functional Assessment of Cancer Therapy-Lymphoma
GDP	Gemcitabine, dexamethasone, cisplatin
Gem-OX	Gemcitabine, oxaliplatin
HRQoL	Health related quality of life
ICE	Ifosfamide, carboplatin, etoposide
ICU	Intensive care unit
IME	Ifosfamide, methotrexate, etoposide
IPI	International Prognostic Index
IRC	Independent Review Committee
IV	Intravenous
IVE	ifosfamide, etoposide, epirubicin

IVIG	Intravenous immunoglobulins
KM	Kaplan-Meier
MCM	Mixture Cure Model
NHL	Non-Hodgkin lymphoma
NoMA	Norwegian Medicines Agency
ORR	Overall Response Rate
OS	Overall Survival
OUS	Oslo University Hospital
PFS	Progression-free survival
PD	Progressive disease
PMBCL	primary mediastinal large B-cell lymphoma
PR	Partial Response
SD	Stable disease
QALY	Quality Adjusted Life Year
r/r	Relapsed or refractory
SmPC	Summary of product characteristics
STA	Single Technology Assessment
TFL	Transformed follicular lymphoma

1 BACKGROUND

1.1 SCOPE

This single technology assessment (STA) concerns the treatment of adult patients with relapsed or refractory (r/r) diffuse large B-cell lymphoma (DLBCL) and r/r primary mediastinal large B cell lymphoma (PMBCL) in second or later relapse with the CAR-T cell therapy axicabtagene ciloleucel (axi-cel, Yescarta) in Norway.

Health service interventions are to be evaluated against the three prioritisation criteria in Norway – the benefit criterion, the resource criterion and the severity criterion. Axi-cel is compared to chemotherapy in cost-utility analyses (CUA). NoMA's assessment is primarily, but not exclusively, based on the documentation presented by Gilead.

1.2 RELAPSED/REFRACTORY (R/R) DIFFUSE LARGE B CELL LYMPHOMA (DLBCL) AND R/R PRIMARY MEDIASTINAL LARGE B CELL LYMPHOMA (PMBCL)

DLBCL and PMBCL are both aggressive subtypes of non-Hodgkin lymphoma (NHL). The clinical manifestations of aggressive B-cell lymphomas 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 illness, sometimes associated with "B-symptoms" of fever, drenching night sweats, and weight loss. Generalized pruritus may also be present.

DLBCL is the most common subtype of B-cell NHL, accounting for around 30-35% of all NHL cases. Around 340 people are diagnosed with DLBCL each year in Norway. Although DLBCL can occur in childhood, the incidence generally increases with age, with a median age of 70 years at the time of diagnosis.

PMBCL has distinct clinical, pathological, and molecular characteristics from other B-cell NHL subtypes. About 5 patients per year are diagnosed with PMBCL in Norway. PMBCL is typically identified in younger patients (median age 35 years) and the majority of patients are women.

The DLBCL and PMBCL populations relevant to this STA consist of patients who have relapsed or refractory disease, after two or more lines of systemic therapy. According to Norwegian clinicians contacted by NoMA, approximately 20 patients with r/r DLBCL and r/r PMBCL are expected to be candidates for treatment with CAR-T cell therapy each year in Norway.

1.3 SEVERITY AND SHORTFALL

The prognosis in patients with r/r DLBCL and r/r PMBCL 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 1) for estimating the level of severity

based on absolute shortfall. In the calculation we have used the average age from the patients enrolled in ZUMA 1, that includes both patients with r/r DLBCL and PMBCL. The age of PMBCL patients is expected to be lower than the age of DLBCL patients. There are very few patients with PMBCL in the patient population, and both populations combined are assessed in this STA.

NoMA estimates the absolute shortfall based on current standard care with chemotherapy to be approximately 15-16 QALYs.

1.4 TREATMENT OF R/R DLBCL AND PMBCL

1.4.1 Treatment with axi-cel

Therapeutic indication
Axi-cel is indicated for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) and primary mediastinal large B-cell lymphoma (PMBCL), after two or more lines of systemic therapy.

Mechanism of action
Axi-cel is an autologous, immunocellular cancer therapy that involves reprogramming of 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 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.

The CAR is comprised of a murine single chain antibody fragment that recognises CD19 and is fused to two intracellular signalling domains, the T cell receptor associated CD3 zeta complex and the costimulatory receptor CD28. The CD3 zeta component is critical for initiating T cell activation and anti-tumour activity, while CD28 enhances the activation, expansion, persistence and function of axi-cel. Upon binding to CD19-expressing cells, the CAR transmits a signal promoting T cell activation, expansion, inflammatory cytokine production, and acquisition of effector functions, such as cytotoxicity, of axi-cel. This in turn leads to apoptosis and necrosis of CD19 expressing target cells.

Posology
Manufacturing of axi-cel occurs at a central facility and must be coordinated closely with the treatment centre to ensure timely management of each patient leading up to infusion.

Step 1: Leukapheresis
The patient's own peripheral blood mononuclear cells (PBMC) containing T cells are collected by leukapheresis. These cells are then shipped to the manufacturing facility in the United States , after screening and processing in the Netherlands.

Step 2: Axi-cel manufacturing
At the manufacturing facility, the patient's T cells are genetically modified *ex vivo* using retroviruses to insert the DNA for the chimeric protein into the DNA of the patient's T cells. The newly engineered cells are then further expanded, harvested and cryopreserved, and shipped back to the treating institution. Manufacture and release of axi-cel is estimated by Gilead to take about 3-4 weeks in the commercial setting.

Step 3: Pre-treatment conditioning - Lymphodepleting chemotherapy
A lymphodepleting chemotherapy regimen consisting of intravenous cyclophosphamide 500 mg/m^2 and fludarabine 30 mg/m^2 should be administered on the 5th, 4th, and 3rd day before infusion of axi-cel.

Step 4: Axi-cel infusion
Axi-cel treatment is administered as a single intravenous infusion at a dosage of 2 x 10^6 CAR-positive viable T cells per kg of body weight, or maximum of 2 x 10^8 CAR-positive viable T cells for patients 100 kg and above.

Step 5: Monitoring after infusion
Patients should be monitored daily for the first 10 days following infusion for signs and symptoms of potential cytokine release syndrome (CRS), neurological events and other toxicities. Physicians should consider hospitalisation for the first 10 days post infusion or at the first signs/symptoms of CRS and/or neurological events. After the first 10 days following the infusion, the patient should be monitored at the physician's discretion. Additionally, patients should be instructed to remain within proximity of a qualified clinical facility for at least 4 weeks following infusion.

Adverse reactions
Upon activation in the patients, the CAR-T cells proliferate and subsequently kill tumor cells, and concomitantly release inflammatory cytokines in order to enhance an effective immune response. The release of pro-inflammatory cytokines can cause cytokine resease syndrome (CRS) with symptoms of high fevers, low blood pressure, and respiratory distress. Another common and serious side effect of CAR T-cell therapy is neurotoxicity. The most common signs or symptoms associated with neurologic adverse reactions include encephalopathy, tremor, confusional state, aphasia and somnolence.

The most serious and frequently occurring adverse reactions are CRS (93%), encephalopathy (37%), and infections (42%). Grade 3 or higher neutropenia, thrombocytopenia, and anaemia still present at Day 30 or beyond occurred in 26%, 24% and 10% of the treated patients, respectively.

Both higher-grade CRS and neurotoxicity can be life threatening and require care in an intensive care unit (ICU). A detailed CRS management algorithm is therefore given in the SmPC for axi-cel. Tocilizumab (an anti-IL-6 medicinal product) is used to treat moderate or severe CRS, and a minimum of four doses of tocilizumab is required to be on site and available for administration prior to axi-cel infusion. Corticosteroids may be administered in cases where tocilizumab is insufficient to control a life-threatening event of CRS.

1.4.2 Treatment guidelines

Treatment of adult patients with DLBCL and PMBCL is described in national guidelines from The Norwegian Directorate of Health: "*Nasjonalt handlingsprogram med retningslinjer for diagnostikk behandling og oppfølging av maligne lymfomer*" (1). The treatments recommended for patients with PMBCL are similar to those for DLBCL. In addition, younger patients with PMBCL <60 years receive G-CSF support to standard front-line treatment, often in combination with etoposide

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). Approximately 30% of the DLBCL patients experience a relapse and 20% have refractory disease to first-line therapy.

The recommended second-line treatment for patients <65-70 years with good performance status and no major organ dysfunction is rituximab and chemotherapy (i.e. R-IME, R-ICE, R-GDP or R-DHAP), followed by high dose chemotherapy and autologous stem cell transplant (HDC-ASCT) in patients who respond to second-line therapy (approximately 50%). Among patients proceeding to HDC-ASCT, about 60% will relapse after transplantation. For elderly patients, and patients not considered to be candidates for HDC-ASCT, the treatment goal is life-prolonging palliation and have to be adjusted for each patient.

For patients who are refractory to last line or those who have had a second or later relapse, allogeneic stem cell transplant (alloSCT) is recommended. However, these patients have to be strong enough to succeed and have a biology that allows them to receive this treatment. Patients that are candidates for alloSCT are often younger. In addition, they have to obtain a new long-lasting remission in response to chemotherapy before they may be offered alloSCT. In total, 2-5 patients are expected to be eligible for alloSCT annually in Norway. For other patients who are refractory to last line, a new regimen of chemotherapy may be tested, with a slightly different combination of the chemotherapy selected. The majority of these patients are expected to receive palliative chemotherapy within a short period of time. Hence, although therapeutic options exist for adult patients with r/r DLBCL after two or more lines of systemic therapy, the prognosis remains poor.

1.4.3 Comparator

Axi-cel is intended as a treatment option for adult patients with r/r DLBCL and r/r PMBCL after two or more lines of systemic therapy. The currently available treatment option for these patients is various combinations of chemotherapy. According to Norwegian clinical experts, it is common to add rituximab to all of the regimens. Depending on patient response, there are sometimes an attempt to consolidate with ASCT or alloSCT.

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

2 RELATIVE EFFECTIVENESS

2.1 OVERVIEW OF RELEVANT CLINICAL STUDIES

Axi-cel was granted marketing authorisation (MA) in Norway on 23 August 2018 for the treatment of adult patients with r/r DLBCL and PMBCL, after two or more lines of systemic therapy. The clinical efficacy and safety of axi-cel was demonstrated in one pivotal phase II study (ZUMA-1) in 101 adult patients with r/r DLBCL (incl. patients with transformed follicular lymphoma, TFL) and r/r PMBCL.

The clinical trial was designed as a single arm study. Gilead has therefore conducted adjusted indirect comparisons with historical controls in order to document the relative efficacy.

2.1.1 Axi-cel efficacy studies

The ZUMA-1 study is separated into 3 distinct phases designated as the Phase 1 study, Phase 2 pivotal study (Cohort 1 and Cohort 2), and Phase 2 safety management study (Cohort 3, Cohort 4, and Cohort 5). In the phase 1 part of ZUMA-1, 7 patients were treated with axi-cel, and the primary objective was to evaluate the safety of axi-cel regimen. The results of the phase 1 study led to the initiation of the pivotal ZUMA-1 phase 2 registration trial. NoMA considers the ongoing phase 2 part of ZUMA-1 as the most relevant clinical evidence to this STA. In addition, since assessment of quality of life data was not included within the endpoints of ZUMA-1 phase 2, European Quality of Life-5 Dimensions (EQ-5D) data from cohort 3 of ZUMA-1 are included in the health economic analyses.

Table 1 Methods – the phase II of the ZUMA-1 study

	ZUMA-1		
Design	Phase II, Single arm, Multicentre		
Patients	Adult patients with r/r DLBCL (incl. TFL) or PMBCL age ≥18 years having no response to last chemotherapy or relapsed ≤ 12 months post-ASCT. Enrolled patients: N = 111 Infused patients: N = 101		
Intervention	Axi-cel; Single IV infusion of 2×10^6 (± 20%) CAR^+ viable T cells per kilogram of body weight (minimum 1×10^6 CAR T cells/kg)		
Comparator	none		
Primary endpoint	ORR (CR and PR), determined by study investigators based on the IWG 2007 criteria		
Some secondary endpoints	ORR according to the blinded independent central review, DoR, PFS, OS and Safety		
Data cut-off (DCO) date		DCO	Median follow-up infused patients
	Primary analysis:	27 Jan 2017	8.7 months
	Analysis used for MA:	11 Aug 2017	15.4 months
	Latest analysis:	11 Aug 2018	27.1 months

ASCT = autologous stem cell transplantation. CR = complete response. DoR = Duration of overall response. IV = Intravenous. MA = marketing authorisation. ORR = Overall response rate. OS = Overall survival. PFS = Progression-free survival.

The ZUMA-1 phase 2 study consisted of the following sequential periods: screening, enrolment at the commencement of leukapheresis, pre-treatment with lymphodepleting chemotherapy, one single dose of axi-cel infusion, post treatment assessment period, and follow-up period (Figure 1). Long-term follow-up for disease status and survival continued every 3 months through Month 18, then every 6 months through 5 years, and then annually for a maximum of 15 years (still ongoing). Systemic bridging chemotherapy was not allowed after leukapheresis and before administration of axi-cel. Patients who had an initial response (PR or CR) and then had disease progression at least 3 months after the first dose of axi-cel could be retreated.

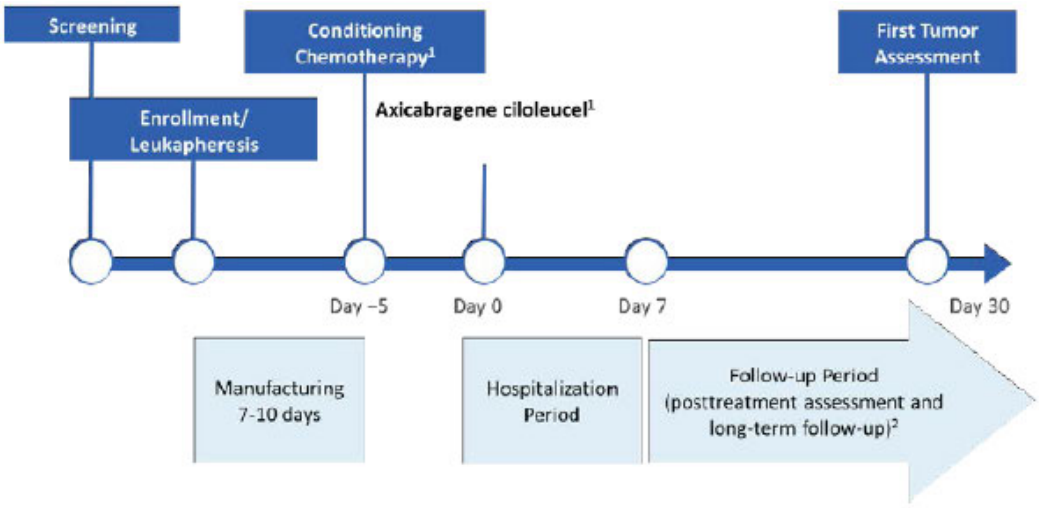

Figure 1 Study periods of the Phase II ZUMA-1 study

The primary end point in the ZUMA-1 study was the objective response rate (ORR) defined as the combined rates of complete response (CR) and partial response (PR), as assessed by the study investigators according to the International Working Group (IWG) Response Criteria for Malignant Lymphoma (6). Progression-free survival (PFS) and overall survival (OS) were secondary endpoints in the ZUMA-1 study. PFS was defined as the time from the axi-cel infusion date to the date of disease progression or death from any cause. OS was defined as the time from the axi-cel infusion to the date of death from any cause.

ZUMA-1 has been conducted at 21 USA sites and 1 Israel site. No EU sites have been involved.

NoMA's assessment of the submitted clinical evidence

The ZUMA-1 study is considered to have considerable shortcomings to inform the STA:

- The ZUMA-1 study lacks a control arm. No head-to-head comparison has been conducted and the indirect comparison with historical controls comes with limitations.

- The ZUMA-1 study included a relatively small number of patients (111 enrolled patients, of which 101 received the study drug) with a relatively short median follow-up time (27.1 months for patients

treated with axi-cel at the latest DCO of 11-Aug-2018).

- The primary endpoint was the objective response rate (ORR) defined as the combined rates of complete response (CR) and partial response (PR), as assessed by the study investigators. ORR based on independent central review was a secondary endpoint. Study investigator assessment showed a tendency towards better efficacy outcomes. Efficacy assessment based on the independent external radiographic review committee is clearly preferred to minimize potential bias, particularly concerning the open-label, single-arm study design. ORR is relevant as it provides a direct measure of the antitumor activity of this CAR-T cell therapy. Time-to-event results (i.e. PFS, OS) are considered more clinically relevant despite being immature.

- CAR-T cell therapy represents a new treatment modality. There is a particular uncertainty about the long-term efficacy and safety of these products. Thus far, none of the trials for CAR-T therapy have followed patients for a sufficient time to ascertain whether adult patients with r/r DLBCL who have an ongoing response could be considered cured. The median follow-up time in the ZUMA-1 study at the latest DCO was just above 2 years, i.e. 27.1 months. Despite a poor prognosis, the Norwegian clinicians who were contacted by NoMA anticipated that r/r DLBCL patients with a response lasting above 2 years will have a better prognosis. Still, these patients are expected to have slightly increased mortality compared to the general population.

2.1.2 Indirect treatment comparisons

Due to the single arm trial design of ZUMA-1, Gilead presented an indirect treatment comparison to a historical control study SCHOLAR-1 (2). Four comparator options were available in the model:

1. Gilead's base case: SCHOLAR-1 data were adjusted by removing patients with an Eastern Cooperative Oncology Group (ECOG) score of 2–4 and post-refractory SCT.
2. Scenario 1: No adjustment of SCHOLAR-1
3. Scenario 2: Patients with ECOG 2-4 and post-refractory SCT were excluded. SCHOLAR-1 was next adjusted to align with patient characteristics from ZUMA-1 via Propensity Score (PS)-weighting.
4. Scenario 3: Crude adjustment of SCHOLAR-1 where patients with ECOG 2-4 were excluded to match ZUMA-1

NoMA focused on the PS-adjusted analysis (Scenario 2) as a method of reducing the bias of estimating relative treatment efficacy based on single arm trials or observational studies. The impact of Gilead's base case is explored in Section 4.2.1. The propensity score is the probability of treatment assignment as a function of a set of observable covariates. Inverse probability of treatment weights (IPTW) was used to adjust OS for SCHOLAR-1 patients. Every person was weighted by the inverse probability, i.e. propensity score, of receiving the treatment (axi-cel in this case).

SCHOLAR-1 is the largest international, multicohort retrospective research study that characterised response rates and survival of salvage chemotherapy among patients with refractory DLBCL. The key advantage of using SCHOLAR-1 as the source for the comparator data was that the included patients

matching the inclusion criteria for refractoriness in ZUMA-1 and that Gilead has access to patient-level data from both arms.

For the purpose of the PS-adjusted analysis, Gilead selected patients who had patient characteristics collected within 3 months from the refractory status. This was important as the PS analysis relies on the quality, timing and the number of variables included in the model. In addition, patients with ECOG 2-4 were excluded from SCHOLAR-1 to match ZUMA-1. Gilead also excluded patients from SCHOLAR-1 with unknown disease stage and those who received a subsequent SCT. Exclusion of patients with unknown disease status or patients with disease status collected 3 months or more of the date of refractory determination resulted in the biggest sample loss (375/593 patients excluded).

During the review process, NoMA requested an updated PS-analysis where patients with subsequent SCT are retained in SCHOLAR-1. In the analysis provided by Gilead, those patients were excluded as, according to the clinical experts, the proportion of patients who would receive SCT in clinical practice is much lower than 29% reported in SCHOLAR-1. However, NoMA intend to select those patients from the SCHOLAR-1 dataset that could have been included in a theoretic ZUMA-1 control arm. NoMA considers the patient population in clinical practice not representative of the patient population that would be eligible for inclusion in ZUMA-1. A recent analysis based on 295 US real-world patients treated with axi-cel showed that 43% of patients in this analysis would not have met the eligibility criteria for the ZUMA-1 study at the time of leukapheresis (7). Common criteria that would have made these patients ineligible for ZUMA-1 included platelets < 75 (n = 13), active deep vein thrombosis/pulmonary embolism (n = 9), prior CD-19 or CAR-T therapy (n = 8), glomerular filtration rate < 60 (n = 8), a history of CNS lymphoma (n = 8), symptomatic pleural effusion (n = 4), left ventricular ejection fraction < 50% (n = 4) and prior allogeneic transplant (n = 2). In the analysis one of the covariates associated with ongoing CR at Day 90 was eligibility for ZUMA-1 (62 [65%] patients) vs not (27 [47%] patients, p=0.037).

NoMA assumes that ZUMA-1 patients were fitter than patients in clinical practice and would therefore likely be more eligible for SCT. Hence, it is not appropriate to remove patients from SCHOLAR-1 who received post-chemotherapy SCT. NoMA believes that exclusion of post chemotherapy SCT patients would underestimate the efficacy in the SCHOLAR-1 arm. These patients would likely have a better prognosis as a prerequisit for SCT. As these patients experience a response to chemotherapy treatment they would also be medically fit for transplant. Results of a scenario where all post chemotherapy SCT patients are exluded from the analysis is discussed in section 3.4.2 and section 4.2.6.

In the new analysis, OS was measured from the beginning of chemotherapy in the patients who subsequently received SCT as opposed to from the timing of SCT. This is because the whole length of the comparator treatment pathway (chemotherapy + SCT) is used in the model to calculate costs and effects as opposed to a single component (chemotherapy or SCT). The application of NoMA's inclusion criteria improved the survival in SCHOLAR-1 (Figure 2).

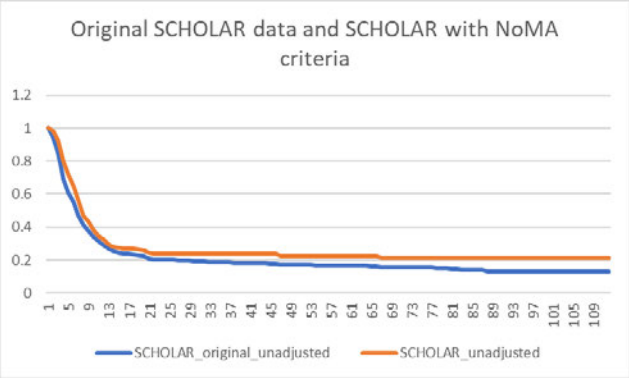

Figure 2: NoMA's inclusion criteria (orange line) shows improved survival in SCHOLAR-1

For the PS-adjustment, NoMA also requested that individual components of the IPI score (i.e. age and disease stage) are used for PS as opposed to the IPI score itself. The reason for this request is that there is more missing data for IPI than the disease status, and it was important to retain as many patients as possible. The use of individual variables did not affect the analysis as the survival in SCHOLAR-1 remained similar to the one where NoMA's selection criteria were applied. OS Kaplan Meier curves for ZUMA-1 and PS-adjusted SCHOLAR-1 are presented below (Figure 3). SCHOLAR-1 curves were almost identical when adjusted to ZUMA-1's mITT and ITT populations with a median OS of 6.4 months for both. Median OS in the ITT population of ZUMA-1 was 16.3 months, and has not been reached in the mITT population.

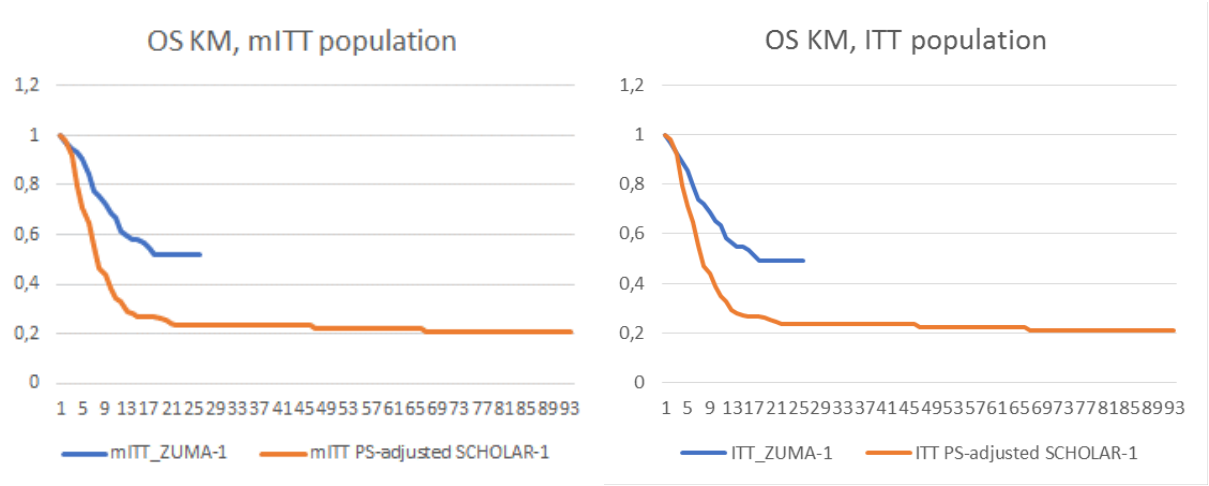

Figure 3 OS KM curves for ZUMA-1 (mITT population, left and ITT population, right) versus PS-adjusted OS for SCHOLAR-1.

After applying NoMA's inclusion criteria, but before PS-adjustment, patients in SCHOLAR-1 were younger (50 years old vs 56 in ZUMA-1 mITT), had better disease stage (34% in stage I-II as opposed to 18% in ZUMA-1 ITT) and had less prior lines of chemotherapy (100% had 1-2 lines, as opposed to 30% in ZUMA-1). There were also large imbalances in percentage of patients who relapsed within 12 months after ASCT, who were primary refractory or refractory to at least 2 consecutive lines of therapy.

After PS-adjustment patient characteristics were generally more aligned but the remaining bias was not fully eliminated (the median and mean bias was around 24% and 50% in the adjusted analysis). Since there are no patients with more than two previous lines of chemotherapy in SCHOLAR-1 after applying NoMA's inclusion criteria, the model forces a larger proportion of patients in SCHOLAR-1 to have two prior lines of chemotherapy to be aligned with ZUMA-1. Consequently, the proportion of patients in SCHOLAR-1 with two prior lines increased from 70% (unadjusted analysis) to 98% (PS-adjusted analysis) as compared to 27% in the ZUMA-1 ITT population. On the other hand, more patients in PS-adjusted SCHOLAR-1 had a primary refractory status (11% vs 3% in the ITT of ZUMA-1), and primary refractory disease has been found to be a significant risk factor for failing to respond to second-line therapy (11). In addition, the analysis did not adjust for disease subtypes. In the mITT of ZUMA-1, 8 patients (8%) had PMBCL and 16 (16%) had TFL. In the SCHOLAR-1 publication, the proportions were much lower (2.2% and 4.2%, respectively). It is unclear how these imbalances in patient characteristics affected the efficacy results.

NoMA has validated the results with Norwegian clinical experts and has learned that in clinical practice the long term survival of 20% for the comparator arm is overoptimistic. The proportion of patients who would receive a subsequent SCT is estimated at about 15% and some patients would still relapse and die. Therefore, long term survival in clinical practice may be closer to 10%. The clinicians agree, however, that it is uncertain what the long term survival would be in patients with characteristics similar to ZUMA-1.

Overall, NoMA accepts SCHOLAR-1 as a source of historical control for ZUMA-1. NoMA has focused on the PS-adjusted analysis as a method of reducing the bias of estimating relative treatment efficacy based on single arm trials or observational studies. Due to availability of patient-level data, individuals from SCHOLAR-1 with missing data or with mismatched patient characteristics could be excluded from the data set. Nevertheless, it is noted that the PS-adjustment did not result in perfectly aligned patient characteristics between ZUMA-1 and SCHOLAR-1. It is also noted that the populations in SCHOLAR-1 (mix of observational and experimental studies) and ZUMA-1 will intristically never be fully aligned in terms of eligibility criteria or treatment management. For instance, ZUMA-1 included only patients with adequate renal, hepatic, pulmonary and cardiac function. In contrast, it is assummed that inclusion criteria in the observational studies were less stringent. A comparison of axi-cel with Gilead's preferred choice of comparator data (SCHOLAR-1 excluding ECOG 2-4 and post-refractory SCT) as well as a comparison with Scenario 3 (SCHOLAR-1 excluding ECOG 2-4) is tested in scenario analyses (see section 4.2.6). The comparator's long term survival in those two scenarios is 8% and 13%, respectively.

Lastly, NoMA has requested PS-adjusted comparison of ZUMA-1 vs CORAL extension studies (8, 9) which were one of the components of SCHOLAR-1. Interestingly, the mITT PS-adjusted OS results for SCHOLAR-1 and CORAL are almost identical, suggesting that CORAL is the key study influencer after applying NoMA's selection criteria. The comparison with CORAL was not tested in a scenario analysis.

Detailed description of the methodology, results and the assessment of comparison vs SCHOLAR-1 can be found in Appendix 2.

2.1.3 Ongoing and initiated studies

ZUMA-7 is a randomised, open-label, international, phase 3 study designed to evaluate the efficacy and safety of axi-cel versus standard-of-care second-line treatment after first-line rituximab and anthracycline-based chemotherapy for patients with r/r DLBCL (NCT03391466). Standard of care in ZUMA-7 will consist of a protocol-defined, platinum-based combination chemotherapy regimen followed by HDC-ASCT in those patients who respond to chemotherapy.

Another study, ZUMA-12, a open-label, multicenter, phase 2 study evaluating the efficacy and safety of axi-cel as first-line therapy in patients with high-risk large B-cell lymphoma is onging and currently in the recruiting phase (NCT03761056).

Two ongoing studies are evaluating axi-cel combination therapy in refractory DLBCL; ZUMA-6 (axi-cel in combination with atezolizumab, NCT02926833), and ZUMA-11 (axi-cel in combination with utomilumab)

3 PICO[1]

3.1 PATIENT POPULATION

Norwegian clinical practice

Axi-cel is intended as a treatment option for adult patients with r/r DLBCL and r/r PMBCL after two or more lines of systemic therapy.

Given the waiting period between leukapheresis and infusion (median time: 23 days in ZUMA-1), the need for lymphodepleting chemotherapy, and the risk of serious adverse events (SAEs) associated with axi-cel, candidates for CAR-T cell treatment need to be sufficiently fit prior to infusion. Hence, CAR-T cell therapy may not be a treatment option for patients with deteriorating clinical status and rapidly progressing disease, patients who experience persistent toxicities from recent chemotherapy, or patients with an active infection.

According to Norwegian clinicians contacted by NoMA, approximately 20 adult patients with r/r DLBCL and r/r PMBCL will be candidates for treatment with CAR-T cell therapy each year in Norway.

Submitted clinical studies

The ZUMA-1 phase 2 study included adult patients with histologically confirmed DLBCL (n=77, mITT), PMBCL (n=8, mITT) or DLBCL arising from follicular lymphoma (n=16, mITT). Eligible patients had refractory disease defined as PD or SD as best response to last line of therapy, or disease progression within 12 months after ASCT. Patients must have received at least prior anti-CD20 antibody therapy and an anthracycline-containing regimen. Patients with central nervous system (CNS) lymphoma or a history of alloSCT were excluded.

Among the 111 patients enrolled in the ZUMA-1 phase 2 study, 101 received infusion with axi-cel. In total, 10 enrolled patients (9%) discontinued prior to axi-cel infusion due to the following reasons: adverse events (n=4), deaths (n=3), non-measurable disease before lymphodepleting chemotherapy (n=2), and manufacturing failure (n=1). The median time from leukapheresis to delivery of axi-cel was 17 days (range: 14 to 51 days), and the median time from leukapheresis to infusion was 23 days (range: 15 to 72 days).

[1] Patients, Intervention, Comparator, Outcome.

Table 2 Patient characteristics in the ZUMA-1 phase 2 study

	Enrolled (ITT) (n=111)	Infused (mITT) (n=101)
Age		
Median (min-max)	58 (23-76)	58 (23-76)
Sex		
Male	69%	67%
Female	31%	33%
ECOG status		
ECOG 0	41%	42%
ECOG 1	59%	58%
Disease status		
Refractory to ≥ 2 prior lines of therapy	77%	76%
Relapsed within 1 year of ASCT	20%	21%
Number of prior therapies		
Median (min-max)	3 (1-10)	3 (1-10)
IPI 3/4	46%	46%
Disease stage III/IV	85%	85%

Submitted health economic analyses

Adult patients with r/r DLBCL and r/r PMBCL, after two or more lines of systemic therapy, were included in the economic model. The starting age in the model is 56 years (mean age in ZUMA-1). Gilead included the modified intent-to-treat (mITT) population (infused patients) from the combined Phase 1 and 2 of ZUMA-1 in their base case and the ITT population (enrolled patients) in a scenario analysis.

NoMA´s assessment

The patient population evaluated in the ZUMA-1 study has been used to inform the economic analyses.

The median age of the enrolled patients in the clinical study was 58 years (range 23-76). The Norwegian patient population expected to be eligible for treatment with axi-cel is estimated by the Norwegian clinicians to be mainly between 50 and 70 years, with a median age around 60 years . In real-world experience with axi-cel treatment in the US the median age was 60 years (range 21-83) (7). However, the studied patient population in the ZUMA-1 study does not fully reflect the variety of DLBCL patients intended for axi-cel. Both the inclusion and exclusion criteria applied in the study may have introduced a selection bias of patients likely to benefit from the treatment, but unlikely to be at high risk of being harmed by axi-cel (e.g. ECOG PS 0-1, adequate organ functions, and no CNS involvement).

ZUMA-1 has mainly been conducted in the United States, only one patient was recruited at one site in Israel, and no EU sites were involved. The median time from leukapheresis to delivery of axi-cel was 17 days in the study. This process will be longer for European patients due to shipping to the manufacturing facility in the United States, and additional process steps in the Netherlands before manufacturing (screening and processing) and after manufacturing (quality assurance and release). According to Gilead,

the current average from leukapheresis to product delivery for European patients is 3 to 4 weeks. A prolonged waiting period in clinical practice compared to that observed in the ZUMA-1 study, may result in a higher dropout rate due to i.e. deaths or disease progressions of patients with a worse prognosis. In addition, the status of those who receive the infusion will worsen during the waiting period. The impact of such a prolonged waiting period on the efficacy of axi-cel in clinical practice compared to that observed in the ZUMA-1 study is currently unknown. Therefore, some uncertainties remain regarding the true magnitude of the efficacy estimates for axi-cel. According to Gilead, a new production facility will be established the Netherlands from 2020, and the waiting period from leukapheresis to delivery will then probably be reduced for European patients.

Gilead evaluated the mITT population (infused patients only) in their base case. NoMA considers both the ITT population (enrolled patients) and the mITT population to be relevant for this STA. The reasons are described in more details below.

In the ITT population, the efficacy of axi-cel is measured from the time of enrolment to account for the time period required to manufacture the CAR-T cells. It is considered important to include these aspects in the analysis for several reasons, as listed below:

- Patients would have received the comparator treatment at the time of enrolment if they had not waited for infusion with axi-cel.
- Some patients who underwent leukapheresis, i.e. 9% of all the enrolled patients, did not receive axi-cel infusion in the ZUMA-1 study. This should be reflected in the economic analysis.
- Lymphodepleting chemotherapy should be considered as an essential element of the treatment strategy. The ITT analysis evaluates the efficacy of all the sequential treatment phases associated with this CAR-T cell product, including the lymphodepleting chemotherapy regimen patients received prior to infusion, and not only axi-cel alone.
- The time span from apheresis to the CAR-T administration may have enriched the patient population included in the mITT analysis. Only patients that survived the waiting period and were able to receive infusion were assessed in the mITT analysis, and this may have led to the inclusion of healthier patients in the mITT population. Consequently it is difficult to separate the influence of patient characteristics and (unobserved) prognostic factors from the treatment effect of axi-cel in the infused set. The mITT population is likely to introduce selection bias and it is difficult to rule out overestimation of the treatment effect.

In the mITT population, the effect of axi-cel is measured only in infused patients from the time of infusion. Thus, patients who did not receive the infusion because of death prior to infusion, AEs, or manufacturing failure, were excluded from the analysis. The relevance of the mITT analysis for this STA is listed below:

- The historical control studies included only patients who received treatment (i.e. mITT population).
- The ITT analysis is affected by the timing of enrolment in the clinical trial. In the ZUMA-1 study, enrolment started at the commencement of leukapheresis. The timing of enrolment and leukapheresis in various CAR-T cell trials might differ and are likely to affect both the waiting time and dropout rates observed in the period from leukapheresis to infusion, and might have a considerable

impact on the efficacy results observed in the ITT population. Thus, in order to assess CAR-T products on equal terms, NoMA considers the mITT analysis to be useful.

3.2 INTERVENTION

Norwegian clinical practice

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 the axi-cel infusion will be followed in clinical practice (see section 1.4.1).

Treatment with bridging chemotherapy during the waiting period from apheresis to CAR-T administration was not allowed in ZUMA-1 but will presumably be needed to stabilise the clinical state for some of the patients in clinical practice while waiting for infusion. A recent analysis based on 295 US real-world patients treated with axi-cel showed that 55% of patients in this analysis received bridging therapy (7)

Submitted clinical studies

Axi-cel:
The planned dosage of axi-cel in ZUMA-1 was similar to the dosage that is now recommended in the SmPC (2 x 10^6 CAR-positive viable T cells per kg of body weight or maximum 2 x 10^8 CAR-positive viable T cells for patients≥100 kg). The median dose in ZUMA-1 was 2 x 10^6 CAR-positive T cells/kg (range: 1.1 to 2.2 x 10^6 cells/kg).

Patients who had an initial response (PR or CR), and then had disease progression at least 3 months after the first dose of axi-cel, could be retreated. A total of 9 patients were retreated with axi-cel in the Phase 2 of ZUMA-1 (DCO: 11 Aug 2017).

Lymphodepleting chemotherapy:
A standard fludarabin/cyclophosphamide based regimen was used in the clinical study. Among the 111 patients enrolled in the ZUMA-1 study, 103 (93%) patients received lymphodepleting chemotherapy after enrolment. All the 101 patients who were treated with axi-cel received lymphodepleting chemotherapy on the 5th, 4th, and 3rd day prior to axi-cel infusion.

Bridging chemotherapy:
Treatment with systemic bridging chemotherapy was not permitted in the period between enrolment, leukapheresis and before administration of axi-cel in ZUMA-1.

Submitted health economic analyses

Axi-cel:
In the mITT analysis, all patients received axi-cel infusion. In the ITT analysis (all enrolled patients), the proportion of patients who received infusion was 91% derived from ZUMA-1.

Axi-cel infusion is given once as a single infusion. In ZUMA-1, some patients were retreated in line with the study protocol (9.3%; 10/108 subjects were retreated based on the August 2017 data cut; 9 patients

from the phase 2 and 1 patient from the phase 1 part of the study). Both the efficacy outcomes and additional costs for the retreated patients are included in the model.

Lymphodepleting chemotherapy:
Lymphodepleting chemotherapy includes intravenous infusions of cyclophosphamide 500 mg/m^2 and fludarabine 30 mg/m^2 once daily on the 5th, 4th and 3rd day prior to infusion of axi-cel.

In the mITT analysis, a multiplier of 1.019 (N=110/108) was used to adjust both the lymphodepleting chemotherapy costs and the associated hospitalisation costs to account for the two additional patients in ZUMA-1 who were treated with lymphodepleting chemotherapy but did not receive axi-cel.

NoMA´s assessment

The intervention arm for the economic analysis corresponds to the intervention in the ZUMA-1 trial, including retreatment with axi-cel for 9.3% of the patients. The retreated patients are included in the efficacy outcomes as there was no censoring at the time of retreatment for the OS endpoint in ZUMA-1. NoMA therefore considers it appropriate to include the costs associated with retreatment in the analyses. However, the SmPC does not include an option of retreatment with axi-cel.

3.3 COMPARATOR

Norwegian clinical practice

Different chemotherapy combinations with rituximab, followed by SCT in eligible patients, is a relevant comparator in Norway for adult patients with r/r DLBCL or r/r PMBCL after two or more lines of systemic therapy according to clinical experts.

The various combinations of chemotherapy used in Norwegian practice varies with the patients' characteristics and aim of treatment. The most common treatments would be:

- R-GDP (rituximab, gemcitabine, dexamethasone, cisplatin),
- R-EPOCH (rituximab, etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin),
- R-DHAP (rituximab, dexamethasone, cytarabine, cisplatin),
- R-Gem-OX (rituximab, gemcitabine, oxaliplatin), and
- R-ICE (rituximab, ifosfamide, carboplatin, etoposide) in rare cases

Submitted clinical studies

SCHOLAR-1 is used as the source for the comparator data. Due to potential selection bias in the ZUMA-1 trial (se section 3.2), the SCHOLAR-1 population has been adjusted to be comparable with the population in the ZUMA-1. See section 2.1.2 and Appendix 2 for the ZUMA-1 vs SCHOLAR-1 for detailed explanation of the comparison.

In SCHOLAR-1, the specific chemotherapy regimens used by the patients were mainly the combination treatments DHAP, GDP, IME and ICE according to Gilead. In this study, 29% of the patients received ASCT or alloSCT at any time after determination of refractory status. After NoMA's requested adjustment of the

patient population to better fit with the ZUMA-1 population (see section 2.1.2), the proportion of patients who received SCT in the SCHOLAR-1 dataset increased from 29% to 30%.

Submitted health economic analyses

Combination chemotherapy regimens +/- rituximab is the comparator in the submitted health economic analysis. The treatment cost of the comparator is estimated based on the distributed proportion of use of four different chemotherapy regimens, as follows:

- (R)- IME (rituximab, ifosfamide, mitoxantrone, etoposide) – 50%
- (R)-DHAP (rituximab, dexamethasone, cytarabine, cisplatin) – 20%
- (R)-GDP (rituximab, gemcitabine, dexamethasone, cisplatin) – 20%
- (R)- ICE (rituximab, etoposide, methylprednisolone, cytarabine, cisplatin) – 10%

In the base case, no SCT costs were assumed in the comparator arm, as patients who received SCT were excluded. In a sensitivity analysis, the cost of SCT was applied. The proportion of patients in the comparator arm receiving SCT was sourced from SCHOLAR-1.

NoMA´s assessment

NoMA chose chemotherapy combinations with rituximab, followed by SCT in eligible patients as the comparator (see section 1.4.3).

There is no standard chemotherapy regimen for r/r DLBCL and r/r PMBCL in Norway. According to Norwegian clinicians, there are several regimens considered to be equally effective for treating these patients, and the most common would be R-GDP, R-EPOCH, R-DHAP, R-Gem-OX, and R-ICE in rare cases. In the health economic analyses, NoMA has calculated the costs of the comparator treatment based on these regimens (see section 4.1.3). In line with Norwegian clinical practice, NoMA has added the costs of rituximab to all the chemotherapy regimens, but has not adjusted for the potential impact on the efficacy outcomes due to lack of data.

NoMA considers SCHOLAR-1 as being an acceptable source of a historical control in the Norwegian setting. Both the axi-cel and comparator studies lack control arms. Thus it is not possible to compare outcomes from these trials without a high degree of uncertainty. To be able to compare the SCHOLAR-1 population with the population studied in ZUMA-1, the SCHOLAR-1 population is adjusted. This result in a higher proportion of patients in the SCHOLAR-1 receives subsequent SCT (30%). This is also higher than experienced in clinical practice. NoMA has explored the effect of subsequent SCT in scenarioanalysis. See section 3.4.2 and 4.2.6.

3.4 OUTCOMES

3.4.1 Efficacy

Submitted clinical studies

The median follow-up time from axi-cel infusion to the DCO of 11-Aug-2018 of the ZUMA-1 study was 27.1 months, with a maximum of 32.4 months.

According to independent central review committee (IRC) assessment, 74% (95% CI: 65 to 82) of the patients who received axi-cel had a best overall objective response of either CR or PR. In total, 54% (95% CI: 44 to 64) achieved a CR and 20% (95% CI: 13 to 29) obtained a PR.

In the ITT population (n=111), the median PFS using central assessment was 9.5 months (95% CI: 6.1 to 15.4) and the median OS was 17.4 months (95% CI: 11.6 to NE). The PFS and OS probabilities were 45.9 % (95% CI: 35.9 to 55.2) and 59.5% (95% CI: 49.7 to 67.9), respectively, at 12 months, and 38.2% (95% CI: 28.6 to 47.7) and 47.7% (95% CI: 38.2 to 56.7) at 24 months after enrolment/leukapheresis.

In the mITT population (n=101), the median PFS using central assessment was 9.1 months (95% CI: 5.7 to not estimable) and the median OS was not reached (95% CI: 12.8 to not estimable) at the latest DCO. The PFS and OS probabilities were 47.4% (95% CI: 37.0 to 57.1) and 60.4% (95% CI: 50.2 to 69.2), respectively, at 12 months, and 41.4% (95% CI: 31.2 to 51.3) and 50.5% (95% CI: 40.4 to 59.7) at 24 months after enrolment/leukapheresis.

Table 3 Efficacy results in the mITT (infused) and ITT (enrolled) patient populations in the ZUMA-1 study (DCO: 11-Aug-2018)

	ZUMA-1	
	Infused (n=101)	**Enrolled (i.e. all patients) (n=111)**
Objective response (ORR) – n (%)		
Investigator assessment (primary endpoint)	84 (83%)	86 (77%)
(95% CI)	(74, 90)	(69, 85)
IRC assessment	75 (74%)	75 (68%)
(95% CI)	(65, 82)	(58, 76)
Complete response (CR) – n (%)		
Investigator assessment	59 (58%)	61 (55%)
IRC assessment	55 (54%)	55 (50%)
Progression-free survival (PFS)*		
Events – n (%)	55	63
Median (months) (95% CI)	9.1 (5.7, NE)	9.5 (6.1, 15.4)
% event free probability at 12 months	47%	46%
% event free probability at 24 months	41%	38%
Overall survival (OS)*		
Events – n (%)	50	58
Median (months) (95% CI)	NE (12.8, NE)	17.4 (11.6, NE)
% event free probability at 12 months	60%	60%
% event free probability at 24 months	51%	48%

*PFS and OS from the time of infusion in the mITT (infused) patient population, and from the time of leukapheresis in the ITT (enrolled) patient population. PFS based on IRC assessment, censoring of SCT. NE = not estimable. IRC = independent review committee.

The Kaplan-Meier (KM) plots of PFS using clinical investigator assessment and OS in the mITT population is presented in Figure 4 and Figure 5, respectively.

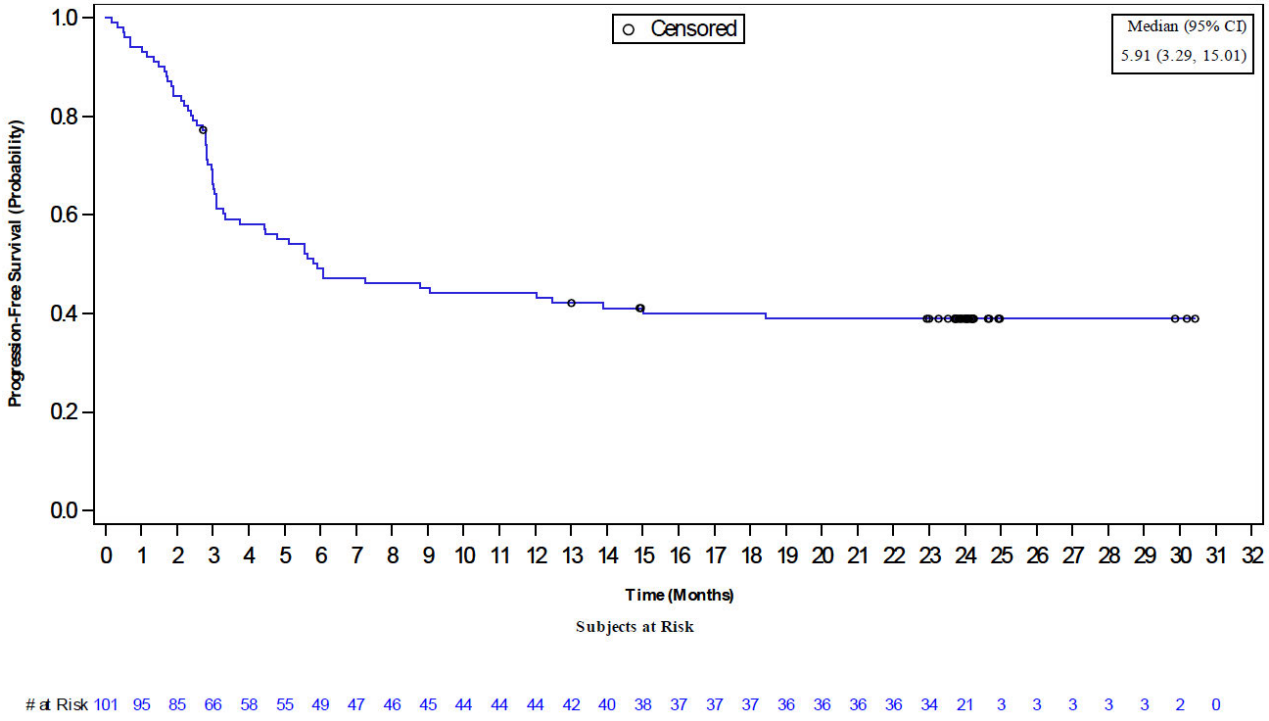

Figure 4 KM plot of PFS using clinical investigator assessment in the mITT population (DCO: 11-Aug-2018)

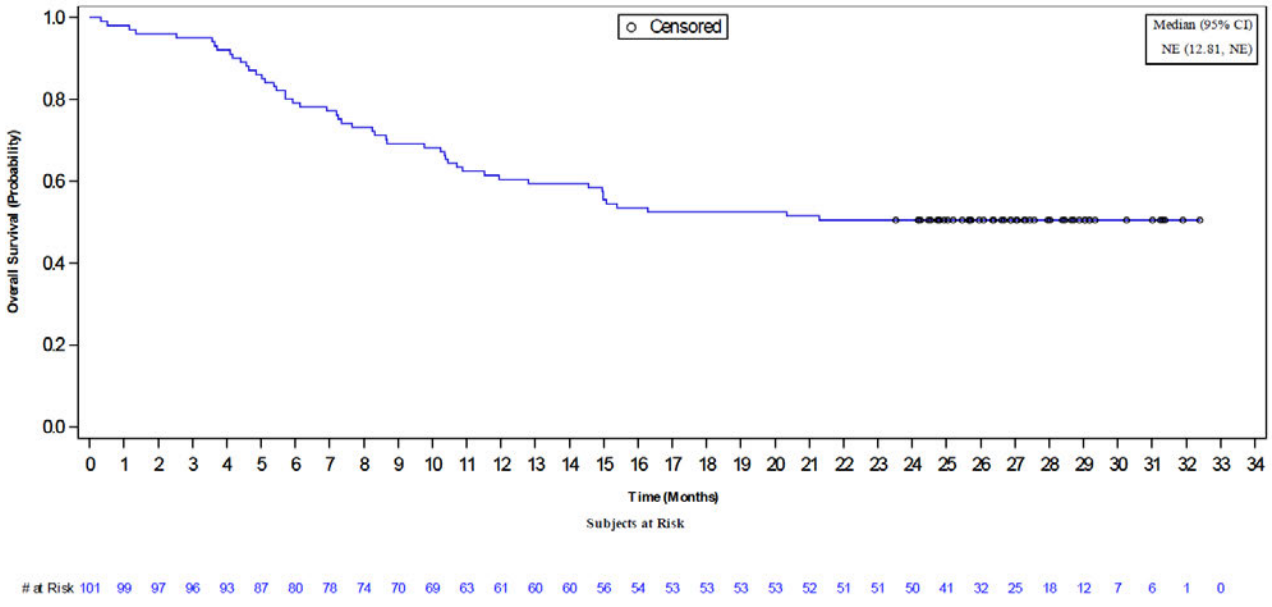

Figure 5 KM plot of OS in the mITT population (DCO: 11-Aug-2018)

The duration of responses (DoR) in patients obtaining a best disease control rate of CR or PR in ZUMA-1 indicates that sustained responses can be achieved in these patients, predominantly in patients who

obtained a CR. The KM plot of DoR per central review among the 75 responding patients in the mITT population who achieved a best overall response rate of CR or PR is presented in Figure 6. The response were ongoing and censored at the DCO of 11-Aug-2018 in 46 patients (61%) of the mITT population, including 35 patients (47%) with ongoing CR. Five of the patients with ongoing responses underwent alloSCT, and none underwent ASCT while in axi-cel-induced remission.

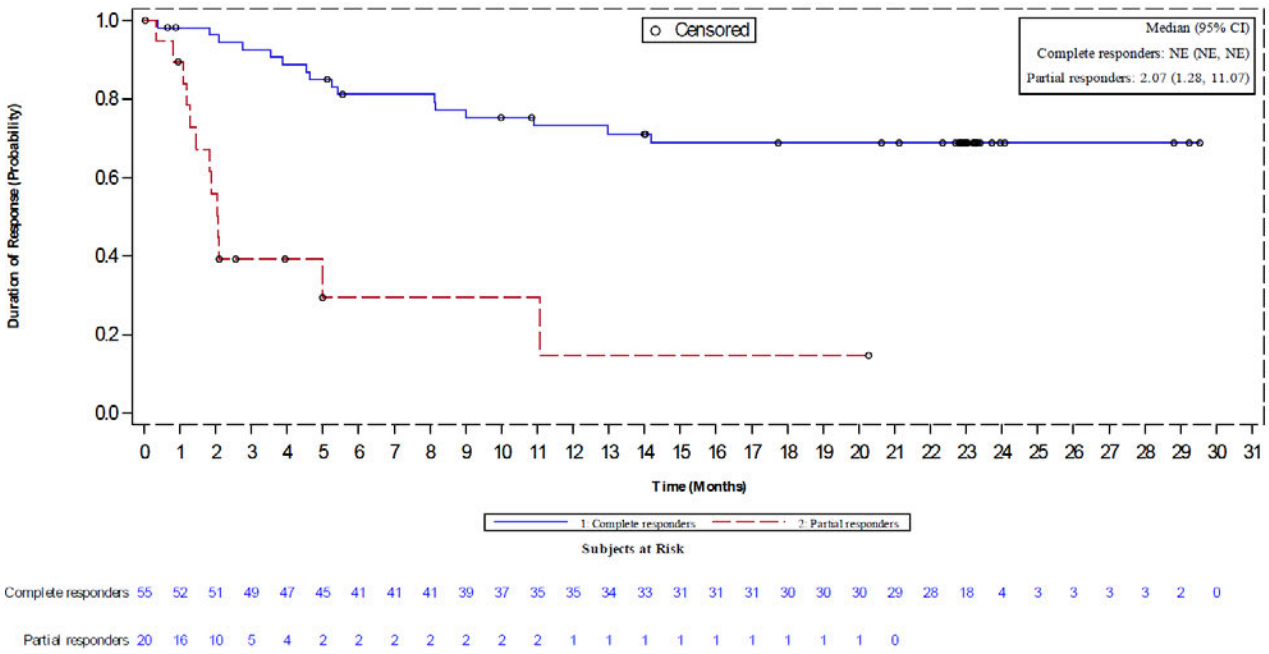

Figure 6 KM plot of DoR by response group using central assessment in patients who achieved CR versus PR in the mITT population (n=75; DCO: 11-Aug-2018)

3.4.2 Extrapolation of efficacy

Submitted health economic analyses - projection of OS

As discussed in section 2.1.2, NoMA accepts SCHOLAR-1 as the source for comparator data. For axi-cel, data are sourced from ZUMA-1, DCO of 11 Aug 2017, with a median follow-up of 15.4 months. In this section, OS and PFS as modelled by Gilead in its submission are discussed, followed by NoMA's evaluation and exploration of alternative modelling assumptions. Gilead's preferred scenario is based on SCHOLAR-1 data that were adjusted by removing patients with an ECOG score of 2–4 and post-refractory SCT. NoMA's preferred scenario is based on PS-adjusted SCHOLAR-1 data as described in section 2.1.2, which will be referred to as the "updated PS-adjusted" analysis.

Axi-cel

Gilead provided a number of standard parametric models and mixture cure models fitted to the OS data of the mITT and ITT populations in ZUMA-1. Gilead only discussed the mITT analysis in its original submission, and argued that standard parametric curves did not provide a plausible estimate of OS for axi-cel due to crossing of the OS curves with chemotherapy (BSC) (Figure 7).

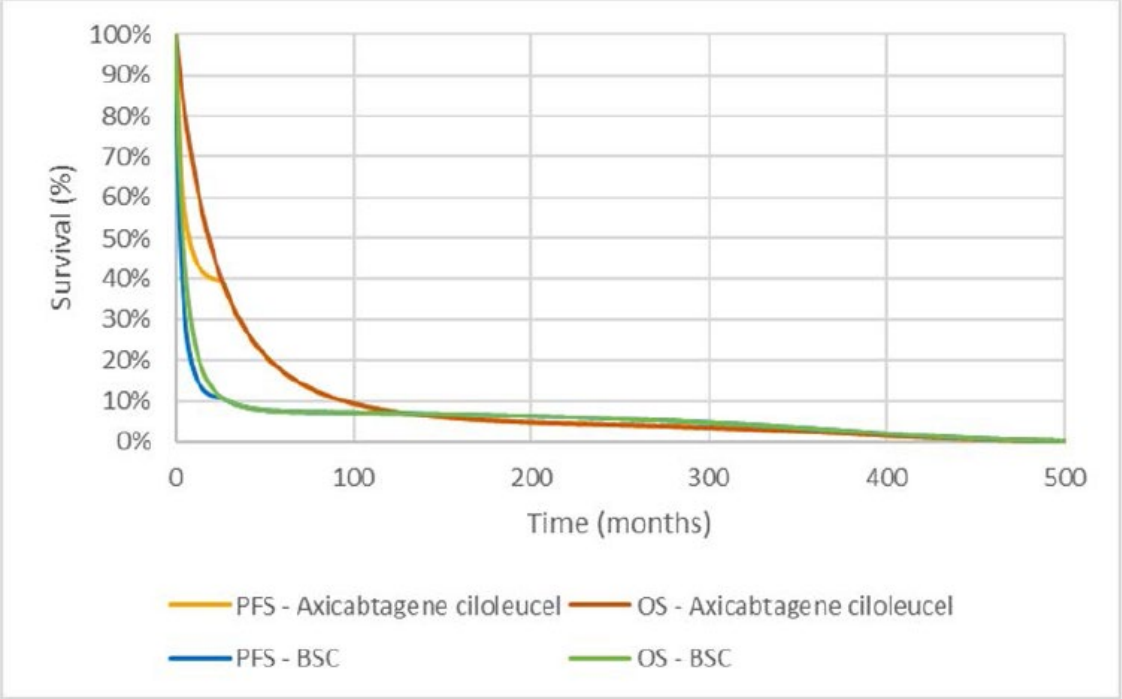

Figure 7: Extrapolation of OS and PFS for axi-cel and chemotherapy in Gilead's mITT analysis based on Gompertz models for PFS and OS for axi-cel and OS for chemotherapy

In its base case, Gilead selected a mixture-cure model where survival of the "uncured" proportion of patients follows a Weibull distribution, and survival of the "cured" proportion of patients follows the survival of the age- and gender-matched Norwegian general population (Figure 8). The probability of obtaining a cure was estimated in a logistic regression. Gilead considered the Weibull mixture cure model (MCM) to be the best fitting MCM based on statistical fit (Table 4), visual inspection and clinical rationale for a substantial cure proportion. The estimated cure fraction is 0.50 for the Weibull MCM, compared to 0.01 and 0.53 for the lognormal and gamma MCM, respectively (Table 5). This implies that in Gilead's base case, approximately 50% of the patients on axi-cel is assumed to achieve long-term remission after about 26 months.

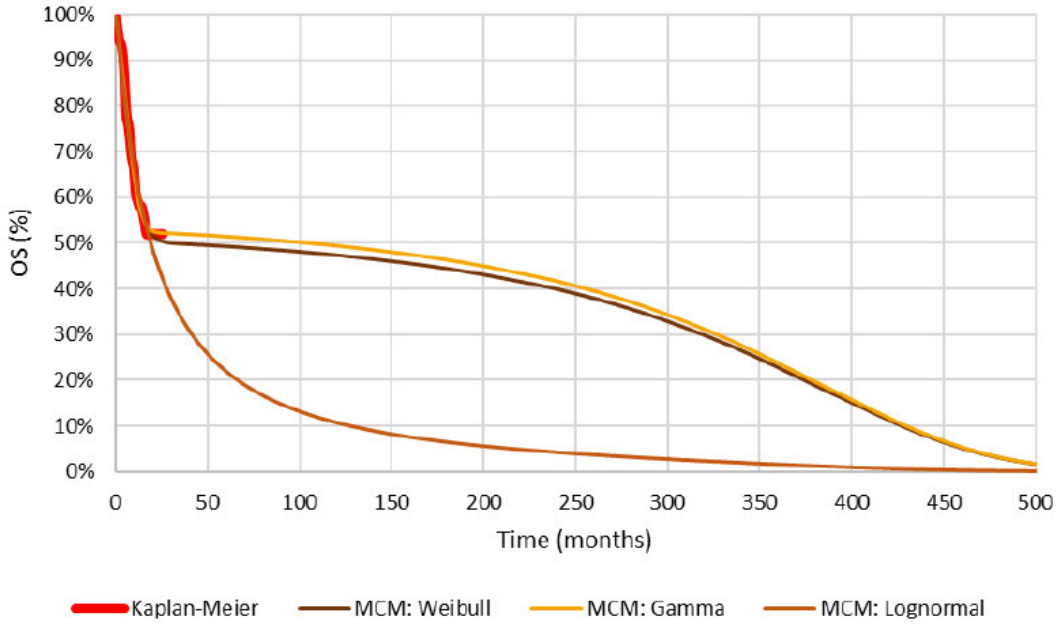

Figure 8: OS for axi-cel in Gilead's mITT analysis based on alternative mixture cure models

Table 4: AIC and BIC for alternative mixture cure models for OS for axi-cel in Gilead's mITT analysis

Model	AIC	BIC
Weibull	170.51	178.56
Gamma	171.93	182.66
Lognormal	173.83	181.87
Key: AIC, Akaike information criterion; BIC, Bayesian information criterion.		

Table 5: Coefficients for alternative mixture cure models for OS for axi-cel in Gilead's mITT analysis

Distribution	Parameter	Mean
Weibull	Pi	0.02
	Implied "cure fraction"	0.50
	Constant	0.42
	ln(gamma)	0.42
Gamma	Pi	0.108
	Implied "cure fraction"	0.53
	Constant	-0.23
	ln(sigma)	-0.61
	Kappa	1.41
Lognormal	Pi	-4.27
	Implied "cure fraction"	0.01
	Constant	0.47
	ln(sigma)	0.37

Upon request by NoMA, Gilead submitted mixture cure models for the ITT population where survival of the uncured patients follows either a Weibull, gamma or lognormal distribution, presented in the figures below. The Weibull model had the best statistical fit according to AIC and BIC, with an estimated cure fraction of 46.80% (Table 6).

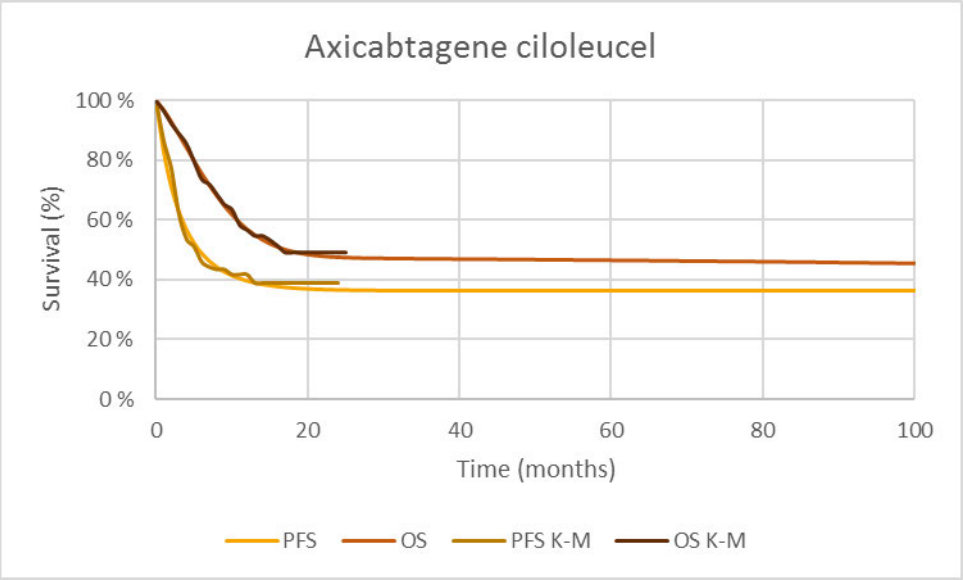

Figure 9: OS for axi-cel in the Gilead's ITT analysis based on a gamma mixture cure model. PFS is based on a Gompertz function and additional assumptions by Gilead.

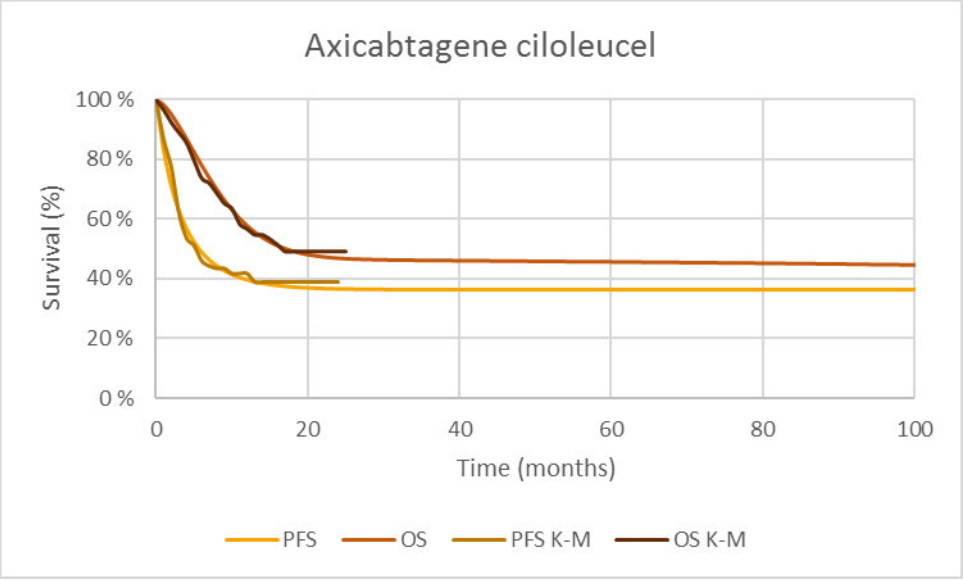

Figure 10: OS for axi-cel in Gilead's ITT analysis based on a Weibull mixture cure model. PFS is based on a Gompertz function and additional assumptions by Gilead.

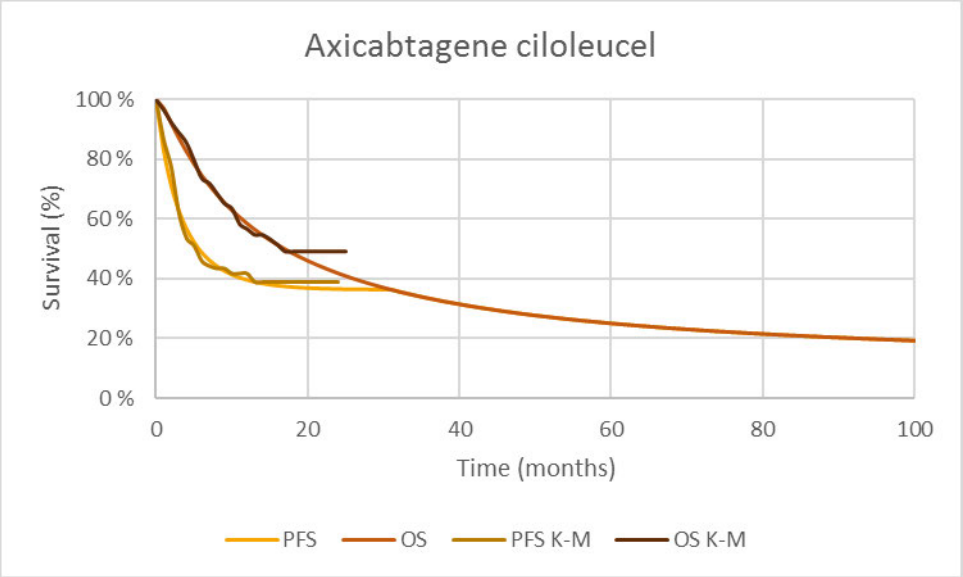

Figure 11: OS for axi-cel in Gilead's ITT analysis based on a lognormal mixture cure model. PFS is based on a Gompertz function and additional assumptions by Gilead.

Table 6: Coefficients for alternative mixture cure models for OS for axi-cel in Gilead's ITT analysis

Distribution	Parameter	ITT (ZUMA-1, n=119*)	LL (model)	AIC	BIC	Estimated cure fraction
Weibull	pi	-0.128	-90.3	186.6	194.9	46.80%
	ln(p)	0.448				
	Constant	0.443				
Gamma	pi	-0.092	-91.1	188.2	196.5	15.23%
	Constant	-0.302				
	ln(sigma)	-0.420				
	Kappa	1.240				
Lognormal	pi	-1.788	-90.2	188.4	199.5	48.56%
	Constant	0.066				
	ln(sigma)	0.331				

**ITT in ZUMA-1 phase 2 (n=111) and phase 1 (n=8)*

Comparator

Gilead fitted both standard parametric and mixture cure models to the comparator arm. In its base case, Gilead did not consider mixture cure models and selected the Gompertz single parametric curve (Figure 12). The AIC and BIC values are shown in

Table 7.

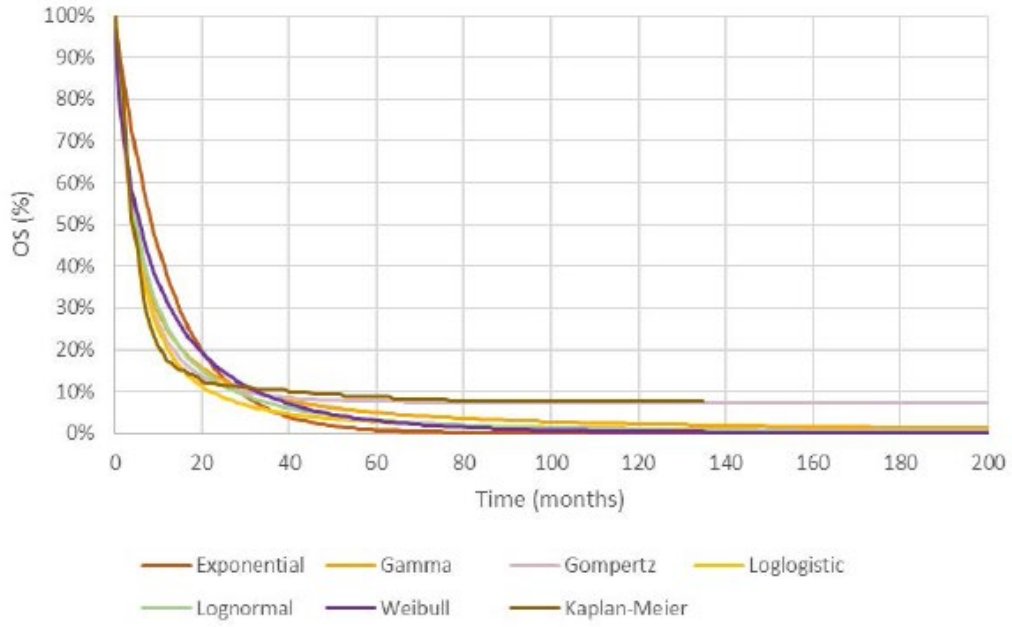

Figure 12: OS for salvage chemotherapy in Gilead's mITT analysis based on alternative standard parametric models

Table 7: AIC and BIC for alternative standard parametric models for OS for salvage chemotherapy in Gilead's mITT analysis

	N	AIC	BIC
Gompertz	527	2090.48	2098.32
Loglogistic	527	2094.19	2102.03
Gamma	527	2106.31	2118.07
Lognormal	527	2124.99	2132.83
Weibull	527	2251.18	2259.02
Exponential	527	2362.23	2366.15

In the health economic model, Gilead also incorporated options for selecting alternative mixture cure models for OS for the comparator arm. The cure models presented below are based on the updated PS-adjusted population as described in section 2.1.2.

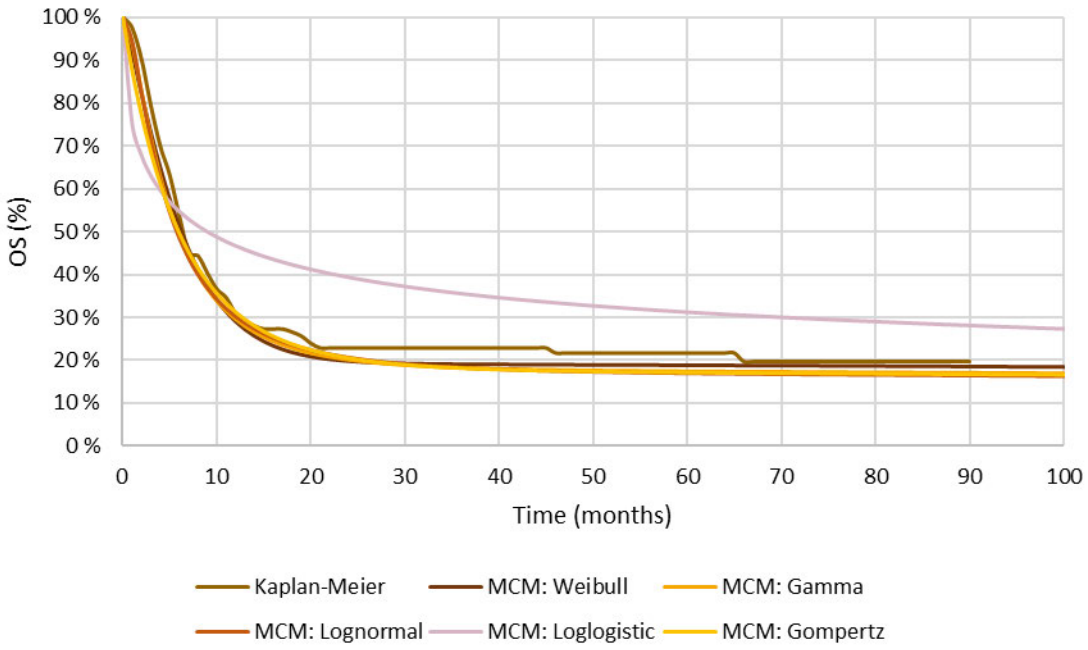

Figure 13: Alternative mixture cure models for OS for salvage chemotherapy based on the updated PS-adjusted mITT analysis

Table 8: AIC and BIC for alternative mixture cure models for OS for salvage chemotherapy in the updated PS-adjusted mITT analysis

	N	AIC	BIC	Cure fraction
weibull	527	259,21	268,63	19,3 %
gamma	527	245,58	258,15	17,7 %
lognormal	527	244,64	254,06	16,9 %
loglogistic	527	239,93	249,35	16,4 %
gompertz	527	282,90	292,33	17,3 %

Submitted health economic analyses - projection of PFS

Axi-cel

PFS for axi-cel in the health economic model was based on an extrapolation of patient-level data from ZUMA-1 using standard parametric functions (Figure 15). The AIC and BIC values are shown in

Table 9. Gilead selected the Gompertz function in its base case analysis.

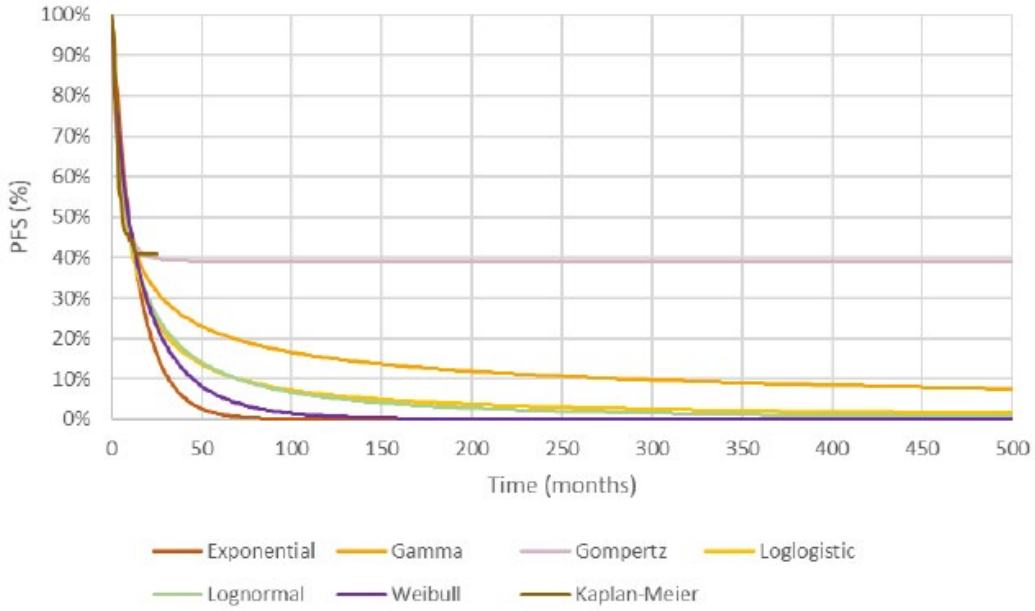

Figure 14: Extrapolation of PFS for axi-cel in Gilead's mITT analysis based on standard parametric curves

Table 9: AIC and BIC for alternative standard parametric models for PFS for axi-cel in Gilead's mITT analysis

	N	AIC	BIC
Gompertz	108	425.87	431.23
Gamma	108	427.74	435.79
Lognormal	108	432.17	437.54
Loglogistic	108	435.77	441.13
Weibull	108	445.78	451.15
Exponential	108	450.48	453.16

Gilead claimed they did not have PFS data for the ITT population in ZUMA-1. Gilead therefore submitted a scenario where the same parametric functions fitted to the mITT data were used, with the additional assumptions that patients not surviving the trial period were assumed to have progressed in month 1, and patients who survived the whole trial period were assumed to be in PFS for the whole trial period (Figure 15).

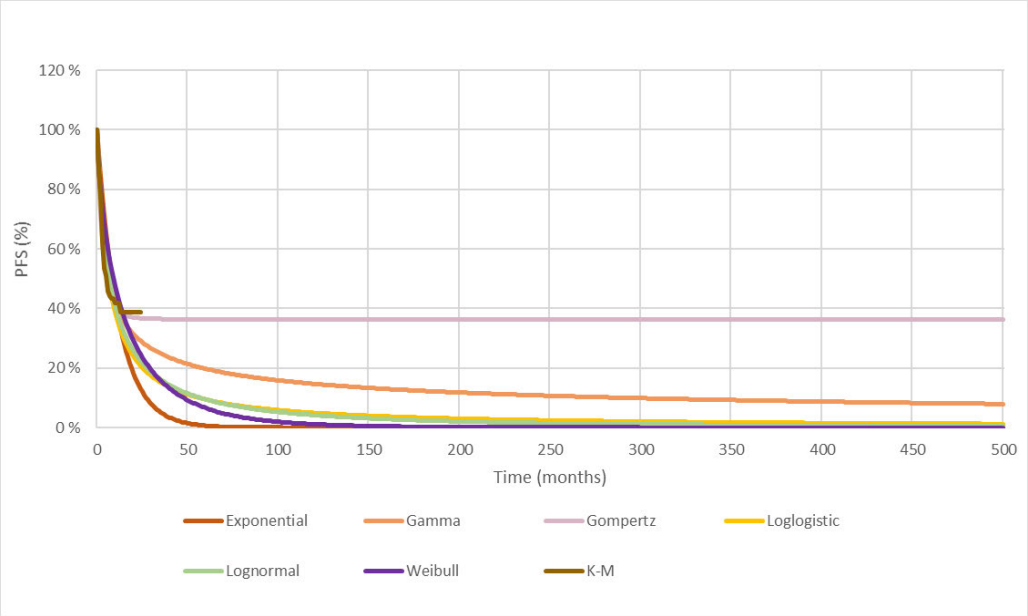

Figure 15: Extrapolation of PFS for axi-cel based on single parametric functions fitted to the mITT population with incorporation of Gilead's additional assumptions for the ITT population

Comparator

As data on progression status was not collected in SCHOLAR-1, Gilead applied a time-dependent ratio to the OS curve for the comparator derived directly from the modelled OS and PFS for axi-cel. Both PFS and OS as modelled by Gilead for salvage chemotherapy are shown in Figure 16.

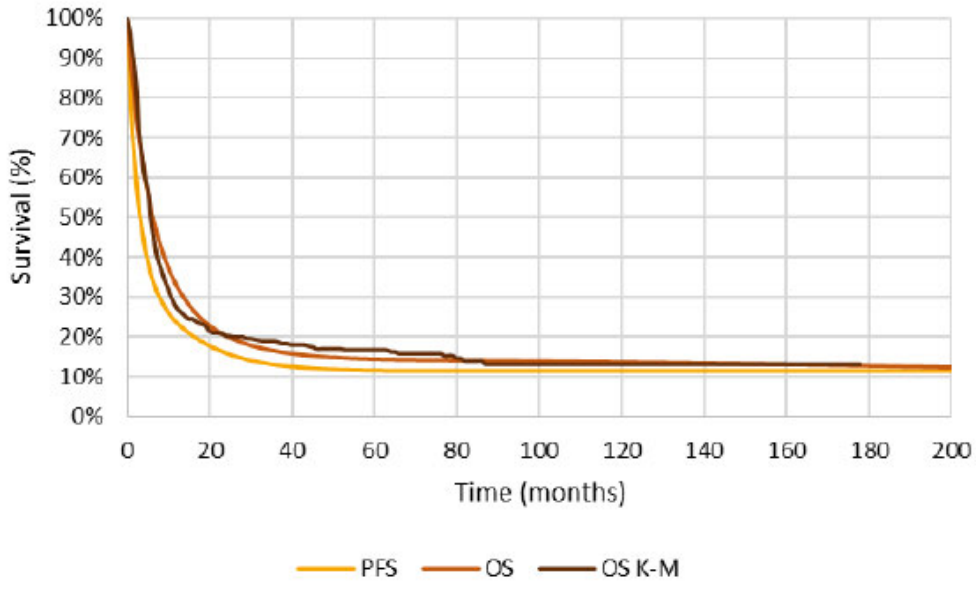

Figure 16: PFS and OS for salvage chemotherapy in Gilead's mITT analysis based on the ratio between modelled PFS and OS for axi-cel.

NoMA's assessment of OS

Axi-cel

NoMA agrees with Gilead that the use of standard parametric functions for axi-cel over the entire model time horizon results in implausible estimates. However, NoMA considers the mixture cure model approach by Gilead to be overly optimistic. In the cure model methodology, a cure is said to occur when the mortality in the patient population returns to the same level as the general population. This definition refers to a statistical cure from a population perspective – it does not imply that all individual patients are medically cured. For some cancer diseases, the relative survival curve appears to plateau after a certain number of years (10). This plateau indicates that the mortality in the patient population has become similar to the general population, i.e. the patient population can be considered "cured".

The Weibull mixture cure model approach by Gilead implies that by month 26, 50% of the patients that were infused with axi-cel are assumed to be cured from the disease and return to the same mortality as the general population. The OS curves and PFS curves do not converge until after 21 years post-treatment, which implies that Gilead assumes a significant number of patients that progressed after axi-cell will be "cured" and have a long-term prognosis. Furthermore, Gilead assumes that patients that have not progressed by the end of the follow-up period in ZUMA-1, will not experience any late progressions nor death (i.e. 100% survival) during a period of close to 20 years. NoMA notes that in order to robustly estimate the "cure fraction", i.e. the proportion of patients that are considered cured with mortality similar to the general population, the presence of a survival plateau based on long-term follow up and large sample sizes is generally required, and censoring from loss to follow-up during the period when events can occur must not be excessive (10, 11). NoMA noted that the data from ZUMA-1 is too immature to robustly estimate the cure fraction, as the required long-term survival plateau could not be observed. The widely varying estimates of the cure fractions, ranging from 0.01 to 0.53, also indicate that the data is too immature for a robust estimation.

PFS flattens out at 41% after 13 months, while the estimated cure fraction for OS was 50%. This inconsistency means that either a significant number of patients will become cured after having progressed on axi-cel, or that the OS data from ZUMA-1 is not sufficiently mature for robustly estimating a cure fraction. A cure after progression is unlikely given that there are very few effective treatment options left after progression on axi-cel, and progressed patients are therefore unlikely to become long-term survivors. NoMA considers it more plausible that the follow-up in ZUMA-1 is not long enough to capture the mortality in patients that experienced a late progression. Furthermore, application of the mortality of the general population to the "cured" fraction is implausible given evidence from studies with a much longer follow-up, which suggest the presence of excess mortality in patients with DLBCL up until 10 years after therapy initiation (2, 12-14). This is in accordance with the statement of Norwegian clinical experts who claim that the mortality rate of patients with DLBCL do not return to the general population level despite being in CR for longer than 2 years. NoMA therefore considers that the mixture cure model approach by Gilead is likely to result in an overly optimistic projection of the survival benefit of axi-cel. Hence, patients in ZUMA-1 would need to be followed-up for a longer time period in order to reduce the large degree of uncertainty concerning the cure fraction and long-term outcomes of axi-cel.

The likely overestimation of the survival benefit of axi-cel is further supported by additional information submitted by Gilead during the NICE single technology assessment for Yescarta, where the evidence review group (ERG) was presented with an alternative approach for modelling overall survival based on a state transition modelling approach (15). In a state transition modelling approach, the transitions from progression free to progression, progression free to death and post-progression to death are explicitly estimated. The difference with the partitioned survival analysis approach in Gilead's base case, where OS and PFS are modelled independently, is therefore that a state transition approach utilizes data on both pre- and post-progression mortality (instead of pooling this data). The KM data and the parametric curves fitted by Gilead to estimate these transitions are presented in the figures below.

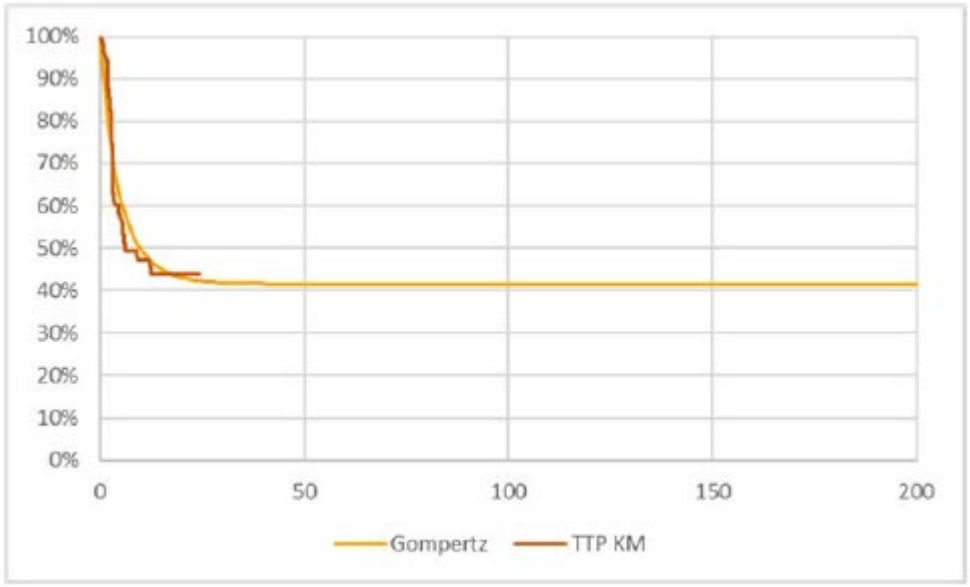

Figure 17: State transition approach– Progression free to progressed state (taken from NICE committee papers)

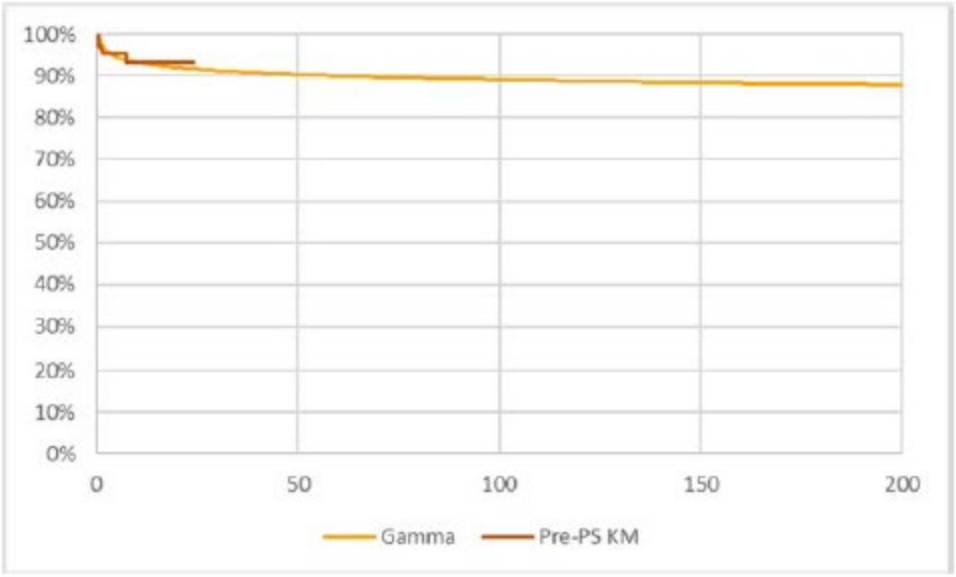

Figure 18: State transition approach– Progression free to death (taken from NICE committee papers)

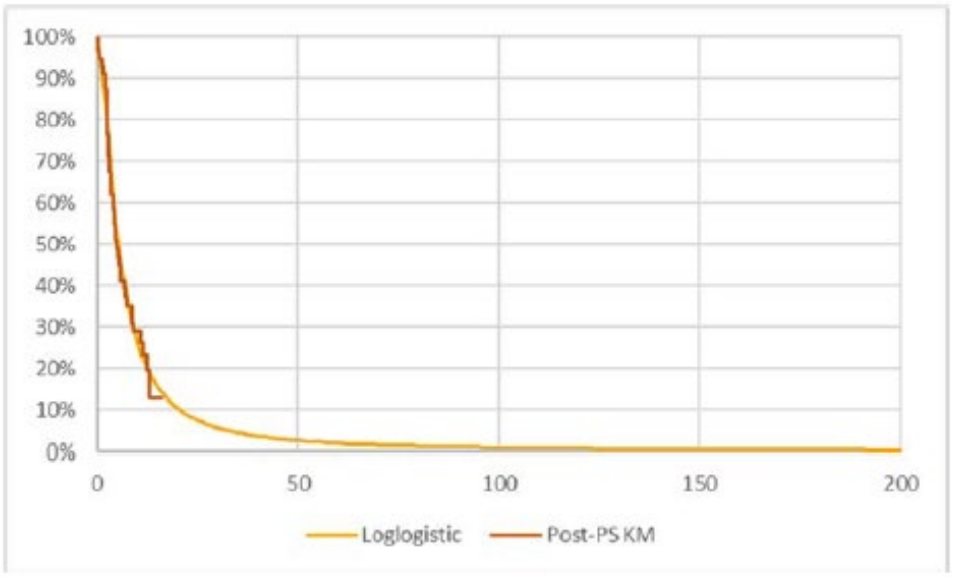

Figure 19: State transition approach – Post-progression to death (taken from NICE committee papers)

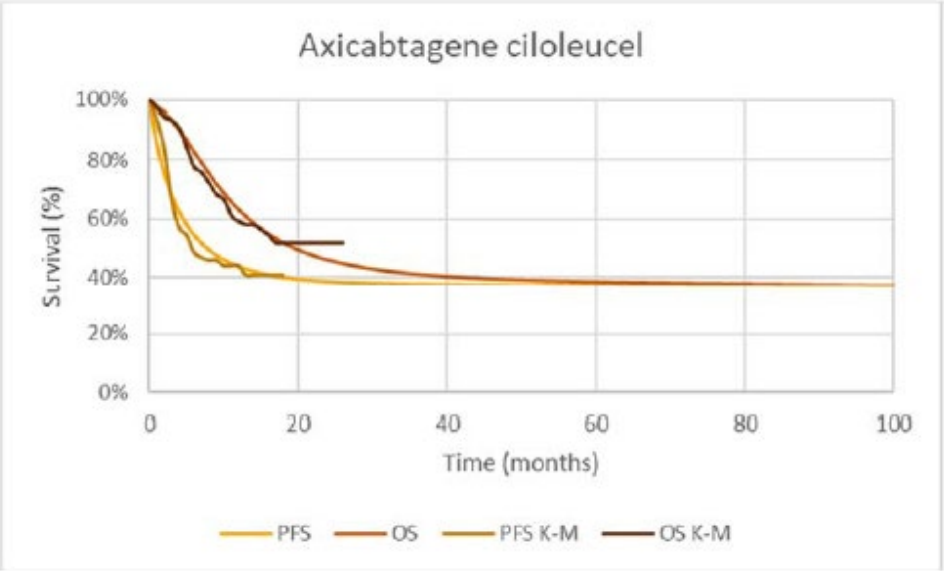

Figure 20: State transition approach by Gilead – overall survival and progression free survival (taken from NICE committee papers)

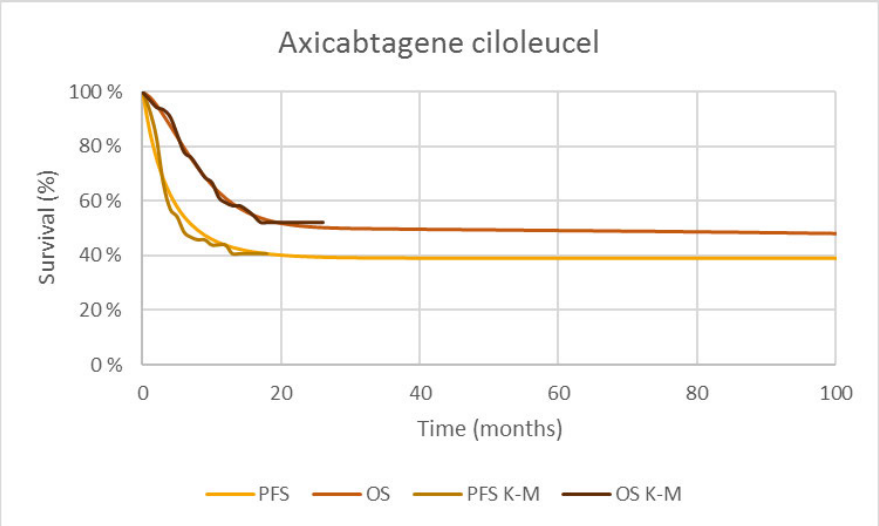

Figure 21: Base case by Gilead - OS for axi-cel in the mITT analysis based on a Weibull mixture cure model, progression free survival based on a Gompertz function

The KM data for post-progression mortality in Figure 19 demonstrates a high mortality rate in progressed patients. Median survival after progression was less than 6 months in ZUMA-1, and by the end of the approximately 16 month follow-up, more than 85% of the progressed patients had died. This finding does not support the MCM approach in Gilead's base case (Figure 21) where a significant proportion of progressed patients are assumed to be long-term survivors (since the OS and PFS curves do not converge until year 21 post-treatment). NoMA considers it more plausible, based on the available evidence on post-

progression mortality in ZUMA-1 and clinical plausibility given the absence of curative therapy options after progression on axi-cel, that the follow-up in ZUMA-1 was not long enough to capture the mortality in patients that had a late progression. NoMA considers the assumption that the OS and PFS curve converge sooner (Figure 20), to be based on better utilization of the trial data and clinically more plausible than Gilead's base case. This assumption has been validated and found clinically plausible by clinical experts. NoMA was however not presented with this additional state transition analysis, and was therefore not able to further validate the statistical approach.

Flexible spline models

Since the use of standard parametric functions did not result in plausible extrapolations of the axi-cel data when used for the full model time horizon, NoMA requested a more flexible modelling approach based on spline functions (16), which was later submitted by Gilead. Gilead fitted cubic spline models with 1, 2 and 3 knots using the standard approach described in Royston & Parmar (2002) (17). The statistical and visual fit of the alternative spline models and the two standard parametric functions with the lowest AIC are compared in the table and figures below.

Table 10: AIC and BIC for alternative standard parametric and flexible spline model for OS for axi-cel in the mITT analysis

	AIC	BIC
Exponential	251,18	253,86
Loglogistic	251,00	256,37
Spline 1 knot	253,70	259,31
Spline 2 knots	251,63	259,12
Spline 3 knots	253,33	262,69

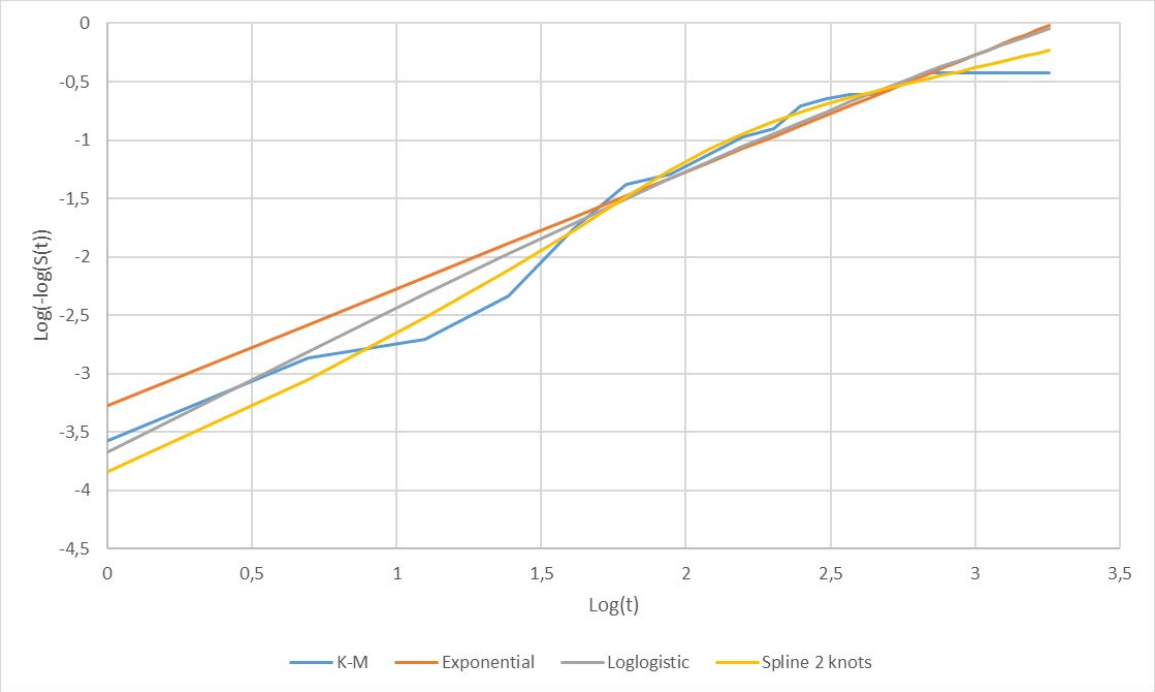

Figure 22: Log cumulative hazard plot for OS for axi-cel in the mITT analysis

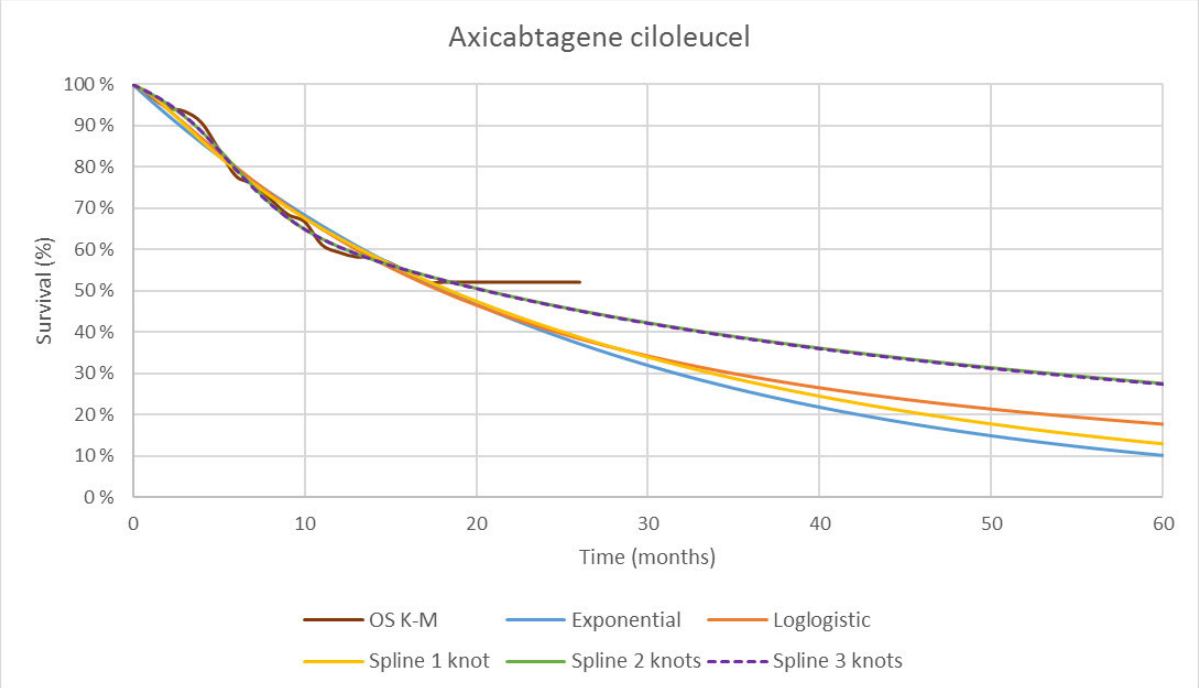

Figure 23: OS for axi-cel in the mITT analysis based on flexible spline and standard parametric models

The AIC for the spline model with 2 knots was the lowest among spline models and similar to the best fitting standard parametric functions (loglogistic and exponential). Inspection of the log cumulative hazard plot indicates that an exponential function would not be appropriate, as the log cumulative hazard function for axi-cel is not a straight line. There is also little clinical rationale for a constant mortality hazard function for axi-cel. The change in hazard observed at later points in time may be somewhat better captured by the spline model with 2 knots than the loglogistic function.

Although the spline model with 2 knots has a similar statistical fit but suggests a somewhat better visual fit to the ZUMA-1 data than the standard parametric functions, NoMA does not consider the application of any single parametric or flexible spline function for the full model time horizon to sufficiently reflect a curative potential of axi-cel.

NoMA therefore made the following modifications for axi-cel:

- OS for axi-cel is extrapolated using the spline function with 2 knots until the OS and PFS curves converge
- At the time point when the OS and PFS curves converge (36 months), no patients that have progressed after treatment with axi-cell are alive. From then on, all patients that have remained progression free follow the same mortality rate as modelled for long-term survivors in the comparator arm, to reflect the excess mortality that has been observed in studies of DLBCL patients with longer follow up (2, 12-14).

A comparison of the key assumptions in Gilead's base case and NoMA's alternative base case for axi-cel OS is presented below.

Table 11: Comparison of key assumptions in Gilead's base case and NoMA's base case for axi-cell OS

	Gilead's base case	**NoMA's base case**
OS survival function	Weibull mixture cure model	- Spline model with 2 knots constrained by the PFS curve - Mortality rate as modelled for the SCHOLAR-1 comparator arm from point of convergence
Cure assumption	Both progression-free and progressed patients are "cured" at year 2 post-treatment	Patients that remain progression-free are considered "cured"
Long-term mortality	Equal to the general population	Long-term survivors experience excess mortality as observed in DLBCL studies with longer follow-up
Convergence of OS and PFS curves	Convergence at year 21 post-treatment	Convergence at month 36 post-treatment

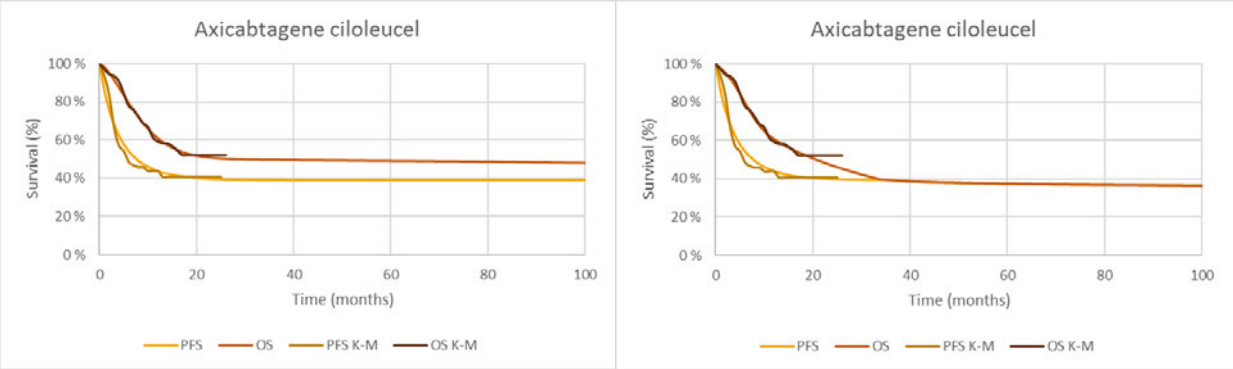

Figure 24: Gilead's Weibull mixture cure model base case (left) and NoMA's spline 2 knots model bas ecase (right) for the mITT analysis of axi-cell OS. PFS is modelled using a Gompertz function in both analyses.

NoMA also explored an alternative assumption for modelling long-term survival for axi-cel, based on the application of standardized mortality ratios (SMRs) obtained from a Norwegian study of DLBCL patients by Smeland et al. 2016 (14). The SMRs that have been obtained from the study by Smeland are 4.3 and 1.7 for respectively month 36 – 60 and month 60 – 120 post-treatment. From month 120 post-treatment, mortality was assumed to be equal to the general population. In Figure 25 below, conditional survival from month 36 (i.e. the point where the OS and PFS curves for axi-cel converge) are compared for the approaches based on data from SCHOLAR-1 and from Smeland et al. 2016. The difference in predicted survival between the two approaches is minimal.

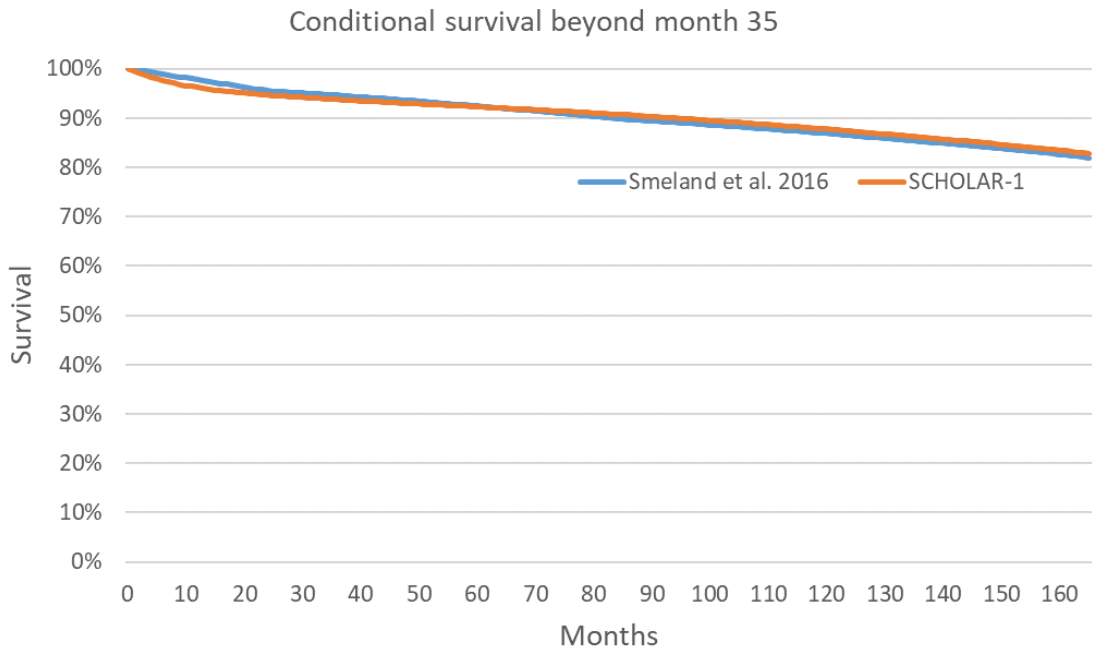

Figure 25: Comparison of conditional survival beyond month 35 based on either Smeland et al. 2016 or SCHOLAR-1

Comparator

NoMA does not find Gilead's choice to only consider standard parametric models for the comparator arm in its base case to be sufficiently justified. This approach is also inconsistent with the cure model approach undertaken for axi-cel. Since SCHOLAR-1 has a longer follow-up and greater sample size than ZUMA-1, the survival data would likely be more appropriate for fitting a cure model and robustly estimating a cure fraction than the data from ZUMA-1. Furthermore, if some patients in the axi-cel arm are assumed to have a long-term survival prognosis, it is clinically plausible that this also applies to the comparator arm (although with a smaller proportion of "cured" patients). The cure fractions for the submitted cure models for the comparator arm ranged from 17% to 19% for the updated PS-adjusted population as described in section 2.1.2. None of the cure models however seemed to visually fit the observed survival data particularly well.

Consistent with the approach taken for axi-cel, NoMA explored the use of cubic spline models fitted to the updated PS-adjusted OS data from SCHOLAR-1. In the figure below, the best fitting (according to AIC and visual fit) standard parametric and MCM models are compared with the spline functions for the updated PS-adjusted mITT populations of SCHOLAR-1 as described in section 2.1.2. Although the AIC for the loglogistic MCM was lowest out of the available cure models, it resulted in an implausible extrapolation and very bad fit to the observed data (Figure 13). The lognormal MCM had the second lowest AIC out of the cure models, but this model has been described to be forced to have a long tail for cancers with a high excess mortality hazard rate in the first weeks, thus underestimating the cure fraction (10). NoMA therefore presented the gamma MCM in the comparisons below based on visual and statistical fit to the data, together with the two best fitting standard parametric functions according to AIC (gamma and Gompertz).

Table 12: AIC and BIC for alternative standard parametric and flexible spline model for OS for salvage chemotherapy in the updated PS-adjusted mITT analysis

	AIC	BIC
Gamma	665,58	675,17
Gompertz	762,08	768,48
Spline 1 knot	620,11	629,70
Spline 2 knots	621,76	634,55
Spline 3 knots	622,99	638,98

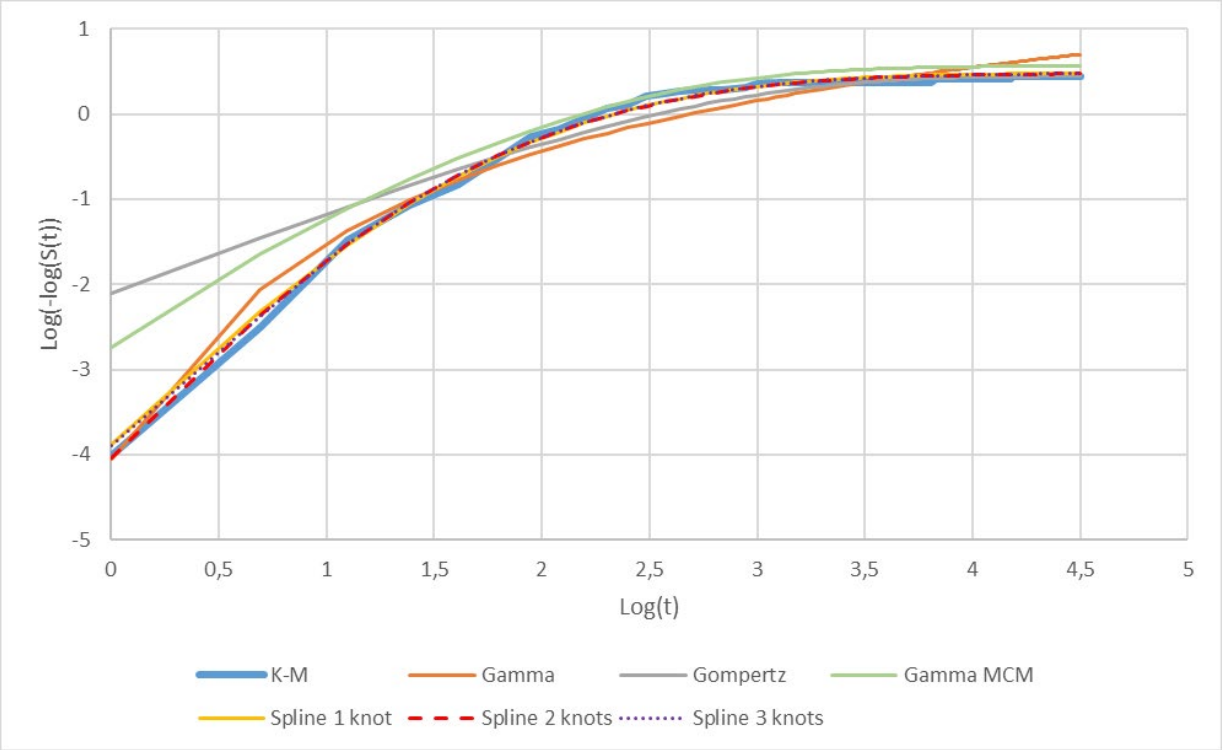

Figure 26: Log cumulative hazard plot for OS for salvage chemotherapy in the updated PS-adjusted mITT analysis

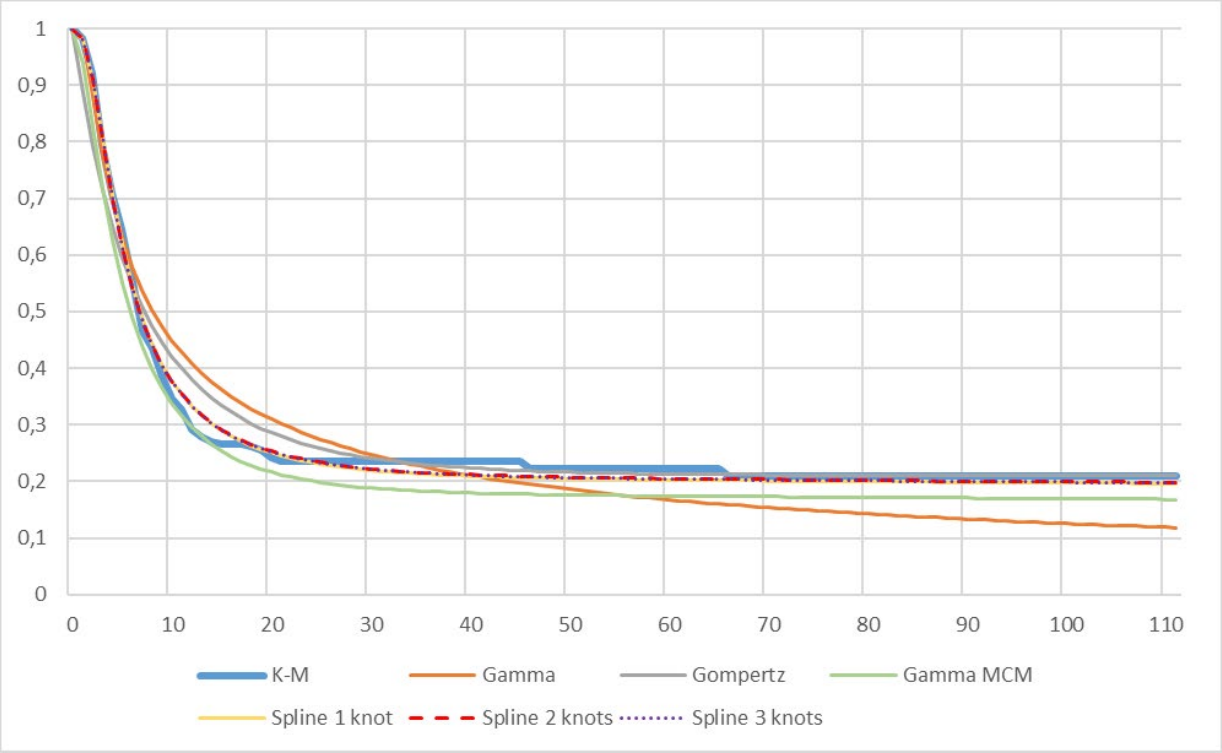

Figure 27: OS for salvage chemotherapy in the updated PS-adjusted mITT analysis based on alternative survival models.

The spline models resulted in both a better visual fit and statistical fit to the observed data according to AIC compared with the standard parametric models. NoMA did not have the information to make a direct comparison with the AIC of the mixture cure models, but visual inspection suggests the spline models provide a better fit to the observed data, as the gamma MCM substantially underestimates observed survival from month 15 and beyond. The AIC was lowest for the 1 knot spline model, but there was little difference in predicted survival between the alternative 2- and 3 knot spline functions.

In its base case, NoMA selected the spline function with 1 knot to model survival for salvage chemotherapy, constrained by background mortality based on Norwegian life tables. Gilead's base case and NoMA's base case for the mITT analysis are presented in the figure below.

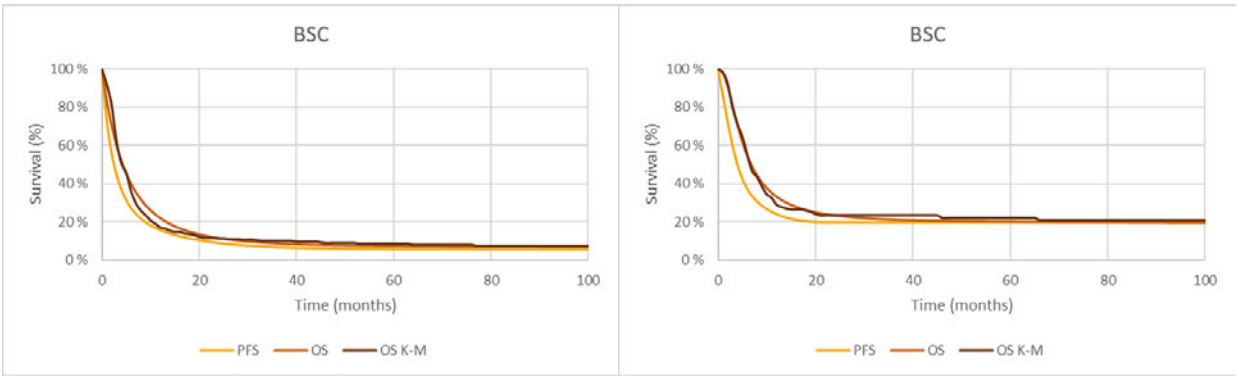

Figure 28: Gilead's Gompertz single parametric base case (left) and NoMA's spline 1 knot model base case (updated PS-adjusted analysis, right) for the mITT analysis of salvage chemotherapy OS. PFS is modelled using the ratio between OS and PFS as modelled for axi-cel in both analyses.

Exploration of subsequent SCT on overall survival for comparator

Due to potential selection bias in the ZUMA-1 trial (see section 3.2), the SCHOLAR-1 population has been adjusted to be comparable with the ZUMA-1 population via propensity score-weighting. This resulted in a higher proportion of patients receiving subsequent SCT than experienced in the Norwegian clinical practice. In the base case, NoMA retained all the patients in SCHOLAR-1 who received a post chemotherapy SCT as those patients were likely respondents to chemotherapy and their removal would underestimate the survival in the comparator arm. NoMA has also explored the effect of subsequent SCT in a scenario analysis (section 4.2.6). A survival curve of SCHOLAR-1 where patients who received a subsequent SCT are removed is presented in Figure 29.

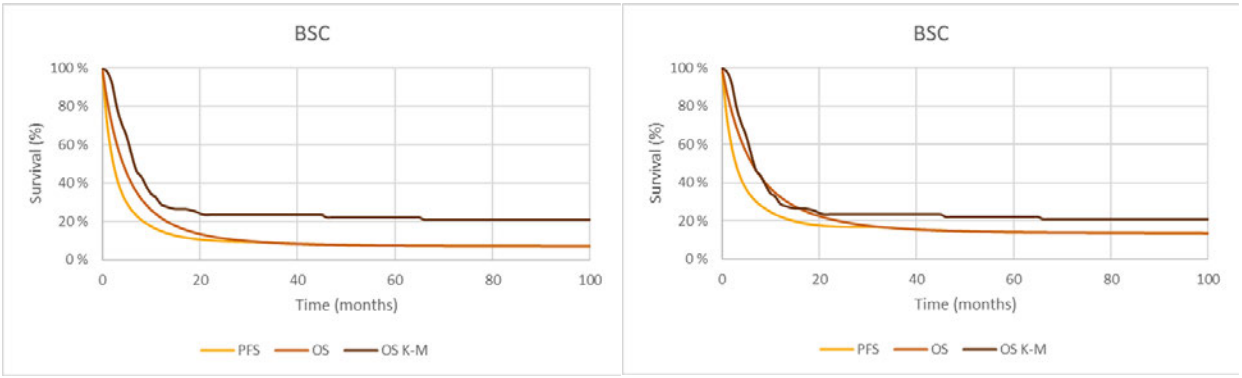

Figure 29 NoMA's spline 1 knot model base case with exclusion of subsequent SCT (left) and unadjusted SCHOLAR-1 population (right) where 29% received subsequent SCT.

NoMA's assessment of PFS

Axi-cel

The Gompertz function selected by Gilead to model PFS for axi-cel flattens out at 39% after approximately 28 months. Based on visual inspection, none of the standard parametric curves seems to fit the observed PFS data very well. Although the Gompertz function has the best statistical fit according to AIC, the flattening of the curve implies that no more patients will progress or die after about 2 years. NoMA considers this to be an optimistic scenario, as the risk of late relapses and death due to other causes is excluded. However, the Gompertz function is the only standard parametric function that captures the emerging plateau in PFS, and the impact of the assumption that no more patients will progress or die after about 2 years is limited in NoMA's base case where OS and PFS converge after 36 months.

Although the mixture cure model methodology has primarily been used in registry-based analysis of cancer survival, NoMA notes that this approach could also have been explored by Gilead for PFS. If a proportion of DLBCL patients can be "cured" in terms of OS, it is likely that a similar proportion of patients can be "cured" in terms of PFS. This is because it is unlikely that a significant number of patients that progress after axi-cel, and are therefore not "cured" in terms of PFS, will be "cured" in terms of OS. NoMA notes that PFS in ZUMA-1 flattened out at 41% after 13 months, while the Weibull mixture cure model for OS predicted a cure fraction of 50%. NoMA considers it more plausible that the follow-up in ZUMA-1 is not long enough to capture mortality in patients that experienced a late progression, than the assumption by Gilead that a significant proportion of progressed patients will be "cured" at month 26 post-treatment with survival returning to general population levels.

The lack of PFS data for the ITT analysis increases uncertainty surrounding the extrapolation. NoMA notes that the assumption by Gilead, that patients that did not survive the trial period are assumed to have progressed in month 1, may be conservative, as progression may have occurred at a later time point. Gilead's assumption that patients who survived the whole trial period were assumed to be in PFS for the whole trial period is however optimistic, as the possibility of surviving the trial period and having progressed at some time point during the trial period is excluded.

Similar to Gilead's base case, NoMA selected the Gompertz function in its base case to model PFS until the time point when OS and PFS converge. From this point both OS and PFS follow the same mortality rate as modelled for long-term survivors in the comparator arm. The resulting PFS curve for the adjusted mITT analysis is presented in Figure 24.

Comparator

The application of a time-dependent ratio to the OS curve for the comparator arm, derived from the ratio between the modelled OS and PFS for axi-cel, results in significant uncertainty in the modelled PFS for salvage chemotherapy. NoMA noted however that this assumption has limited impact on the ICER, and is not a main driver of the results opposed to the assumptions concerning the modelling of OS. In its base case, NoMA therefore accepts the approach by Gilead. The resulting PFS curve for the updated PS-adjusted mITT analysis for salvage chemotherapy is presented in Figure 28.

3.4.3 Safety

Submitted clinical axi-cel studies

The safety profile of axi-cel is not only affected by the infusion alone, but also by the cytotoxic lymphodepleting chemotherapy regimen patients received prior to infusion, and the medications needed to treat various adverse events (AEs) post-infusion such as antibiotics, gammaglobulines, antipyretics and anti-IL-6 based therapy (e.g. tocilizumab). The rates of AEs described below are based on the latest DCO of ZUMA-1 (N=108; 7 patients in Phase 1 and 101 patients in Phase 2) of 11-Aug-2018 (median follow-up: 27.1 months). All observed AEs were monitored continuously from enrolment until month 3 after axi-cel infusion. After 3 months, only AEs suspected to be treatment-related and serious AEs (SAEs) in the categories of neurological events, haematological events, infections, autoimmune disorders, and secondary malignancies were reported until 24 months or disease progression.

Axi-cel is observed to be associated with frequent AEs. All patients in ZUMA-1 who received axi-cel had an adverse event after treatment. AEs over grade 3 happened in 98% of the patients. Further, 54% (All grades; Grade ≥3: 47%) experienced SAEs post-infusion. Four patients died due to an AE, 1 patient in the phase 1, and 3 patients in the phase 2 of ZUMA-1. Two of the deaths that occurred in the phase 2 were considered related to axi-cel. In one case, the initiating event was a grade 4 CRS with cardiac arrest, the second case was a patient who developed haemophagocytic lymphohistiocytosis, a rare disorder following CRS.

The most frequently reported, serious and life-threatening AE related to axi-cel is CRS, which was seen in 93% (All grades; Grade ≥3: 11%) of the infused patients. CRS is a direct effect of axi-cel expansion, activation and tumour cell killing. In ZUMA-1, CRS events were graded on the syndrome level per the modified criteria of Lee and colleagues (18). CRS occurred within 1 to 12 days with a mean time to onset of 2.8 days, and lasted for a mean time of 8.6 days (range: 2 to 58 days) in patients where the symptoms were resolved. CRS was reversible in most cases and was managed with supportive care and anti-cytokine therapy as needed in 98% of the patients. The most common signs or symptoms associated with CRS include pyrexia (83%), hypotension (44%), tachycardia (24%), hypoxia (23%), and chills (20%). The most common Grade ≥3 CRS symptoms were pyrexia (12%), hypotension (10%), and hypoxia (8%).

Neurological AEs represent a concern with axi-cel treatment and were observed in 67% (Grade ≥3: 32%) of the infused patients in ZUMA-1. The mean time to onset of neurological events was 5.2 days (range: 1 to 17 days) and the mean time to resolution was 48 days (range: 1 to 451 days) in patients where the symptoms were resolved. The majority of the neurological events resolved completely, but 4% of the patients were not recovered at the time of DCO. The most common signs and symptoms associated with the neurological events were encephalopathy (All grades: 37%; Grade ≥3: 23%), tremor (All grades: 31%; Grade 3: 2%), confusional state (All grades: 27%; Grade 3: 9%), aphasia (All grades: 18%; Grade 3: 7%), somnolence (All grades: 17%; Grade ≥3: 8%), and agitation (All grades: 9%; Grade 3: 5%). Other manifestations included memory impairment, mental status changes, seizures, and delirium. The underlying cause of the neurological AEs is currently unclear and an overlap with CRS seems likely. Patients with a prior history of CNS disorders such as seizures or cerebrovascular ischemia may be at increased risk.

Both occurrence of CRS and severe neurotoxicity elicited the need for intensive care treatment. However, data on the proportion of patients who needed intensive care unit (ICU) level care, at which time post-infusion, and how long they stayed at the ICU are missing in ZUMA-1. In total, treatment with tocilizumab was required for 45% (49/108) of the patients in ZUMA-1, and 27% (29/108) needed subsequent treatment with glucocorticoid. Only one patients (1%) were treated with glucocorticoids alone.

B-cell aplasia is a direct effect of axi-cel and treated patients may therefore experience hypo- or agammaglobulinemia as long as axi-cel persists in the patients. Axi-cel infusion exhibited an initial rapid expansion phase achieving maximal concentration (Cmax) within the first 14 days after the infusion in all evaluable patients and showed a decrease towards background levels by 3 months of the infusion (range: 0 to 15.8 cells/µL). However, cells were measurable in most evaluable (i.e., responding) patients at the last assessment. Hence, the persistence of axi-cel in treated patients with resulting depletion of normal B-cells and development of hypogammaglobulinemi constitute a high risk of the treatment.

As expected, successful treatment with axi-cel resulted in acquired hypogammaglobulinemia due to loss of normal B cells. Hypogammaglobulinaemia secondary to B-cell aplasia was seen in 16% (All grades; Grade ≥3: none) of the infused patients. Since occurrence of hypogammaglobulinemia might render patients more susceptible to infections, patients who develop hypogammaglobulinemi need to be maintained on supplemental treatment with intravenous gamma globulins (IVIG). Immunoglobuline replacement therapy was given to 31% (33/108) of the infused patients post axi-cel infusion, including 44% (17/39) of patients with ongoing responses. Data on the duration of IVIG treatment patients in ZUMA-1 received is missing.

The risk of infections is significantly elevated in patients with DLBCL due to disease- and chemotherapy-induced neutropenia and prior infectious exposures. In addition, development of secondary hypogammaglobulinemia as a result of B-cell aplasia in response to axi-cel therapy may render the patients more susceptible to infections. Infections occurred in 42% (All grades; Grade ≥3: 28%) of the patients who received axi-cel. Twenty-seven patients (25%) had Grade 3 events, and 3 patients (3%) had Grade 4 events.

Prolonged cytopenias are an emerging class-effect of CAR-T cells (19), and constitute one of the major burdens experienced by patients who received the treatment. The aetiology of the cytopenias could be the CAR-T cell therapy itself, the underlying DLBCL, preceding therapies and the lymphodepleting chemotherapy patients received prior to infusion. Patients may exhibit cytopenias for several weeks following lymphodepleting chemotherapy and axi-cel infusion. Hence, the frequency of grade ≥3 cytopenias at month 3 or later were assessed in ZUMA-1. Grade ≥3 neutropenia (including febrile neutropenia), thrombocytopenia, and anaemia occurred in 80%, 40%, and 45% of the patients, respectively. Prolonged (still present 30 days after treatment) Grade ≥3 neutropenia, thrombocytopenia, and anaemia were observed in 26%, 24%, and 10% of the patients, respectively. Any grade ≥3 cytopenia present on months 3 or later were observed in 17% of the patients, including 11% with neutropenia, 7% with thrombocytopenia, and 3% with anaemia. Management of hematopoietic cytopenias was blood product support, growth factors and/or antibiotics as indicated.

Submitted health economic analyses

AE costs and disutilities for axi-cel are considered in the health economic model. No AEs were modelled for the comparator arm. AE costs are described and assessed in section 4.1.3. In summary, the costs related with CRS Grade ≥3 were included in the model. The CRS rate input for axi-cel was obtained from the phase 2 of ZUMA-1. AEs disutilities are described and assessed in section 3.4.4. The AE rates inputs for axi-cel were obtained from data of the phase 2 of ZUMA-1. Specifically, Grade ≥3 AEs associated with axi-cel and pre-treatment with lymphodepleting chemotherapy occurring in ≥10% of the patients in ZUMA-1 were modelled.

NoMA´s assessment

Treatment with axi-cel is associated with considerable known risks to the patients, although the safety profile is considered manageable and acceptable with regards to the poor prognosis of the patients intended for the treatment. All patients in ZUMA-1 who received axi-cel experienced an AE after treatment, and 98% of the patients had a grade ≥3 AEs. Important AEs associated with axi-cel are CRS, neurotoxicity, and hypogammaglobulinaemia secondary to B-cell aplasia, which might render patients more susceptible to infections. Both CRS and B-cell aplasia could be associated with substantial resource use and should be reflected in the cost-effectiveness modelling (see section 4.1.3).

Long-term safety data is limited due to the short follow-up time and limited number of patients included in the clinical study. There may therefore be risks associated with axi-cel that have not yet been identified based on the current clinical safety data, but might be revealed with longer follow-up time. Some important safety concerns in the long-term are the risk of delayed neurological reactions and an expected acquisition of opportunistic infections due to B-cell aplasia. On the other hand, current treatment options with salvage chemotherapy are intensive therapies associated with significant toxicities (i.e. hair loss, mucositis, diarrhoea, and nausea), high treatment related mortality and a poor quality of life. These AEs are not included in the comparator arm of the health economic analyses.

3.4.4 Health related quality of life

Submitted clinical studies

ZUMA-1 study

Health-related quality of life (HRQoL) data were not collected in ZUMA-1 phase 2. In a safety management cohort of ZUMA-1 (Cohort 3) Gilead collected EQ-5D data. Please refer to section 2.1.1 for an overview of the ZUMA-1 cohorts.

Published HRQoL studies

Gilead has not conducted a systematic literature search to identify relevant documentation for health state utility values. Gilead refer to the utility values and adverse event disutilities used by NICE in the STA of pixantrone monotherapy for treating multiply relapsed or refractory aggressive non-Hodgkin´s B-cell lymphoma, in 2014. In this STA a systematic literature review was conducted to identify utility data for patients with aggressive non-Hodgkin's lymphoma (DLBCL is a subgroup of non-Hodgkin disease) or in a similar disease area.

Submitted health economic analyses

Health state utilities

In their base case, Gilead used health state utilities based on EQ-5D data collected in Cohort 3 of ZUMA-1. In total, 34 patients were included in Cohort 3, resulting in 87 observations. Of 54 observations collected after screening, 49 were in PFS and 5 in PD. In scenario analysis Gilead used the health state utility values from the NICE STA of pixantrone.

Table 13 Health state utilities used in the model

Health state	Utility value	
	Base case (ZUMA-1, Cohort 3)	Scenario analysis (NICE pixantrone STA)
Progression-free disease	0.72	0.76
Progressed disease	0.65	0.68

Disutility of AEs

AEs disutilities are applied to grade ≥3 AEs associated with axi-cel and lymphodepleting chemotherapy occurring in ≥10% of patients in the phase 2 of ZUMA-1 (DCO 27 Jan 2017). No AEs were modelled for the comparator arm.

Gilead used the AE utility decrements reported in the pixantrone STA from NICE. For disutilities that could not be identified, a disutility equal to the maximum of the identified non-CRS adverse event disutilities was assumed. This approach was used in the pixantrone STA. For grade ≥3 CRS Gilead assumed a utility of zero in line with the NICE mock appraisal(20).

All AE disutilities were applied as a one-off decrement to the first cycle of the model.

Table 14 AEs disutilities for the intervention arm (axi-cel and lymphodepleting chemotherapy)

Adverse event	Proportion	Utility decrement	Duration (days)
Anaemia	41 %	0,12	14
Cytokine release syndrome	13 %	0,83	8
Encephalopathy	21 %	0,15	9
Febrile neutropenia	46 %	0,15	6
Hypophosphataemia	11 %	0,15	16
Hypotension	11 %	0,15	5
Leukopenia	15 %	0,15	21
Lymphocyte count decreased	19 %	0,15	64
Neutropenia	48 %	0,09	47
Neutrophil count decreased	28 %	0,15	17
Platelet count decreased	13 %	0,11	50
Pyrexia	12 %	0,11	2
Thrombocytopenia	23 %	0,11	63
White blood cell count decreased	27 %	0,15	40

Age adjustment of utility values

Gilead assume based on input from clinical expert that patients who remain in the PFS state for at least 2 years may experience long term side effects. They have therefore assumed that the patients will revert to a 5% lower HRQoL than the age and gender matched general population. For utility values of the general population, Gilead has used data from Burstrøm et al (21).

NoMA´s assessment

Health state utilities

Gilead used health state utilities derived from EQ-5D-5L data collected in Cohort 3 of ZUMA-1 in the base case analysis. The use of EQ-5D with UK tariffs is recommended in the NoMA guidelines (22), and data from 5L should be converted to 3L using the method described by Hout et al. However, it is not clear from the submitted documentation how Gilead used the EQ-5D-5L data to estimate the health state utilities.

The Cohort 3 of ZUMA-1 is the only source of EQ-5D data in the relevant population. However, this is not the same population as the Phase 2 ZUMA-1 population, the source of input-data for efficacy and safety. The collection of patient reported outcomes in the ZUMA-1 study raises some issues. Patient reported outcomes may be biased in an uncontrolled, open label trial design. Furthermore, utility scores were only available for 34 patients. The PD health state was informed by very few observations (5 observations), and only 49 observations informed the PFS health state. The clinical study did not address the effect of

axicabtagene ciloleucel on quality of life. Hence, the estimated impact axi-cel had on the quality of life in patients who received the treatment is highly uncertain.

The QALY-weight of the PFS health state in ZUMA-1 (0.72) is lower than the QALY-weight representing the general population at the same age in Sweden (0.80).(21, 23). The latest EQ-5D assessment in ZUMA-1 Cohort 3 was scheduled at Month 6 according to the study protocol. The utility of long term survivors of CAR-T cell therapy in patients with r/r DLBCL is unknown. Gilead has reduced utility score by 5% to the general population, suggested by a clinical expert due to the possibility of patients experiencing side effects.

In the NICE pixantrone STA the utility data were identified from published sources for similar patient populations, and for disease areas with similar expected survival, disease progression, nature of the disease and quality of life. These were patients with DLBCL, chronic myelogenous leukaemia (CML), chronic lymphocytic leukaemia (CLL), follicular lymphoma (FL), renal cell carcinoma and melanoma.

NICE considered utility values for patients receiving second- and subsequent lines of treatment for renal cell carcinoma as acceptable (0.76 for the pre-progression health state and 0.68 for the post-progression health state). Quality of life in elderly patients with aggressive DLBCL were considered (pre-progression 0.81, post-progression 0.60) to be potentially inappropriate, partly because the reported utility values were higher than those derived for healthy elderly patients in the UK.

NoMA struggles to validate the representativeness of the utility data from the pixantrone STA derived from a patient population with renal cell carcinoma for the target population of patients with r/r DLBCL.

For consistency reasons, NoMA has chosen to use the utility data provided in the submission of STA for the CAR-T cell therapy tisagenlecleucel (Kymriah) for the treatment of second or later r/r DLBCL(24). The patient population is similar and intended to treat the same patients in Norway. Furthermore, the data collected in the tisagenlecleucel study JULIET is somewhat more robust with collection of data for 105 patients. The utility data are somewhat higher than the input data used by Gilead.

Table 15 QALY-weights used by NoMA

Health state	Utility value	
	Main scenario (JULIET study)	Scenario analysis (NICE pixantrone STA)
Progression-free disease	0.83	0.76
Progressed disease	0.71	0.68

Disutility of AEs

Disutility from AEs associated with lymphodepleting chemotherapy and axi-cel was applied as a one-off 0.03 QALY decrement in the first cycle of the model for axi-cel patients. NoMA does not consider AEs disutility to be an important driver in the model since the impact of axi-cel AEs probably will occur over a very limited time period compared to the model time horizon.

No AEs were modelled for the comparator arm. It seems that AEs only to be present in the comparator arm are accounted in the intervention arm. This seems to be a miscalculation that NoMA has adjusted. In our base case AEs of both comparator and intervention are accounted for according to the ZUMA-1 trial.

Gilead has not applied AE utility decrements for SCTs in the model. It is likely that patients that undergo SCTs will have AEs that results in lower utility for a certain period of time. NoMA has included disutility of 0.3 for 72 days for patients that underwent SCTs in both arms. Similar approach are used in the STA for tisagenlecleucel for the treatment of second or later r/r DLBCL.

Age adjustment of utility values

NoMA has changed the utility values of the general population in line with the description in the NoMA guidelines, Table 1 in Appendix 3 and Table 2 in Appendix 4 (22). The utility data is based on both Sun et al (23) and Burstrøm et al (21), as described in our guidelines. NoMA acknowledge that the patients may experience a somewhat reduced quality of life compared to general population due to long term side effects of all lines of treatments. The 5% reduced quality of life compared to the general population is a pragmatic approach, however, not an evidence based estimate. NoMA has not included a 5% reduction in long term quality of life, to be consistent reasons with the assessment of the submission of STA for the CAR-T cell therapy tisagenlecleucel (Kymriah) for the treatment of second or later r/r DLBCL (24).

4 HEALTH ECONOMIC ANALYSES

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 r/r DLBCL and r/r PMBCL, 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 the calculation of costs, life-years gained, and quality-adjusted-life-years (QALYs) gained.

4.1 MODEL, METHOD AND ASSUMPTIONS

4.1.1 Model description

Gilead used a three-state partitioned survival (PartSA) model to assess the cost-effectiveness of axi-cel compared to salvage chemotherapy. A simplified representation of the model structure is shown in Figure 30. The three states include pre-progression, post-progression and death. At any time point, the proportion of patients under the PFS curve is in the pre-progression health state. The proportion of patients over the OS curve is in the state of death. The remaining patients are in the post-progression health state. Survival curves in the PartSA approach are typically based on independent analyses of OS and PFS endpoints, and a correlation structure between OS and PFS is therefore not explicitly modelled. In this STA a correlation between OS and PFS has been assumed in the salvage therapy arm, as discussed in section 3.4.2.

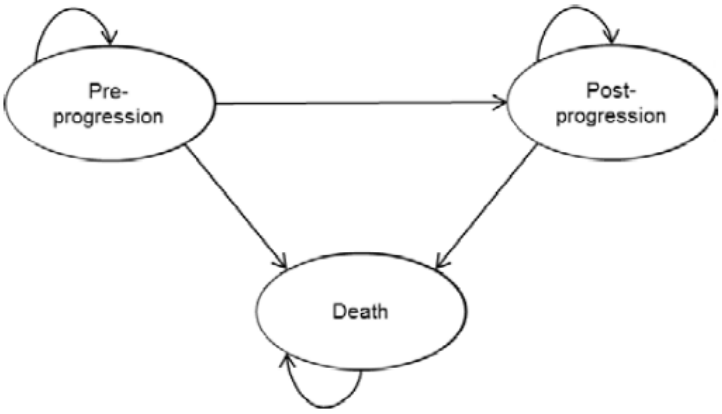

Figure 30 Model structure (source: submission by Gilead)

Patients enter the model in the pre-progression health state at study enrolment in the ITT analysis and at infusion in the mITT analysis. At the end of each month (cycle length in the model), patients can either remain at this health state or move to the post-progression health state or to death. Costs and health effects (utility weights) are calculated separately for each health state. Costs and benefits are summarised per treatment arm for the specified time horizon.

NoMA´s assessment

The model is well described in the submission by Gilead, and the implementation of the model in Excel is relatively transparent, and important parameters and assumptions are easy to change. The PartSA model is a common approach in oncology to estimate the effect of treatment based on data from clinical trials. The model takes into account the effect of treatment on survival, disease-related symptoms and treatment-related side effects. PartSA models are described in detail in the literature (25). Strengths include the direct relationship between reported study endpoints and survival functions used in the PartSA model to estimate the proportions of patients in the alternative health states in the model. This makes development and communication of the model relatively easy. An important limitation of PartSA models is that the survival functions are typically modelled independently, which can be problematic since events are often structurally dependent and prognostic (such as progression and survival). This may imply that extrapolation of trends beyond the study period is not always appropriate, especially when study data is immature (e.g., median OS or PFS is not reached). Since transition probabilities (e.g. survival for progressed patients) are not explicitly modelled in PartSA models, the possibility of evaluating the plausibility of the extrapolation is limited. Alternative approaches such as state-transition models may include explicit transitions, but it may be challenging to find sufficient data to estimate all relevant transition probabilities.

The approach to estimate the number of patients in the pre- and post-progression health states in the model is described in section 3.4.2.

4.1.2 Analysis perspectives

The main analysis by Gilead is performed from a Norwegian extended healthcare perspective and does not include indirect costs. VAT is not included. Health outcomes include patients' life-years and health-related quality of life. Discounting of costs and effect is set to 4% per year. The model uses a monthly cycle length, and a lifetime horizon.

NoMA´s assessment

The healthcare perspective and the discount rate are in accordance with the Norwegian guidelines. The monthly cycle length is sufficient for reflecting short-term changes in costs and health states. The lifetime horizon is appropriate for capturing a curative potential of axi-cel (22).

4.1.3 Resource-use and costs

Submitted documentation

The following cost components are considered in the model: leukapheresis and lymphodepleting costs for axi-cel arm, drug and procedure acquisition costs for axi-cel and comparators, associated drug administration costs, associated hospitalisation and ICU costs, adverse event costs, subsequent SCT costs, follow-up and monitoring costs, and terminal care costs.

Leukapheresis

Gilead assumed the cost of leukapheresis to be 9 728 NOK, equal 2 times the DRG-code 816 "Transfusjon av andre blodkomponenter". An adjustment factor of 1.102 (119/108) was used in the model to account for the 11 patients in Phase 1/2 of ZUMA-1 who underwent leukapheresis but did not proceed to receive axi-cel. Therefore, the average modelled cost of leukapheresis is NOK 10 720.

Lymphodepleting chemotherapy

Patients treated with axi-cel receive lymphodepleting chemotherapy before infusion. Lymphodepleting chemotherapy includes intravenous infusions of cyclophosphamide 500 mg/m^2 and fludarabine 30 mg/m^2 on the 5th, 4th and 3rd days prior to infusion of axi-cel. List prices (AUP excluding VAT) for cyclophosphamide and fludarabine were sourced from the Norwegian Medicines Agency.

Gilead included an outpatient administration cost (NOK 1 433) for lymphodepleting chemotherapy. Gilead argued that to avoid double counting, each of the three visits (5th, 4th and 3rd day prior to infusion of axi-cel) incurs one administration cost each, regardless of the number of chemotherapies given during the visit. An alternative, higher, cost of lymphodepleting chemotherapy was explored in a sensitivity analysis.

Gilead adjusted the cost with a multiplier of 1.019 (110/108) to account for the two patients in Phase 1/2 of ZUMA-1 who were treated with lymphodepleting chemotherapy but not axi-cel. Furthermore, the additional costs of lymphodepleting chemotherapy for the retreated patients were also accounted for. The total costs of daycare at hospital, administration and treatment costs for lymphodepleting therapy were 12 896 NOK. The specific costs are summarised in Table 16.

Table 16 Cost inputs used by Gilead

Cost inputs used by Gilead for pre-treatment procedures		
	Cost in NOK	Source
Hospitalisation cost for administration	1 320	Cost per infusion in NoMA's Jevtana report of 2014
Daycare cytostatics treatment	113	DRG-code 743b: Fremstilling og gransking av cytologiske preparater
Fludarabine (dose: 30 mg/m2/day)	2 215	NoMA official price list
Cyclophosphamide (dose: 500 mg/m2/day)	214	NoMA official price list
Added cost inputs for sensitivity analyses		
Hospitalisation cost for administration	400	DRG-code 126: Intravenøs behandling med cytostatika/sykdomsmodifiserende legemidler gitt av, eller under oppsyn av, spesialist i onkologi eller revmatolog
Daycare cytostatics treatment	7 426	DRG-code: 981X: Innleggelse uten overnatting for andre tilstander

Treatment costs

Treatment costs consisted of drug/procedure acquisition costs and administration costs. Vial sharing was not considered when estimating the drug costs in the base case.

Table 17 Treatment costs

Treatment strategy	Total treatment cost (NOK)
Axi-cel	3 189 734
Chemotherapy	103 614

Axi-cel

The price of axi-cel in the model is NOK 3 110 000 (list price, excluding pharmacy mark up).

Gilead claimed that cost of the drug will only be payed by the hospital if axi-cel is administered to the patient, so the acquisition cost of axi-cel is only applied to patients who received axi-cel (no multiplier).

The infusion of axi-cel and subsequent monitoring is assumed to incur the cost of hospitalisation for 7 days, and the cost of cell infusion. The resulting cost is NOK 56 152. Unit costs are summarised in Table 18.

Table 18 Unit costs for treatment procedures

Cost inputs used by Gilead for treatment procedures		
	Cost in NOK	Source
Hospitalisation cost (one bed day)	7 426	DRG-Code 981X: Innleggelse uten overnatting for andre tilstander
Cell infusion	4 169	DRG-code 816R: Transfusjon av fullblod eller røde blodlegemer

Chemotherapy

Gilead modelled chemotherapy as as a mixed comparator, comprised of 20% DHAP, 20% GDP, 50% IME and 10% ICE, based on input from a clinical expert in Norway. The model applied costs (list prices, AUP excluding VAT) for each regimen, multiplied by their distribution of use in Norway.

According to inputs from a Norwegian clinical expert, Gilead assumed an average of 5 treatment cycles.

An administration cost of 1 433 NOK was added to each treatment in each cycle. The administration cost for comparator chemotherapy is assumed equal to the administration cost for lymphodepleting chemotherapy (Table 16).

Table 19 Drug prices and dosage used in the model

Chemotherapy	Mg/day (27)	Mg/unit	Cost (NOK)/unit	Administrations per cycle
Gemcitabine	1000 mg/m^2	1000 mg	1,430	2 (day 1 and day 8)
		200 mg	311	
Betamethasone	30 mg/m^2	30 mg	133	4 (days 1, 2, 3 and 4)
Cisplatin	100 mg/m^2	50 mg	198	1 (day 1)
		100 mg	338	
Rituximab	375 mg/m^2	100 mg	4,220	1 (day 1)
		500 mg	10,535	
Cytarabine	2000 mg/m^2	1000 mg	207	2 (2 doses day 2)
Etoposide	100 mg/m^2	100 mg	145	3 (day 1, 2 and 3)
Metotrexate	30 mg/m^2	25 mg	59	1 (day 3)
Carboplatin	550 mg	450 mg	2,246	1 (day 2)
		50 mg	275	
Ifosfamide	5000 mg/m^2	2000 mg	724	ICE: 1 (day 2) IME: 5 (day 1-5)
		1000 mg	366	
		500 mg	197	

Subsequent SCT

In ZUMA-1 (phase 1/2, DCO: 11-Aug-2017) , two subjects out of 108 (2%) underwent alloSCT while in response after treatment with axi-cel and one subject (1%) underwent ASCT. The costs of alloSCT is therefore applied to 2% of patients in the axi-cel arm of the model and the costs of ASCT to 1% of patients.

In SCHOLAR-1, the proportion of patients who underwent SCT differs dependent on the subset of SCHOLAR-1 data used. According to Gilead the type of SCT (alloSCT or ASCT) is not known for the SCHOLAR-1 population. Gilead originally assumed ASCT for all patients who received SCT.

After NoMA's requested PS-adjustment of the patient population to better fit with the ZUMA-1 population (see section 2.1.2), the proportion of patients who received SCT in the SCHOLAR-1 dataset increased from 29% to 30%.

In their base case, Gilead excluded patients that received post-refractory SCT from the SCHOLAR-1 dataset, see section 2.1.2. Hence, the efficacy and costs of SCT were not included in the comparator arm.

The cost of alloSCT (NOK 1 040 318) was based on DRG for SCT (26). The cost of ASCT (NOK 340 875) was sourced from a regional price list (27). Gilead assumed follow-up after both alloSCT and ASCT to include haematologist visits 2 times per month the first 3 months, then 1 time per month for one year, based on input from a Norwegian clinical expert.

Follow-up costs

Medical resource use is dependent on progression status and was modelled by applying different unit costs for each health state. The estimated monthly cost for the progression-free state was NOK 588 and for the progressed disease state NOK 20 615. Resource use per health state is based on input from a Norwegian clinical expert.

Table 20 Resource use per health state and unit costs

Resource	Progression free state	Progressed disease state	Unit cost	Source
Outpatient care				
Physician visit (e.g. oncologist, haematologist)	Every 3rd month	1 visit per month	NOK 1,370	NoMA 2012 (37), adjusted for inflation
Inpatient care				
Inpatient days	-	2 visits per month	NOK 7,426	Helsedirektoratet 2018 (31)
Other care				
Home care	-	50% of patients, daily	NOK 400	NoMA 2012 (37), adjusted for inflation
Tests				
Full blood counts	Every 3rd month	1 visit per month	NOK 141	NoMA 2012 (37), adjusted for inflation
Serum level of lactate dehydrogenase (LDH)			NOK 44	Assumed same as calcium
Immunoglobulin			NOK 44	
Renal function			NOK 60	NoMA 2012 (37), adjusted for inflation
Liver function			NOK 60	
Calcium phosphate			NOK 44	Sentrallaboratoriet 2018 (38)

Adverse event costs

AE costs for Grade 3-4 events with incidence ≥10% in ZUMA-1 were included for the axi-cel treatment arm. That means only CRS was considered in the economic model.

Gilead calculated CRS event costs as the sum of the ICU admission cost and tocilizumab ("antidote") treatment and administration costs. Length of stay at the ICU were assumed to be 4 days, and the ICU unit cost NOK 7 426 based on the DRG 981X – hospitalisation without overnight stay. The resulting cost of CRS was estimated to be NOK 33 675.

Gilead did not includef B-cell aplasia in the economic model because the primary manifestation of B-cell aplasia, hypogammaglobulinemia, did not present as a Grade 3 or 4 AE in any patients in ZUMA-1. Hypogammaglobulinemia presented as a Grade 1 or 2 AE in 11 patients (11%) in ZUMA-1.

Terminal care costs

Patients who die incur a one-off cost of NOK 169 371, sourced from the literature.

NoMA´s assessment

Hospitalisation cost

Gilead has estimated the costs of hospitalisation to be NOK 7 426 per day for both ICU and general ward by using the DRG-code for hospitalisation without overnight stay.

A recent study by Lindemark et al (2017) assessed the cost effectiveness of the Norwegian ICU compared with the general ward (3). In this study they calculated a mean cost of general ward and ICU stay in Norway. The mean cost used in this study was NOK 8 000 (4 000-12 000) per bed day at general ward and NOK 50 000 (30 000-70 000) per bed day at ICU (28). The data are sourced from personal interviews with four hospital trusts in Norway.

Lindemark based the mean cost of an ICU and general ward stay on the following assumptions:

> "*1) The assumption that treating the critically ill in a ward setting would probably attract resources to the most advanced functions. Hospitals deal with levels of care below high level ICU (multi-organ support) differently, therefore we chose a mean from the higher range of reported data, and*
>
> *2) The fact that in 2001, the ratio of the cost per ICU day to hospital bed day was estimated to be six (this is the latest study of the cost of an ICU bed-day in Norway available). The ratio here would be 50 000/8 000 = 6.25*."

The Lindemark study exhibits large variations in the reported costs for the different hospital trusts. Lindemark stated that the variation in cost estimates between different hospitals can partly be explained by local adaptation of the national cost per patient specification..

Lindemark et al assumed that the cost per day in the ICU is highest in the first 24 hours and then falls substantially, with reference to Kahn et al (29) and Dasta et al (30). Normalised to the average cost of an ICU bed day, Lindemark modelled ICU daily costs such that ICU days 1 and 2 were 3- and 1.5-times more costly, respectively, than ICU from day 3 onwards. The average days at ICU in Lindemark was 5 days.

NoMA has adapted the same methodology as Lindemark et al. Stay at ICU days 1 and 2 were 3- and 1.5-times costlier, respectively, than ICU from day 3 onwards.

Day one	Day two	Day three and onwards
NOK 70 000	NOK 35 000	NOK 23 333

NoMA used the following cost estimates in the analysis:

A bed day in general ward is equal to 8 000 NOK, with reference to the LIndemark study. This is somewhat similar to the cost estimate by Gilead. Clinicians NoMA has contacted has, however, assumed that about 5% of patients in comparator arm need to be treated at ICU. This increase the average cost to about 9500 NOK per bed day for combined ICU and general ward for the comparator arm.

A bed day at ICU costs NOK 70 000 for the first day, NOK 35 000 for the second day and NOK 23 333 on day three and onwards. This gives an average of 30 116 NOK for 8.6 days in ICU treatment.

This is consistent with the STA of tisagenlecleucel for the treatment of relapsed/refractory acute lymphoblastic leukaemia (ALL) in paediatric and young adult patients (31).

Axi-cel treatment costs

Hospitalisation length of stay

Gilead assumed that lymphodepleting therapy is administered in an outpatient setting. According to Norwegian clinicians, it is likely that the patients are hospitalised for the three days the lymphodepleting therapy is administered. The lymphodepleting pre-treatment is starting five days prior to infusion with axi-cel. NoMA has in the base case assumed that the patients are hospitalised for 4 days prior to the axi-cel infusion. In a scenario analysis NoMA has used 3 days in hospital and 2 days in hotel. The unit costs of the patient hotel is NOK 565 per night (35)

For axi-cel infusion and monitoring, Gilead assumed that the patients are hospitalised for 7 days. According to the ZUMA-1 protocol, all patients were to remain in the hospital for a minimum of 7 days following the axi-cel infusion. Patients were to remain hospitalised for longer periods as needed to meet discharge requirements and were not to be discharged from the hospital until all axi-cel related nonhematological toxicities had returned to ≤ Grade 1 or baseline. According to the ZUMA-1 clinical study report patients were hospitalised for 17.6 days on average following the infusion with axi-cel. This accounts for hospitalisation at general ward and at the ICU for treating complications due to adverse events. According to the SmPC, physicians should consider hospitalisation for the first 10 days post infusion or at the first signs or symptoms of CRS and/or neurologic events, and patients should be instructed to remain within proximity of a qualified clinical facility for at least 4 weeks following infusion. Norwegian clinical experts estimate that the duration of hospitalisation for a standard patient will be about 11 days in Norwegian clinical practice. Patients that live near a qualified clinical facility may stay at home after 11 days. Patients that do not live near the qualified clinical facility may stay at the patient hotel.

NoMA uses the length of stay in hospital reported in the clinical study report. The total average number of days in hospital from axi-cel infusion was 17.6 days and the median number of days was 15 days. This is in line with the first real-world data as reported by Nastoupil et al (2018) which reports a median of 14 days in hospital due to treatment with axi-cel(7).

According to Gilead, 13% of the patients spent some of the hospitalisation days at ICU for treatment of CRS. According to the clinical study report from ZUMA-1 it took on average 8.6 days to resolve the CRS

(range: 2 to 58 days). NoMA uses this estimate as input for average days at the ICU. The clinicians NoMA contacted explained that their experience is that the standard patient will stay 3-4 days at ICU due to CRS. The range of days for resolvement of CRS in the ZUMA-trial is wide, and a few outliers may explain why the average is above the median or standard patient. In the real-world data reported by Nastoupil et al (2018) 32% of the patients were hospitalised at ICU. This is a larger proportion than reported in ZUMA-1(7).

The length of hospitalisation used in NoMA's main scenario is described in Table 21 Length of stay in hospital due to lymphodepleting treatment, axi-cel infusion and monitoring.

Table 21 Length of stay in hospital due to lymphodepleting treatment, axi-cel infusion and monitoring

Reason for hospitalisation	Number of days	Source
Lymphodepleting therapy (general ward)	4 days	Assumption, based on SmPC and clinical expert input
Axi-cel infusion and monitoring	17.6 days	Clinical study report, NICE STA committee papers(32)
Total	21.6 days	Calculation

Total hospital stay used by NoMA for lymphodepleting therapy, axi-cel infusion and monitoring is 21.6 days.

In scenario analyses, NoMA has used 11 days hospitalisation and the remaining days up to 28 days in either patient hotel or at home and 4 days at the ICU.

Leukapheresis

Gilead has assumed that the cost of leukapheresis is 9 728 NOK, with reference to DRG-code 816R: "Transfusjon av fullblod eller røde blodlegemer". NoMA has received an overview of the costs for leukapheresis from Dag Josefsen, Head of the Section of cell laboratory at the OUS (56). These costs represent the average unit costs from the clinical trials of CAR-T cell therapy at OUS.

Table 22 Cost of leukapheresis and preparation of CAR-T cells per patient at OUS

Element of cost	Cost (NOK)
1. Production and shipment of frozen cells:	
Material and reagents	23 566
Working hours for leukapheresis and freezing teams (4 hrs doctor, 10 hrs bio technician)	6 972
Batch documentation, QC and release	11 111
Shipment, including documentation (3 hrs bio technician)	1 308
Total price per production (per patient)	**42 957**
2. Receiving and intermediate storage of cells and documentation	
Storage in liquid nitrogen	2 222
Work in relation to receiving, intermediate storage and documentation (3 hrs bio technician)	1 308
Total price for receiving, intermediate storage and documentation per patient	**3 530**
3. Thawing of cells bedside:	
Preparation of dry shipper, transfer of cells and documentation (1 hr doctor, 3 hrs bio technician)	2 179
Working hours for thawing, documentation and transportation (1 hr doctor, 3 hrs bio technician)	2 179
Total price for thawing bedside (per patient)	**4 358**
Hourly wage doctor: NOK 871 Hourly wage nurse/bio technician: NOK 436	
Total price:	**50 845**

Hourly wage used in the OUS input data is equal to the unit costs of hourly wage in the NoMA unit costs database.

Costs for materials and reagents are provided by Dag Josefsen at OUS. In an article published by R. Lyons (2008), in *The journal of oncology practice* the disposables are estimated to cost between $1500 to $3000, in line with the estimate from the OUS (33).

The OUS produce the cells in a clinical room at the cell laboratory. The cell laboratory is physically separated from the clinical department. This implies that the responsible physician needs to be present the whole time of the procedure, i.e. 4 hours. The physician is according to the OUS source not able to do any other clinical work when situated in the cell lab. The cell laboratory uses the four eyes principle, which requires two bioengineers for 4.5 hours, including 0.5 hour pre-preparations. The procedure and working hours required for the apheresis, as described by Dag Josefsen, is in line with the description in Lyons (33).

T-cell harvesting for the axi-cel product is a somewhat similar procedure as bone marrow harvesting. According to Dag Josefsen the price of stemcell harvest product from the cell lab to the Benmarggiverregisteret (The Norwegian Bone Marrow Donor Registry, NBMDR) is 39 000 NOK. The cost

of production and documentation for T-cell harvesting seems to be in line with the price of the bone marrow harvest produced at the cell lab for the NBMDR.

The cost specified for batch documentation includes all documentation activities in connection to the production of the cells according to regulated quality standards. According to OUS, the work load is expected to be similar in a commercial setting as in a clinical study setting.

NoMA uses the OUS esimate of leukapheresis costs.

Axi-cel

The price of axi-cel in the submitted model was NOK 3 110 000. This price did not reflect the pharmacy markup, as Gilead assumed that axi-cel could be delivered directly to hospitals. According to NoMA's guidelines the maximum pharmacy selling price (PSP), including the pharmacy markup and excluding VAT, should be used in the analysis.

NoMA regulates the maximum pharmacy markup. The aim of the pharmacy markup is to cover the pharmacy expenses in handling prescribed expeditions. The pharmacy markup consist of a fixed amount of 29 NOK for each package in addition to 2% of the PSP (mark-up as of January 1st 2019). This regulation ensures that the pharmacy is remunerated for handling the prescriptions, and for the cost of storage and risk of scrapping drugs. The package price is closely connected to the costs of capital for the pharmacy with expensive packages leading to higher capital costs and risks compared to cheaper packages.

NoMA writes in the report Evaluation of pharmacy markup from 2016 the following (our translation)(34):

"The current structure [of the markup] is relatively simple and it is taken into account that it should reflect average cost per pack . It will therefore within today's structure be varying degrees of profitability of different packages and various prescription expeditions."

According to Gilead, they will provide replacement of the product or issue credit for unusable products. Axi-cel is shipped directly to the cell lab, the costs of the storage is minimal. However, the pharmacy have other costs associated with axi-cel, for instance, preparing the staff and working hours, and in addition costs of legal advice for specific arrangements with the provider.

The simple structure of the pharmacy markup let the pharmacies to cross subsidize their expenses, as some packages may add an income to the pharmacy less than the cost of expedition, while other packages may add income higher than the cost of expedition. In NoMA's opinion the pharmacy markup is a good proxy estimate of the mean costs for the pharmacy. The pharmacy markup is regulated to cover the total expenses to comply with all prescriptions as regulated by law and regulations. Hence, it will be an important part of the budget consequences for the hospital, and the pharmacy. However, due to the specific circumstances regarding axi-cel, we consider the markup as a transfer cost. According to national guidelines of economic analysis transfer costs should not be included in the analysis of cost effectiveness, however, may be an important part of the budget analysis(35). NoMA will therefore not include the pharmacy markup as a part of the cost effectiveness analysis in this specific case. We include pharmacy markup in a sensitivity analysis. The pharmacy markup will be included in the budget analysis.

Comparator treatment costs

NoMA has contacted Norwegian clinicians for information about the use of different combinations of chemotherapy for r/r DLBCL patients in Norwegian practice. According to the Norwegian clinicians, the type of chemotherapy combinations varies with the patients characteristics and aim of treatment. For r/r DLBCL patients relevant to this STA, the most common treatments would be R-GDP, R-EPOCH, R-DHAP, R-Gem-OX and in rare cases R-ICE. This is summarized in Table 23:

Table 23 Chemotherapy combinations used in clinical practice

Salvage chemotherapy	Number of cycles	Hospital length of stay per cycle	Length of a cycle
R-GDP	4	3 days	21 days
R-EPOCH	3-6	5 days	Not informed
R-ICE	4	3 days	Not informed
R-DHAP	3-4	3 days	21 days
R-Gem-OX	1 (inpatient) 5 (outpatient)	1-2 days (first cycle only)	14 days

In terms of drug cost per treatment, there is only little variation between the listed alternatives of chemotherapy combinations. Notably, it seems to be common to include rituximab to all of the regimens.

In addition Norwegian clinical experts have commented that patients may be hospitalised for adverse events such as febrile neutropenia and infections. They assume that about 50% will be hospitalised for febrile neutropenia. The duration of febrile neutropenia is assumed to be 6 days, by using data from the ZUMA-1 trial.

NoMA uses the estimates obtained from clinical experts as input in our base case. This includes rituximab to all patients, and hospitalisation length of stay in line with the estimates provided in Table 23. Rituximab is more costly per treatment than the other chemotherapy combinations. Adding rituximab to all combinations would also impact the estimated effect of the comparator arm. As we have only updated the cost of rituximab and not adjusted for potential incremental effect this is an optimistic appraoch.

The Norwegian Procurement Agency has launched a tender of rituximab, that came into effect on February 1st 2019. The tender price is lower than the official list price. The tender price is confidential by legislation and cannot be revealed in this report.

Furthermore, Gileads calculation of drug costs of rituximab has used package size of 100 mg doses. The correct package size would contain 200 mg. Therefore, in Gileads calculation twice the number of packages per patient are included, which doubled the cost of rituximab in the model.

Gilead has not included cost of hospitalisation for chemothreapy treatment. This imply that Gilead assumed that all regimens are administered in an outpatient setting. The estimated mean number of days in hospital for all cycles of the different regimens is 11.7 days and in addition 3 days on average for treating febrile neutropenia.

Subsequent SCT

In ZUMA-1 trial 2% received alloSCT and 1% received ASCT while in axi-cel-induced remission. This is reflected in the effect data and included in Gilead's and NoMA's base case scenarios. However, it is unlikely that SCT post CAR-T treatment will be offered in clinical practice.

Gilead assumed that no patients in the comparator arm will receive subsequent SCT. In scenario analysis Gilead assumed that 29% of the patients receive subsequent ASCT. NoMA disagreed with Gilead that post-SCT patients should be excluded from the comparator arm and included the proportion of SCT from SCHOLAR-1 in its base case. After NoMA's requested adjustment of the patient population to better fit with the ZUMA-1 population (see section 2.1.2), the proportion of patients who received SCT in the SCHOLAR-1 dataset increased from 29% to 30%.

The clinical experts contacted by NoMA suggest that approximately 2 Norwegian r/r DLBCL patients treated with salvage chemotherapy will receive alloSCT each year, which constitutes about 10%.

NoMA has calculated the proportion of patients receiving SCT in the CORAL extension studies, which is one of the studies included in the SCHOLAR-1. Of the patients that received SCT, the proportion of patients receiving alloSCT is about 26% and the proportion that received ASCT is about 74%.

Table 24 Proportion of patients receiving SCT in CORAL extension studies

Patients, n (%)	CORAL extension study 1: Relapsed after ASCT (n=75)	CORAL extension study 2: Failed to proceed to ASCT (n=203)	Study 1 + 2 (n=278)
Subsequent SCT	16/75 (21%)	64/203 (31%)	80/278 (29%)
ASCT	3/16 (19%)	56/64 (88%)	59/80 (74%)
alloSCT	13/16 (81%)	8/64 (13%)	21/80 (26%)

NoMA has assumed that the proportion of patients receiving alloSCT and ASCT is similar in SCHOLAR-1 as in CORAL extension studies. We have explored in ascenario analysis how a higher proportion of alloSCT will impact the ICER.

Gilead assumed about 20 000 NOK in follow-up costs the first 12 months after SCT, due to about 15 haematologist visits. For consistency reasons, NoMA uses the same number of visits and similar cost inputs as used in other ongoing CAR-T assessments. These changes reduced the ICER, see table

Table 27 in section 4.2.2.

NoMA has updated the model with the DRG unit costs for 2019. The unit costs of alloSCT and ASCT is reduced in the 2019 DRG estimates, see

Table 25.

Table 25 cost of allo and auto SCT - 2019 DRG estimates

Procedure	DRG used	Unit cost
Cost of procedure alloSCT	DRG 481B	841951
Cost of procedure ASCT	DRG 481A	248 946
Chemo conditioning	DRG 413 and 414	59 836
Follow up visits	917A	1 875
Blood tests and imaging	-	2 500
Follow up costs SCT		
# of visits year one	8	35 004
# of visits year two	6	26 253
Total costs of SCT		
Cost of alloSCT		963 044
Cost of ASCT		370 039

Follow-up

Gilead used input from Norwegian clinical experts to estimate the costs of follow up pre- and post-progression. NoMA accepts these follow up costs. The total monthly costs is approximately the same as used in the STA of tisagenlecleucel for the treatment of second or later r/r DLBCL (24).

Adverse Events

CRS

CRS is an AE that is specific to treatment with axi-cel, and could be associated with substantial resource use. Gilead calculated this by adding the costs of ICU and drug costs for treating CRS.

According to the clinical study report the mean time to resolving of CRS was 8.6 days. Gilead assumed that the patients were admitted to the ICU for 4 days in total. NoMA contacted Gilead to provide documentation for the assumption of 4 days, however, Gilead could not provide this. NoMA has adjusted from 4 days to 8.6 days in line with the clinical study report.

Gilead assumed that the ICU cost is similar to the cost of general ward. NoMA uses the unit costs for hospitalisation from the Lindemark study(3). The costs of 8.6 days at ICU is estimated to be NOK 30 116 per day, see the paragraph *Hospitalisation cost.* Total costs of CRS including costs of tocilizumab is NOK 210 152.

B-cell aplasia

According to the Hospital Procurement trust Panzyga is the preferred pharmaceutical for supplementary IVIG treatment for treating B-cell aplasia since September 2017 (36). This is also confirmed by Norwegian clinical experts.

The recommended dose for Panzyga is 0.2 – 0.4 g per kg every 3-4 weeks. NoMA has assumed an average dose of 0.3 g per kg every 3-4 weeks. When assuming an average weight of 80 kg, this corresponds to approximately 27 g every monthly cycle. This dose requires the following packages:

Brand	Package	Price ex VAT in NOK
Panzyga	100 mg/ml 100 ml (3x)	5 354

Norwegian clinical experts expect that patients will switch treatment from Panzyga to subcutaneous treatment (the medicinal products Hizentra or Gammanorm). These treatments do not require administration costs, however, as the price of these treatments is higher we assume that the monthly costs of Panzyga will be similar to that of Hizentra or Gammanorm. For simplicity we have used a unit price and administration costs of Panzyga for the entire period of IVIG treatment. The total monthly cost used in NoMA's analysis is NOK 18 448.

Gilead did not assume any costs for treating B-cell aplasia, because the primary manifestation of B-cell aplasia, hypogammaglobulinemia, did not present as a Grade 3 or 4 AE in any of the patients in ZUMA-1. However, NoMA noted that 31% (33/108) of the patients that were infused with axi-cel were treated with IVIG due to hypogammaglobulinemia, and NoMA therefore considers it appropriate to include these costs (see section 3.4.3). Clinical experts stated that IVIG treatment is also common for patients on salvage chemotherapy. Hypogammaglobulinaemia secondary to B-cell aplasia was seen in 16% (All grades; Grade ≥3: none) of the patients that were infused with axi-cel. The difference between this 16% and the total IVIG use in 31% of patients could be explained by previous lines of treatment, which can also be expected to be present in the comparator arm. NoMA therefore assumes an average IVIG duration of 12 months (15) in 16% of the infused patients, resulting in an average total cost of NOK 35 420 in the model. The 12 month duration was varied in sensitivity analysis.

Terminal care costs

Gilead assumed the terminal care costs inputs to be NOK 169 000 based on a study of adult patients with breast cancer in Norway from 1999 to 2009 by Moger et al (2015)(5). In NoMA's opinion, cost inputs based on treated DLBCL patients better reflect true terminal care costs as opposed to cost estimates based on breast cancer patients. Therefore, NoMA uses the terminal care costs based on treated DLBCL patients of NOK 57 820 obtained from Wang et al. 2017 (4). This is a cost modelling study of DLBCL patients in the UK newly diagnosed in 2007 and followed for 5 years.

4.2 RESULTS

4.2.1 Gilead's base case analysis

Results for axi-cel versus chemotherapy from Gilead's base case analysis is presented in Table 26. Results are reported per patient and discounted at a discount rate of 4%. Gilead evaluated the mITT population (infused patients only) in their base case. The results are based on comparator efficacy data from a crude SCHOLAR-1 adjustment, excluding patients with ECOG 2-4 and post-SCT. Extrapolation of OS is based on a

Weibull mixture cure model for axi-cel, and a Gompertz single parametric function for chemotherapy. PFS for axi-cel was modelled using a Gompertz function, and PFS for chemotherapy was based on the modelled ratio between OS and PFS for axi-cel.

Table 26 Results from Gilead's base case. mITT population (infused patients).

	Axi-cel	Chemotherapy	Difference
Total costs	3 649 867 NOK	336 334 NOK	3 313 533 NOK
Total QALYs	6.52	1.30	5.22
Total life years	8.51	1.72	6.79
Incremental cost per QALY gained			**635 100 NOK**
Incremental cost per life year gained			488 050 NOK

4.2.2 NoMA´s base case analyses

NoMA has estimated the incremental cost-effectiveness ratios (ICERs) for axi-cel compared to chemotherapy for the mITT population (infused patients) and the ITT population (enrolled patients). In section 3.1 NoMA discussed the relevance of the population characteristics for this analysis. NoMA concluded that it is relevant to present analyses of both the ITT and mITT populations for the decision makers. In the ITT population, the efficacy of axi-cel is measured from the time of enrolment to account for the delay in manufacturing. In the mITT population, the effect of axi-cel is measured only in infused patients from the time of infusion, i.e. patients who did not receive the infusion because of death prior to infusion, physician- or patient decisions to discontinue, manufacturing failures, or AEs, were excluded from the analysis.

Table 27 Changes made by NoMA

Parameter	Gilead's base case	NoMA's base case
Changes applied to the model where survival is measured from enrolment or infusion:		
OS survival function axi-cel	Weibull mixture cure model	Spline model with 2 knots constrained by the PFS curve
OS survival function chemotherapy	Gompertz single parametric curve	Spline function with 1 knot
Long-term mortality axi-cel	General population mortality	Mortality rate as modelled for the comparator arm from point of convergence between the OS and PFS curves for axi-cel
Health related quality of life		
Health state utilities	PFS: 0.72 PD: 0.65 Source: ZUMA-1 Safety cohort	PFS: 0.83 PD: 0.71 Source: JULIET trial
Disutility AEs	Total disutility of AEs: comparator: 0 Axi-cel: -0.03	Total disutility of AEs: comparator: -0.04 axi-cel: -0.01 Source: Submitted model, correct calculation
Age adjustment of health state utilites	Burström (21)	Sun (23) and Burström (21) Source: NoMA guidelines
Adjustment of long term quality of life	5% reduction in quality of life compared to general population. Source: clinical expert	Not included adjustment of long term quality of life.
Resource use		
Leukapheresis costs	NOK 9 728 Source: Helsedirektoratet (2*DRG 816P)	NOK 50 845 Source: Oslo University Hospital
Comparator: Hospitalisation length of stay	0 days Outpatient treatment Source: assumption	14.7 days No outpatient administration costs Source: Clinical expert opinion
Axi-cel Hospitalisation length of stay	7 days Source: assumption	21.6 days, incl. lymphodepleting therapy, infusion, and monitoring Source: ZUMA-1, assumption
Comparator: Drug costs	Rituximab 100 mg package size	Rituximab 200 mg package size Source: Legemiddelsøk
Comparator: Drug costs	Rituximab in combination with DHAP only	Rituximab added to all chemotherapy combinations Source: Clinical expert opinion
Hospitalisation cost per bed day	NOK 7 426	NOK 8 000 (axi-cel) NOK 9 500 (comparator)

	Source: Helsedirektoratet (DRG 981X)	Source: Lindemark (3), clinical expert opinion, and assumptions
ICU cost per bed day	NOK 7 426 Source: Helsedirektoratet (DRG 981X)	Day 1: NOK 70 000 Day 2: NOK 35 000 Day 3 onwards: NOK 23 333 Source: Lindemark (3), assumptions Input data only represent incremental costs of hospital stay at ICU.
SCT costs	AlloSCT: NOK 1 159 560 ASCT: NOK 439 567	AlloSCT: NOK 963 044 ASCT: NOK 370 039 DRG code and unit price updated
Comparator: Subsequent SCT rate	Not included	30% alloSCT: 8% ASCT: 22% Source: PS-adjusted SCHOLAR-1 data
Terminal care costs	NOK 169 371 Source: Moger (5)	NOK 57 820 Source: Wang (4)
AEs – B cell aplasia: IVIG treatment costs	not included	NOK 35 420 Monthly costs of 18 448 NOK for 16% of patients for 12 months. Source: ZUMA-1, NICE axi-cel STA (15)

Red coulor: ICER increase from Gilead's scenario
Green colour: ICER decrease from Gilead's scenario
Yellow colour: relatively small changes in ICER

4.2.3 Effectiveness

The total life years gained (LYG) and quality adjusted life years gained (QALYs) of axi-cel and chemotherapy are summarised in the table below for both the ITT and mITT analyses. Gilead´s base case is the mITT scenario using the mixture cure model. All results are reported per patient and discounted at a discount rate of 4%.

Table 28 Utility of axi-cel and chemotherapy per patient, discounted

	Gilead´s base case		NoMA's base case			
	mITT population		ITT population		mITT population	
	Chemotherapy	Axi-Cel	Chemotherapy	Axi-Cel	Chemotherapy	Axi-Cel
Total LYG	1.72	8.51	3,82	6,28	3,82	6,78
Total QALYs	1.30	6.52	2,96	4,93	2,95	5,32
Incremental LYG	6,79		2.46		2.96	
Incremental QALYs	5.22		1,97		2.36	

A discussion of the assumptions behind Gilead's and NoMA's base case for extrapolating OS and PFS is provided in section 3.4.2. The key differences between Gilead's and NoMA's base case are driven by the selection of patients in SCHOLAR-1 and the method of survival extrapolation.

4.2.4 Costs

The total costs of the different cost components of axi-cel and chemotherapy are summarised in the table below for both ITT and mITT analyses for Gilead´s base case and NoMA's scenarios.

Table 29 The costs components of aci-cel and chemotherapy per patient, discounted

	Treatment	SCT	Medical resource use	AEs	Terminal care	Total costs
Axi-Cel						
Gilead's base case	3 189 734	23 830	317 381	6 298	112 624	3 649 867
NoMA's base case (ITT)	3 069 958	22 103	91 917	58 097	43 521	3 285 595
NoMA's base case (mITT)	3 357 436	22 103	90 877	61 365	42 446	3 574 228
Chemotherapy						
Gileads's base case	103 614	-	74 821	-	157 899	336 334
NoMA's base case (ITT)	272 093	157 454	69 881	-	49 120	548 548
NoMA's base case (mITT)	272 002	157 454	63 944	-	49 161	542 560

For axi-cel, the hospital only pays for the infused patients. That means that in the ITT population the hospital is not charged for the cost of axi-cel for some of the enrolled patients who discontinued prior to axi-cel infusion. This reduces the treatment costs in the ITT population. Higher cost of leukapheresis increase the treatment costs in the NoMA scenarios. Furthermore, NoMA's analysis includes a higher cost of chemotherapy treatment due to hospital stay, cost of subsequent SCT in chemotherapy arm and higher costs of adverse events.

Gilead assumed that a significant proportion of progressed patients would have a long-term prognosis equal to the general population, with a high monthly cost of post-progression follow-up. In NoMA's scenarios, progressed patients do not have this long-term prognosis. The total costs of follow-up post progression is therefore reduced.

4.2.5 Incremental cost effectiveness ratios (ICER)

NoMA has estimated a cost-effectiveness ratio for axi-cel compared to chemotherapy. Multiple important limitations and uncertainties in the analyses were identified. NoMA therefore considers the cost-effectiveness estimates to be highly uncertain. Results from NoMA's base case analyses are presented for both the ITT and mITT populations in the tables below.

Table 30 NoMA´s base case (ITT population) per patient, discounted

	Axi-cel	Chemotherapy	Difference
Total costs	3 285 595 NOK	548 548606 NOK	2 737 047 NOKNOK
Total QALYs	4.93	2.96	1.97
Total life years	6.28	3.82	2.46
Incremental cost per QALY gained			**1 389 581 NOK**
Incremental cost per life year gained			1 112 588 NOK

Table 31 NoMA´s base case (mITT population) per patient, discounted

	Axi-cel	Chemotherapy	Difference
Total costs	3 574 228 NOK	542 560 NOK	3 031 668 NOK
Total QALYs	5.32	2.95	2.36
Total life years	6.78	3.82	2.96
Incremental cost per QALY gained			**1 282 615 NOK**
Incremental cost per life year gained			1 023 856 NOK

4.2.6 Sensitivity and scenario analyses

Gilead has performed one way sensitivity analysis and a probabilistic sensitivity analysis. The key drivers that affect the ICER were the discount rate of outcomes and costs, extrapolation of OS and PFS and utility values. This is presented by a tornado diagram.

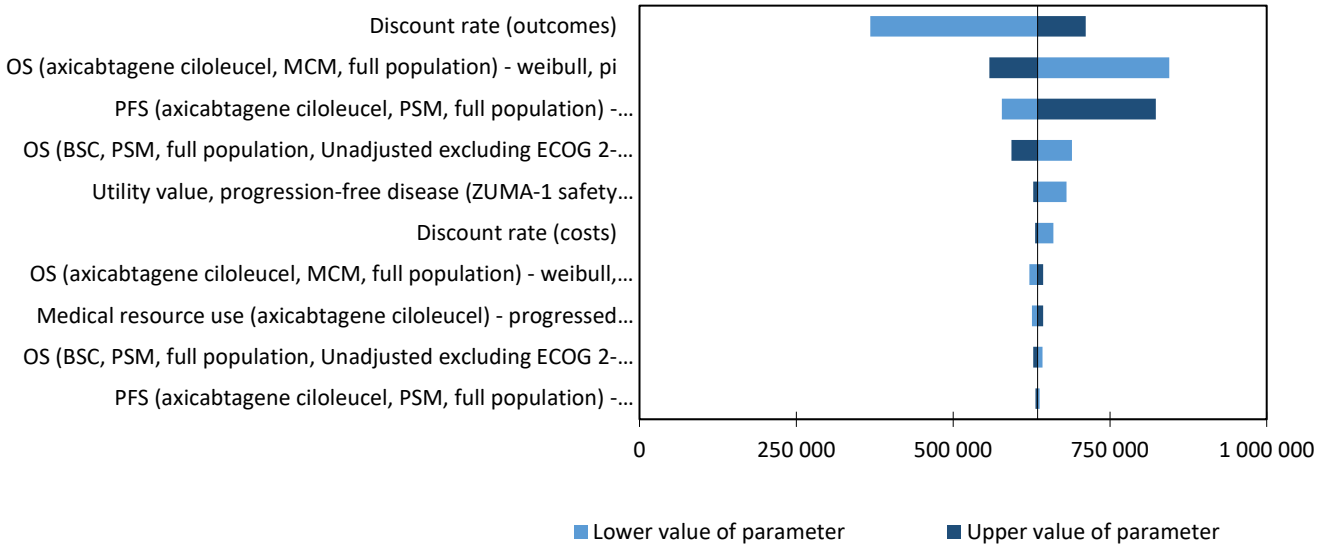

Figure 31 Sensitivity analysis performed by Gilead

NoMA has performed the following scenario analyses (ITT population).

Table 32 Sensitivity analysis performed by NoMA

Parameter	NoMA's base case	Scenario analyses	ICER (NOK)
NoMA's base case (ITT population)	**See 4.2.2 for all changes**	**-**	**1 389 581**
SCHOLAR-1 population	Excluding ECOG 2-4 and patients with unknown disease stage, PS-adjusted	Excluding ECOG 2-4 and SCT, unadjusted. SCT costs excluded OS and PFS for axi-cel are identical to NoMA's base case	814 986
SCHOLAR-1 population	Excluding ECOG 2-4 and patients with unknown disease stage, PS-adjusted	Excluding ECOG 2-4, unadjusted SCT costs adjusted to 29% OS and PFS for axi-cel are identical to NoMA's base case	1 033 960
Health state utilities	PFS: 0.83 PD: 0.71 Source: JULIET trial	PFS: 0.76 PD: 0.68 Source: NICE Pixantrone STA	1 398 860
Axi-cel: Hospitalisation length of stay	21.6 days, incl. lymphodepleting therapy, infusion, and monitoring Source: ZUMA-1, assumption	14 days (lymphodepleting therapy, infusion, and monitoring) + 14 days in patient hotel (NOK 565 per bed day) Source: Clinical expert opinion, SmPC, Regulations of patient travel.	1 359 678
Axi-cel: ICU length of stay	8.6 days of ICU for CRS resolvement Source: ZUMA-1	4 days of ICU Source: assumption by Gilead	1 384 934
Leukapheresis costs	NOK 50 845 Source: Oslo University Hospital	44 502 NOK Source: Rigshospitalet in Denmark	1 386 039
AEs – B cell aplasia: IVIG treatment costs	35 420 NOK - monthly costs of 18 448 NOK for 16 % of patients for 12 months. Source: ZUMA-1, NICE axi-cel STA (15)	Lifelong monthly costs of 18 448 NOK for 16% of patients (adjusted for survival)	1 486 103
AEs – B cell aplasia: IVIG treatment costs	35 420 NOK - monthly costs of 18 448 NOK for 16 % of patients for 12 months. Source: ZUMA-1, NICE axi-cel STA (15)	No IVIG costs Source: Gilead assumption	1 373 288
Axi-cel pharmacy markup	Not included Price of axi-cel: 3 110 000 NOK	Included Price of axi-cel: 3 187 794 NOK	1 425 362
OS survival functions	Spline models for OS constrained by PFS	Weibull Cure Model for axi-cel, Gompertz function for chemotherapy, as in Gileads base case	960 961

The details of input used in scenario analysis for leukapheresis costs and OS survival function is:

Adjustment of SCHOLAR-1 population: Due to potential selection bias in the ZUMA-1 trial (se section 3.2), the SCHOLAR-1 population has been adjusted to be comparable with the population in the ZUMA-1. This result in a high proportion of patients in the SCHOLAR-1 receives subsequent SCT, higher than experienced in clinical practice. NoMA has explored the effect of subsequent SCT in scenarioanalysis. OS of the scenarios are shown in section 3.4.2. The relating costs of SCT are adjusted to the proportion of patients receiving SCT in the different scenarios.

Leukapheresis costs: NoMA has received a cost estimate from the Danish Rigshospitalet in Copenhagen. This estimate is based on the calculations in the table below.

Table 33 Leukapheresis costs estimated by the Danish Rigshospitalet

Leukapheresis product	NOK
Apheresis, incl. Analysis	16 124
Cell Freezing	8 384
Shipment	6 450
Receiving, containing, transport and defrosting	13 544
Per product	44 502

OS survival function: In the scenario with the Weibull cure model we have used the parametric functions provided by Gilead's base case, with all the other changes reported in section 4.2.2 applied.

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

In NoMA's base case analyses, the additional costs for axi-cel compared to chemotherapy, with public list prices ex. VAT for medicines, are:

- 1.4 million NOK per QALY gained in the ITT population (enrolled patients)
- 1.3 million NOK per QALY gained in the mITT population (infused patients)

The long-term survival of 20% for the comparator arm in the model may be higher than experienced in clinical practice. However, it is not appropriate to compare the ZUMA-1 clinical trial with a historical control which approximates clinical practice. NoMA intended to select those patients from the SCHOLAR-1 data that could have been included in a theoretical ZUMA-1 control arm. In this adjusted SCHOLAR-1 dataset, the proportion of patients who received subsequent SCT and hence the long term survival increased. In scenarioanalyses where 1) subsequent SCTs and ECOG 2-4 were removed from the SCHOLAR-1 data, and 2) only ECOG 2-4 was removed, resulted in ICERs of 0.8 and 1 million NOK per QALY gained, respectively.

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

5.1 ESTIMATION OF THE NUMBER OF PATIENTS POTENTIALLY ELIGIBLE FOR TREATMENT

Clinical experts recruited by the regional health authorities have estimated that around 20 patients with relapsed/refractory DLBCL will be eligible for treatment with Yescarta (axi-cel) each year in Norway.

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 34. The number of patients expected to be treated if Yescarta is not recommended is presented in Table 35.

Table 34 The annual number of new patients expected to initiate treatment with Yescarta (axi-cel) in the next 5 years – scenario where Yescarta (axi-cel) is recommended

	År 1	År 2	År 3	År 4	År 5
Yescarta (axi-cel)	20	20	20	20	20
Salvage chemotherapy	0	0	0	0	0
Total	20	20	20	20	20

Table 35 The annual number of new patients expected to initiate treatment with Yescarta (axi-cel) in the next 5 years – scenario where Yescarta (axi-cel) is not recommended

	År 1	År 2	År 3	År 4	År 5
Yescarta (axi-cel)	0	0	0	0	0
Salvage chemotherapy	20	20	20	20	20
Total	20	20	20	20	20

5.2 COST ESTIMATES

NoMA has calculated the budget impact for two scenarios:

1. Drug costs for Yescarta and salvage chemotherapy. All other costs are excluded.
2. All healthcare costs and assumptions considered in the cost-effectiveness model: pre-treatment, drugs, hospitalisation, AEs, follow-up, subsequent alloSCT and terminal care for the ITT analysis.

In both scenarios, costs have been calculated for the ITT and the mITT population and all changes by NoMA as described in section 4.2.2 are incorporated.

Drug costs in NOK per patient per year after treatment initiation according to scenario 1 are presented in Table 36 (ITT population) and Table 37 (mITT population).

Table 36 Drug costs per patient per year after treatment initiation. List price, including VAT and undiscounted, ITT population.

	Year 1	Year 2	Year 3	Year 4	Year 5
Yescarta (axi-cel)	3 539 669	0	0	0	0
Salvage chemotherapy	184 920	0	0	0	0

Table 37 Drug costs per patient per year after treatment initiation. List price, including VAT and undiscounted, mITT population

	Year 1	Year 2	Year 3	Year 4	Year 5
Yescarta (axi-cel)	3 897 653	0	0	0	0
Salvage chemotherapy	184 920	0	0	0	0

Healthcare costs in NOK per patient per year after treatment initiation according to scenario 2 are presented in Table 38 (ITT population) and

Table 39 (mITT population).

Table 38 Healthcare costs per patient per year after treatment initiation. List price, including VAT and undiscounted, ITT population.

	Year 1	Year 2	Year 3	Year 4	Year 5
Yescarta (axi-cel)	3 943 893	3 943 893	3 984 878	3 993 895	3 994 573
Salvage chemotherapy	604 764	604 764	628 183	635 188	638 189

Table 39 Healthcare costs per patient per year after treatment initiation. List price, including VAT and undiscounted, mITT population.

	Year 1	Year 2	Year 3	Year 4	Year 5
Yescarta (axi-cel)	4 301 366	40 278	11 910	736	309
Salvage chemotherapy	600 321	22 200	6 895	2 896	1 557

5.3 BUDGET IMPACT

The estimated budget impact in NOK as a result of drug costs only (scenario 1) for the eligible patient population is presented in Table 40 (ITT population) and Table 41 (mITT population).

Table 40 Estimated budget impact of drug costs for the eligible patient population. List price, including VAT and undiscounted, ITT population.

	Year 1	Year 2	Year 3	Year 4	Year 5
Yescarta (axi-cel) recommended for use	70 793 386	70 793 386	70 793 386	70 793 386	70 793 386
Yescarta (axi-cel) not recommended for use	3 698 406	3 698 406	3 698 406	3 698 406	3 698 406
Budget impact of recommendation	67 094 980	67 094 980	67 094 980	67 094 980	67 094 980

Table 41 Estimated budget impact of drug costs for the eligible patient population. List price, including VAT and undiscounted, mITT population.

	Year 1	Year 2	Year 3	Year 4	Year 5
Yescarta (axi-cel) recommended for use	77 953 059	77 953 059	77 953 059	77 953 059	77 953 059
Yescarta (axi-cel) not recommended for use	3 698 406	3 698 406	3 698 406	3 698 406	3 698 406
Budget impact of recommendation	74 254 653	74 254 653	74 254 653	74 254 653	74 254 653

The estimated budget impact resulting from all healthcare costs considered in the cost-effectiveness model (scenario 2) for the eligible patient population is presented in

Table 42 (ITT population) and Table 43 (mITT population).

Table 42 Estimated budget impact of healthcare costs for the eligible patient population. List price, including VAT and undiscounted ITT population.

	Year 1	Year 2	Year 3	Year 4	Year 5
Yescarta (axi-cel) recommended for use	78 877 863	79 697 554	79 877 894	79 891 454	79 897 135
Yescarta (axi-cel) not recommended for use	12 095 274	12 563 657	12 703 767	12 763 772	12 797 004
Budget impact of recommendation	66 782 589	67 133 897	67 174 128	67 127 682	67 100 131

Table 43 Estimated budget impact of healthcare costs for the eligible patient population. List price, including VAT and undiscounted mITT population.

	Year 1	Year 2	Year 3	Year 4	Year 5
Yescarta (axi-cel) recommended for use	86 027 314	86 832 880	87 071 077	87 085 796	87 091 978
Yescarta (axi-cel) not recommended for use	12 006 418	12 450 412	12 588 308	12 646 224	12 677 363
Budget impact of recommendation	74 020 896	74 382 469	74 482 769	74 439 572	74 414 615

The budget impact of a positive recommendation for Yescarta for the eligible patient population as described in this STA is estimated to be around 67 million NOK including VAT in the fifth year after introduction. The calculations are uncertain and based on simplifications.

In this estimation of budget consequences of introducing Yescarta, NoMA has assumed that all CAR T patients are treated with Yescarta and has not considered market shares divided by Yescarta and other potential CAR T treatments.

6 SUMMARY AND CONCLUSION

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 more acceptable higher resource use will be. Quality and uncertainty associated with the documentation and the budget impact are to be included in the overall assessment of interventions.

NoMA's assessment of the benefit criterion:

The clinical efficacy and safety of axi-cel was demonstrated in one pivotal phase II study (ZUMA-1) in adult patients with r/r DLBCL and r/r DLBCL.

The best objective response rate was 74% among the patients who received axi-cel infusion in the ZUMA-1 trial. The rates of PFS and OS at 24 months were 38% and 48%, respectively, in the ITT population. The median OS was 17.4 months (95% CI: 11.6 to not estimable).

The ZUMA-1 trial was designed as a single arm study, and Gilead has conducted an indirect treatment comparison to SCHOLAR-1 using a PS-adjusted analysis. Gilead has access to patient-level data from SCHOLAR-1. The PS-adjustment did not resolve the imbalance in patient characteristics between ZUMA-1 and SCHOLAR-1, and it is unclear how this affects the efficacy results. Furthermore, the follow up ZUMA-1 is short, and there is large uncertainty surrounding long-term outcomes, including overall survival. Consequently, the relative effect of axi-cel vs. salvage chemotherapy cannot be reliably established.

NoMA's assessment of the resource criterion:

The analyses considered the following cost components: leukapheresis and lymphodepleting chemotherapy costs for the axi-cel arm, drug acquisition, and procedure costs for axi-cel and comparator, drug administration costs, hospitalisation and ICU costs, adverse event costs, subsequent SCT costs, follow-up and monitoring costs, and terminal care costs.

The list price for axi-cel is NOK 3 167 606 excluding VAT. The mean total healthcare cost was approximately 3.3 million NOK per patient for axi-cel and 0.5 million NOK per patient for chemotherapy in NoMA's scenario analyses (ITT population), resulting in a mean incremental healthcare cost of about 2.7 million NOK per patient. The costs for pre-treatment and AEs are higher for axi-cel compared to chemotherapy, and the cost for subsequent SCT are lower. The main cost component is the price of axi-cel.

NoMA's assessment of the severity criterion:

Adult DLBCL patients who are refractory or in relapse after two or more lines of systemic therapy have a poor prognosis. NoMA estimated an absolute shortfall of approximately 15-16 QALYs.

NoMA's assessment of budget impact:

NoMA estimated the budget impact for the specialist health services to be around 67 million NOK including VAT in the fifth year after introduction, if all eliglible adult patients with r/r DLBCL and r/r PMBCL are treated with axi-cel.

NoMA's assessment of quality and uncertainty associated with documentation:

The clinical studies of axi-cel are considered to have considerable shortcomings to inform the STA. The ZUMA-1 trial has a single arm study design, is small (101 infused patients), and with and with a follow-up time just above 2 years.

The study lacks a contol arm, and it is therefore not possible to compare outcomes from this trial with outcomes from the comparator trials without a high degree of uncertainty.

Long-term outcomes, both in terms of efficacy and safety, are currently not known. Since CAR-T cell therapy is a new treatment principle, which involves genetic modification of the patient's own T cells, there is a particular uncertainty about long-term effects, including overall survival. Thus far, none of the trials for CAR-T therapy have followed patients long enough to ascertain whether adult patients with r/r DLBCL or r/r PMBCL who have an ongoing response could be considered cured. Additional follow-up data would be needed to evaluate the long-term outcomes with axi-cel and reduce the large amount of uncertainty in the analysis. New and ongoing studies are expected to report in the coming years (described in section 2.1.3), and data from these studies will likely improve decision making.

Norwegian Medicines Agency, 18-06-2019

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APPENDIX 1 SEVERITY AND SHORTFALL

NoMA has quantified the severity of relapsed/refractory DLBCL and PMBCL 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. According to Norwegian clinicians the median age in clinical practice will be about 60 years. This is consistent with a recent abstract of real-world results on another CAR-T product, axi-cel, where the median age was 60 years (7). NoMA will therefore use 60 years as A.
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 (37) in calculating expected remaining lifetime at different ages. This is combined with age-specific quality of life data to calculate quality adjusted remaining lifetime for different ages. Pending reliable Norwegian figures, we use Swedish age-specific quality of life data, with value sets based on UK general population available for EQ-5D, based on Sun et al (23) and Burstrøm et al (21). See Table 44 below.
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. NoMA has conducted an assessment of another CAR-T product aimed at the same Norwegian population. In order to be consistent with the absolute shortfall measure, we have used similar prognosis for r/r DLBCL in the two assessments. Hence, the measure of the the prognosis in the calculation used in this report is based on the measured prognosis from the tisagenleceleucel report.
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).
5) Absolute shortfall (AS) = $QALYs_A - P_A$

Table 44 Calculation of severity

Age	A	60
Expected $QALYs_A$ without disease (undiscounted)	$QALYs_A$	19.3
Expected number of $QALYs_A$ with disease (undiscounted)	P_A	3.8
Number of lost QALYs with disease (absolute shortfall)	AS	15.5

NoMA estimates the absolute shortfall based on current standard care to be approximately 15.5 QALYs

Expected remaining QALYs in the general population

Table 45 shows the expected remaining QALYs and 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 (37) and the age-specific HSUV in the right hand column.

Pending reliable Norwegian figures, the HSUV from two Swedish studies have been used (21, 23). In the studies, Swedish age-specific quality of life data is combined with British population-based EQ-5D value-setting tariffs (38).

HSUV for the age group 21-73 years are taken from Sun et al (23), which is the most recent of the two Swedish studies and has the greatest number of respondents. In this publication, HSUV for other age groups are not presented. For the age group 0-20 years, we have assumed that HSUV are somewhat higher than for the age group 20-33 years. We have set it at 0.89.

In order to obtain fairly even age ranges, we have established an age group 74-88 years based on data from Burstrøm et al (21). For this group, we have calculated a simplified weighted average which gives a HSUV of 0.76 (rounded). The calculation is based on the following: For the age group 74-79 years we assume a HSUV at 0.79 based on Burstrøm et al. For the age group 80-88 years we use a HSUV of 0.74 from Burstrøm et al.

This gives a drop from 0.80 to 0.76 from the age group 55-73 years to the age group 74-88 years. We assume a corresponding (relative) drop from the age group 74-88 years to the last age group 89-105 years, to which we give a HSUV of 0.72.

Table 45 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	69,1	0,89	36	38,0	0,85	72	11,3	0,8
1	68,3	0,89	37	37,2	0,85	73	10,7	0,8
2	67,5	0,89	38	36,3	0,85	74	10,1	0,76
3	66,6	0,89	39	35,5	0,85	75	9,5	0,76
4	65,7	0,89	40	34,7	0,85	76	9,0	0,76
5	64,8	0,89	41	33,8	0,85	77	8,5	0,76
6	63,9	0,89	42	33,0	0,85	78	8,0	0,76
7	63,1	0,89	43	32,2	0,85	79	7,5	0,76
8	62,2	0,89	44	31,4	0,85	80	7,0	0,76
9	61,3	0,89	45	30,6	0,82	81	6,5	0,76
10	60,4	0,89	46	29,8	0,82	82	6,1	0,76
11	59,5	0,89	47	29,0	0,82	83	5,6	0,76
12	58,6	0,89	48	28,2	0,82	84	5,2	0,76
13	57,7	0,89	49	27,4	0,82	85	4,8	0,76
14	56,8	0,89	50	26,7	0,82	86	4,4	0,76
15	56,0	0,89	51	25,9	0,82	87	4,1	0,76
16	55,1	0,89	52	25,1	0,82	88	3,7	0,76
17	54,2	0,89	53	24,4	0,82	89	3,4	0,72
18	53,3	0,89	54	23,6	0,82	90	3,1	0,72
19	52,4	0,89	55	22,9	0,8	91	2,9	0,72
20	51,6	0,89	56	22,1	0,8	92	2,7	0,72
21	50,7	0,87	57	21,4	0,8	93	2,5	0,72
22	49,9	0,87	58	20,7	0,8	94	2,3	0,72
23	49,0	0,87	59	20,0	0,8	95	2,1	0,72
24	48,2	0,87	60	19,3	0,8	96	2,0	0,72
25	47,3	0,87	61	18,6	0,8	97	1,9	0,72
26	46,5	0,87	62	17,9	0,8	98	1,8	0,72
27	45,6	0,87	63	17,2	0,8	99	1,6	0,72
28	44,8	0,87	64	16,5	0,8	100	1,5	0,72
29	43,9	0,87	65	15,8	0,8	101	1,5	0,72
30	43,1	0,87	66	15,1	0,8	102	1,5	0,72
31	42,2	0,87	67	14,5	0,8	103	1,3	0,72
32	41,4	0,87	68	13,8	0,8	104	1,1	0,72
33	40,5	0,87	69	13,2	0,8	105	0,8	0,72
34	39,7	0,87	70	12,5	0,8			
35	38,8	0,85	71	11,9	0,8			

APPENDIX 2 ZUMA-1 VS SCHOLAR-1 COMPARISON

Kite Pharma has conducted SCHOLAR-1 in order to provide a more rigorous comparison of response and overall survival among the patient population studied in ZUMA-1.

SCHOLAR-1 (2) is a retrospective analysis of patients with refractory DLBCL comprised of data from 4 studies or institutions: MD Anderson Cancer Center (MDACC); Mayo Clinic and University of Iowa (MC/IA) Specialized Program of Research Excellence (SPORE); the National Cancer Institute of Canada (NCIC) Cancer Trials Group (CTG) randomized Phase 3 study LY.12; and the French Lymphoma Academic Research Organization (LYSARC) randomized phase 3 Collaborative Trial in Relapsed Aggressive Lymphoma (CORAL) study. Primary abstraction methods targeted patients with relapsed/refractory disease.

For the subject level data, subjects were included in outcome analyses if they were determined to be refractory and had commenced the next line of systemic therapy for refractory disease. Refractory disease was defined as one of the following: PD as best response to any line of chemotherapy; SD as best response to ≥ 4 cycles of first-line or 2 cycles of later-line therapy; or relapse ≤ 12 months following ASCT. Subjects must have received an anti-CD20 mAb, such as rituximab (unless disease was CD20–), and an anthracycline as one of their prior regimens. Subjects with central nervous system (CNS) disease and with year of diagnosis prior to 2000 were excluded.

For the randomized studies, covariates were measured at randomization and, in some cases, later in the treatment course, depending on the study design. For the retrospective databases, covariates were measured at diagnosis and, in some cases, later in the treatment course, depending on data availability and accessibility. The determination of refractory status may have been distant in time from the measurement of the covariate.

Subjects in SCHOLAR-1 may be refractory to therapy at multiple times throughout the treatment course. Therefore, the refractory subgroup was classified in two ways. The first was based on the refractory status at the first time in the treatment course the subject was determined to be refractory (“first refractory categorisation”). The second was based on the refractory status at the last time in the treatment course the subject was determined to be refractory (“last refractory categorisation”).

The “first refractory categorisation” maximizes the subject cases included in the SCHOLAR-1 analysis. The “last refractory categorisation” is consistent with how analyses of the ZUMA-1 study were conducted and therefore more appropriate to be used for comparisons of SCHOLAR-1 with the ZUMA-1 study. Based on “last refractory categorisation”, 593 SCHOLAR-1 evaluable patients were used in this analysis, among which 562 patients were evaluable for survival.

For the Gilead’s base case, the SCHOLAR-1 data were adjusted by removing patients with an Eastern Cooperative Oncology Group (ECOG) score of 2–4 and post-refractory SCT. Patients with ECOG 2-4 were excluded because only patients with ECOG 0–1 were recruited in the ZUMA-1 trial based on the trial

protocol. Patients who received post-refractory SCT were excluded because a Norwegian clinical expert estimated that only a small share of patients in the SoC arm would receive SCT. Median OS in the base case scenario was 4 months. For the additional scenario analyses (scenario 1: no adjustments, scenario 2: Propensity score (PS)-adjustment, scenario 3: crude adjustment without ECOG 2-4) the median was 6 months (Figure 32). PFS data were not available in SCHOLAR-1.

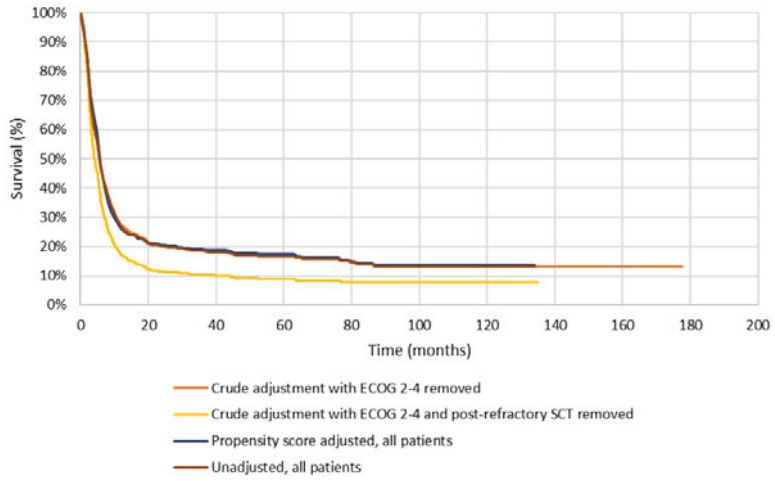

Figure 32 Overall survival in SoC- comparison of SCHOLAR-1 datasets.

NoMA focused on the PS-adjusted analysis as a method of reducing the bias of estimating relative treatment efficacy based on single arm trials or observational studies. The propensity score is the probability of treatment assignment as a function of a set of observable covariates. Inverse probability of treatment weights (IPTW) was used to adjust OS for SCHOLAR-1 patients. Every person was weighted by the inverse probability, i.e. propensity score, of receiving the treatment (Yescarta in this case). The IPTW weights were implemented based on the estimated PS, as follows:

IPTW = 1⁄(1 − PS) for the untreated, and

IPTW = 1⁄PS for the treated.

NoMA has requested an updated PS-adjusted comparison of ZUMA-1 vs SCHOLAR-1 where the following SCHOLAR-1 patients are retained for the new analysis:

- Patients with patient characteristics (as listed below) collected within 3 months from the refractory status (as per company's analysis)
- Patients with ECOG 0-1
- Patients with known disease stage status
- Patients with "first refractory categorization" as opposed to "last refractory status". This analysis retains more SCHOLAR-1 patients.
- Patients with subsequent SCT.

The changes in the sample size are recorded in Table 46 below. In addition, NoMA requested that the OS is measured from the start of chemotherapy for patients who also received SCT as opposed to the start of SCT as proposed by Gilead. The application of NoMA's inclusion criteria improved the survival in SCHOLAR-1 (Figure 33).

Table 46 Patient attrition SCHOLAR-1

Full dataset	**593**
Unknown disease stage	218 (375 excluded)
ECOG status not 0–1	181 (37 excluded)
Patients with or without subsequent SCT	181 (0 excluded)
Patients with "first refractory categorization" or other	181 (0 excluded)
Final sample size	181

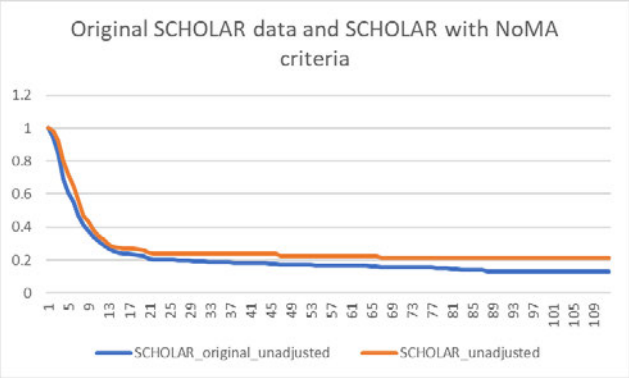

Figure 33 NoMA's inclusion criteria (orange line) improves survival in SCHOLAR-1.

Propensity scores were next estimated by logistic regression with the following predictors:

- Sex (M, F)
- Age at determination of refractory status
- Disease stage (I–II, III–IV)
- Number of lines of prior chemotherapy prior to determination of refractory disease (1, 2, 3, 4+)
- Relapse within 12 months of ASCT (Y/N)
- History of primary refractory disease (Y/N)
- Refractory to at least 2 consecutive lines of therapy (Y/N)

NoMA also requested that the following variables were removed from the analysis:

- Autologous or allogeneic SCT at any time after treatment for refractory disease (Y/N). As mentioned above, this variable is affected by treatment (i.e. the success of chemotherapy determines the chance of receiving SCT) and it is not appropriate to include this varible in PS-adjustment.

- The IPI score. The IPI score includes factors such as age, ECOG, disease stage- factors which are already considered in the selection and PS-adjustment. There is more missing data for IPI than the disease status, and it is important to retain many patients.

Patient characteristics for ZUMA-1 ITT, ZUMA-1 mITT, SCHOLAR-1, PS-adjusted SCHOLAR-1 based on ITT population and PS-adjusted SCHOLAR-1 based on mITT population are presented in

Table 47 and

Table 48. The tests showed that most covariates in the adjusted SCHOLAR-1 arm and the ZUMA-1 arm where not significantly different (t-test) after adjustment. There is no universally accepted threshold of the standardized difference that can be used to indicate important imbalance. A standard difference that more than 10%/less than -10% is sometimes described in the literature. The median and mean bias is around 24% and 50%, respectively, in these cases indicating that there is still some imbalance remaining after matching.

Table 47 Covariate impalance testing mITT population

Variable	ZUMA mITT	SCHOLAR unadj.	PS adjusted SCHOLAR mITT	Standardized diff. (%bias) unmatched /matched	% reduct bias	t-test t unmatched /matched	t-test p>|t| unmatched /matched
Female	0.32	0.35	0.33	-6.2/-1.4	78.2	0.51/-0.06	0.61/0.95
Age (years)	56	50.1	55	48.7/8.4	82.7	4.0/0.38	0.00/0.702
Stage category							
III–IV	0.83	0.66	0.73	41.1/24.2	41.1	3.3/1.2	0.001/0.238
Relapse within 12 months of ASCT	0.23	0.15	0.09	21.0/34.9	-66.3	1.8/1.5	0.08/0.13
Primary refractory	0.03	0.48	0.12	-120/-24.9	79.2	-8.9/-2.0	0.00/0.05
Refractory to at least 2 consecutive lines of therapy	0.89	0.55	0.88	81.9/2.3	97.2	6.4/0.1	0.00/0.89
Number of lines of prior chemotherapy prior to determination of refractory disease							
1	0.03	0.3	.03				
2	0.27	0.7	.97	-94.3/-155.6	-64.9	-7.7/-7.7	0.00/0.00
3	0.31	0.00	0.00	93.4/93.4	0.00	8.9/9.7	0.00/0.00
4+	0.4	0.00	0.00	114.5/114.5	0.00	10.9/11.9	0.00/0.00

Sample	Ps R2	LR chi2	p>chi2	MeanBias	MedBias
Unmatched	0.206	35.2	0	69	81.9
Matched	0.074	5.4	0.369	51.1	24.9

Notes: T-test for the unmatched is an unweighted regression on the entire sample, and for PS-adjusted populations the t-test for the regression is weighted using the propensity score weights. The standardized % bias is the % difference of the sample means in the ZUMA and SCHOLAR samples as a percentage of the square root of the average of the sample variances in ZUMA and SCHOLAR. Overall measure of covariate imbalance is presented as pseudo R2 from the propensity score on all variables; P-values of the likelihood-ratio test of joint insignificance of all the regressors; mean and median bias as summary indicators of the absolute bias.

Table 48 Covariate imbalance testing. ITT population

Variable	ZUMA ITT	SCHOLAR unadj.	PS adjusted SCHOLAR ITT	%bias unmatched /matched	% reduct bias	t-test t unmatched /matched	t-test p>|t| unmatched /matched
Female	0.32	0.35	0.30	-10.9/-0.5	95.2	-0.92/-0.02	0.36/0.98
Age (years)	56	50.1	54	48.1/14.7	69.5	4.0/0.69	0/0.49
Stage category							
III–IV	0.83	0.66	0.75	38.5/17.7	54	3.2/0.9	0.002/0.372
Relapse within 12 months of ASCT	0.23	0.15	0.09	17.9/33.4	-86.6	1.5/1.5	0.124/0.133
Primary refractory	0.03	0.48	0.11	-121.2/23.7	80.5	-9.5/-2.1	0.00/0.04
Refractory to at least 2 consecutive lines of therapy	0.89	0.55	0.89	82.5/0.9	98.9	6.7/0.1	0.00/0.96
Number of lines of prior chemotherapy prior to determination of refractory disease							
1	0.03	0.3	0.02				
2	0.27	0.7	0.98	-94.2/-156	-65.5	-8/-8	0.00/0.00
3	0.31	0	0	89.1/89.1	0	8.5/3.2	0.00/0.00
4+	0.4	0	0	119.9/119.9	0	11.4/4.3	0.00/0.00

Sample	Ps R2	LR chi2	p>chi2	MeanBias	MedBias
Unmatched	0.206	37.4	0	69	81.9
Matched	0.069	5.5	0.364	50.6	23.7

Notes: T-test for the unmatched is an unweighted regression on the entire sample, and for PS-adjusted populations the t-test for the regression is weighted using the propensity score weights. The standardized % bias is the % difference of the sample means in the ZUMA and SCHOLAR samples as a percentage of the square root of the average of the sample variances in ZUMA and SCHOLAR. Overall measure of covariate imbalance is presented as pseudo R2 from the propensity score on all variables; P-values of the likelihood-ratio test of joint insignificance of all the regressors; mean and median bias as summary indicators of the absolute bias.

Surprisingly, PS-adjustment of SCHOLAR-1 population to mITT and ITT populations in ZUMA-1 did not affect the OS for salvage therapy. In Figure 35 PS-adjusted OS curves are aligned with the unadjusted curves for SCHOLAR-1 (where NoMA's inclusion criteria were applied), indicating that modification of inclusion criteria had the biggest impact (Figure 33). OS Kaplan Meier curves for ZUMA-1 and PS-adjusted SCHOLAR are presented below (Figure 34). SCHOLAR-1 curves were almost identical between the mITT and ITT PS- adjustments with median OS of 6.4 months. Median OS in ZUMA-1 (ITT) was 16.3 months, and has not been reached in the mITT population.

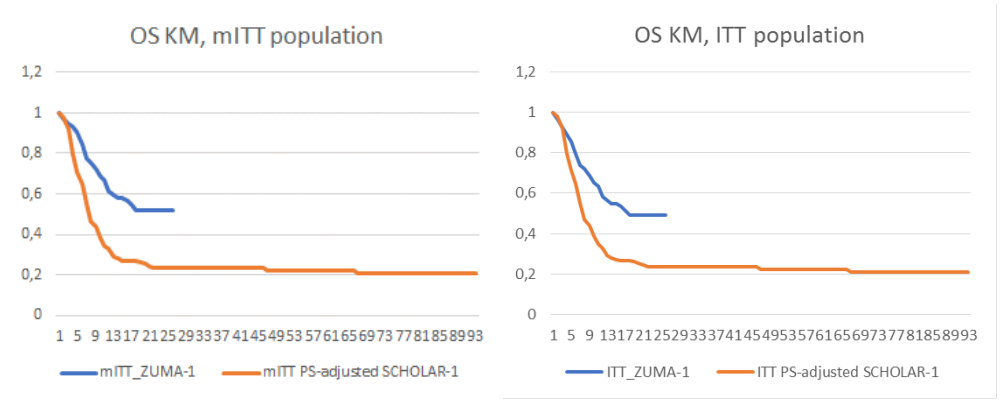

Figure 34 OS KM curves for ZUMA-1 (mITT population, left and ITT population, right) and PS-adjusted SCHOLAR-1.

Lastly, NoMA has requested PS-adjusted comparison of ZUMA-1 vs CORAL extension studies which were one of the components of SCHOLAR-1. The main reason was that in SCHOLAR-1, the registries included all patients who had DLBCL, irrespectively of their performance status, co-morbidities, and life expectancy. Both CORAL and ZUMA-1 on the other hand, are clinical studies with specified inclusion and exclusion criteria, hence including more selected patient populations expected to be fitter than those included in SCHOLAR-1. Figure 35 presents overall survival curves for CORAL (mITT PS-adjusted).

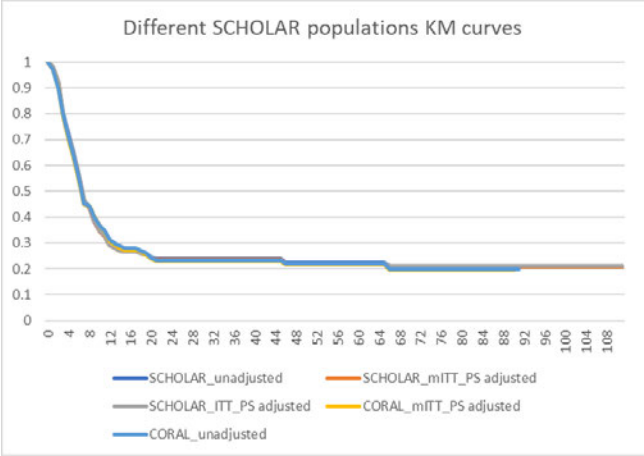

Figure 35 Comparison of OS for salvage therapy with NoMA's inclusion criteria (SCHOLAR_unadjusted and CORAL_unadjusted) and NoMA's PS-requested adjustments (SCHOLAR_mITT_PS adjusted and CORAL_mITT_PS adjusted).

NoMA's assessment

SCHOLAR-1 is the largest international, multicohort retrospective research study that characterized response rates and survival of salvage chemotherapy among patients with refractory DLBCL. The key advantage of using SCHOLAR-1 as the source for the comparator data was that the included patients

matching the inclusion criteria for refractoriness in ZUMA-1 and that Gilead has access to patient-level data from both arms.

For the purpose of the PS-adjusted analysis, Gilead selected patients who had patient characteristics collected within 3 months from the refractory status. This was important as the PS analysis relies on the quality, timing and the number of variables included in the model. In addition, patients with ECOG 2-4 were excluded from SCHOLAR-1 to match ZUMA-1. Gilead also excluded patients from SCHOLAR-1 with unknown disease stage and those who received a subsequent SCT. Exclusion of patients with unknown disease status or patients with disease status collected 3 months or more of the date of refractory determination resulted in the biggest sample loss (375/593 patients excluded).

During the review process, NoMA requested an updated PS-analysis where patients with subsequent SCT are retained in SCHOLAR-1. In the analysis provided by Gilead, those patients were excluded as according to the clinical experts, the proportion of patients who would receive SCT in clinical practice is much lower than 29% reported in SCHOLAR-1. NoMA believes that exclusion of those patients underestimates the efficacy in the SCHOLAR-1 arm as those patients would likely have had a better prognosis as a prerequisit for SCT is having achieved a response to treatment and being medically fit for transplant. In addition, NoMA considers the general patient population in clinical practice not representative of the patient population that would be eligible for axi-cel. In ZUMA-1 patients were fitter and would more likely be eligible for SCT. Hence, it is not appropriate to remove patients from SCHOLAR-1 who received post-chemotherapy SCT. In the new analysis, OS was measured from the beginning of chemotherapy in the patients who subsequently received SCT as opposed to from the timing of SCT. This is because the whole length of the comparator treatment pathway (chemotherapy + SCT) is used in the model to calculate costs and effects as opposed to a single component (chemotherapy or SCT). The application of NoMA's inclusion criteria improved the survival in SCHOLAR-1 (Figure 33).

For the updated PS-adjusted analysis, NoMA also requested that individual components of the IPI score (i.e. age and disease stage) are used for weighting as opposed to the IPI score itself. The reason for this request is that there is more missing data for IPI than the disease status, and it was important to retain as many patients as possible. The use of individual variables did not affect the analysis as the survival in SCHOLAR-1 remained similar to the one where NoMA's selection criteria were applied.

After applying NoMA's includion criteria, but before PS-adjustment, patients in SCHOLAR-1 were younger (50 years old vs 56 in ZUMA-1 mITT), had better disease stage (34% in stage I-II as opposed to 18% in ZUMA-1 ITT) and had less prior lines of chemotherapy (100% had 1-2 lines, as opposed to 30% in ZUMA-1). There were also large imbalances in percentage of patients who relapsed within 12 months after ASCT, who were primary refractory or refractory to at least 2 consecutive lines of therapy.

After PS-adjustment patient characteristics were generally more aligned but the remaining bias was not fully eliminated (the median and mean bias was around 24% and 50% in the adjusted analysis). Since there are no patients with more than two previous lines of chemotherapy in SCHOLAR-1 after applying NoMA's inclusion criteria, the model forces a larger proportion of patients in SCHOLAR-1 to have two prior lines of chemotherapy to be aligned with ZUMA-1. Consequently, the proportion of patients in

SCHOLAR-1 with two prior lines increased from 70% (unadjusted analysis) to 98% (PS-adjusted analysis) as compared to 27% in the ZUMA-1 ITT population. On the other hand, more patients in PS-adjusted SCHOLAR-1 had a primary refractory status (11% vs 3% in the ITT of ZUMA-1), and primary refractory disease has been found to be a significant risk factor for failing to respond to second-line therapy (11). In addition, the analysis did not adjust for disease subtypes. In the mITT of ZUMA-1, 8 patients (8%) had PMBCL and 16 (16%) had TFL. In the SCHOLAR-1 publication, the proportions were much lower (2.2% and 4.2%, respectively). The outcomes for patients with r/r aggressive NHL are expected to be similar, regardless of disease subtype. PMBCL is considered a subtype of DLBCL, but affects mainly young adults (median age of 35 years) and predominantly women. FL on the other hand is the most common indolent (slow-growing) form of B-cell NHL, but turns more aggressive with a worse prognosis than FL after histological transformation to DLBCL (TFL). It is unclear how these imbalances in patient characteristics affected the efficacy results.

Overall, NoMA accepts SCHOLAR-1 as a source of historical control for ZUMA-1. NoMA has focused on the PS-adjusted analysis as a method of reducing the bias of estimating relative treatment efficacy based on single arm trials or observational studies. Due to availability of patient-level data, individuals from SCHOLAR-1 with missing data or with mismatched patient characteristics could be excluded from the data set. Nevertheless, it is noted that the PS-adjustment did not result in perfectly aligned patient characteristics between ZUMA-1 and SCHOLAR-1. It is also noted that the populations in SCHOLAR-1 (mix of observational and experimental studies) and ZUMA-1 will intristically never be fully aligned in terms of eligibility criteria or treatment conduct. For instance, ZUMA-1 included only patients with adequate renal, hepatic, pulmonary and cardiac function. In contrast, it is assummed that inclusion criteria in the observational studies were less stringent.

Lastly, NoMA has requested PS-adjusted comparison of ZUMA-1 vs CORAL extension studies which were one of the components of SCHOLAR-1. Interestingly, the mITT PS-adjusted OS results for SCHOLAR-1 and CORAL are almost identical, suggesting that CORAL is the key study influencer after applying NoMA's selection criteria. The comparison with CORAL will not be tested in a scenario analysis.

VEDLEGG 1 KOMMENTARER FRA PRODUSENT

Fra: Gilead Sciences Norway AS

Til: Beslutningsforum (Bestillerforum/Sykehusinnkjøp)

12.04.2019

Yescarta - CAR-T - Gilead sine synspunkter

Gilead viser til Legemiddelverkets vurdering av Yescarta. Gilead er overrasket over den negative tilnærmingen til Yescarta fra Legemiddelverkets side. Vi er ikke kjent med andre europeiske land som har tilnærmelsesvis samme høye nivå på kostnadseffektiviteten (cost/QALY eller ICER) som Legemiddelverket.

Der nærliggende land som Sverige og Finland ender opp med henholdsvis 1,0 mill. SEK og 69 000 Euro i ICER, ender Legemiddelverket opp med 1,4-1,6 mill. kr pr vunnet QALY, mer enn det dobbelte som i Finland, ut fra samme innsendte modell. Vi mener at Legemiddelverket systematisk på svakt og uklart grunnlag undervurderer effekten av Yescarta og overvurderer effekten av kjemoterapi med ikke-kurativ behandlingsintensjon.

Column1	Sweden/TLV	Finland/Fimea	UK/NICE	UK/ERG	NOMA ITT	Gilead ITT
QALYs Axi-cel	5,48	6,71			4,93	6,52
QALYs BSC	2,35	1,36			2,96	1,3
Net QALYs won Axi-cel	3,14	5,35	4,5	3,78	1,97	5,22
ICER	977 908 SEK	68 372 EUR	[redacted]	[redacted]	1,4 mill. NOK	0,635 mill. NOK
At same list prices in all countries						

Legemiddelverket har også gitt uttrykk for at ettårsdataene ikke er troverdige, mens andre land fatter beslutninger og gjør vurderinger på basis av disse dataene. Tilogmed med toårsdataene tilgjengelige, som bekrefter den positive resultatene fra ettårsdataene, mener SLV at dataene er for umodne for beslutninger. Gilead oppfatter tilnærmingen som radikal. Da toårsdataene for Yescarta ble publisert tidlig i desember 2018, ble det i Lancet Oncology 2. desember[2] publisert en kommentarartikkel av Stephen J Schuster som gir uttrykk for en helt annen og positiv tilnærming til CAR-T generelt og Yescarta spesifikt enn Legemiddelverket legger til grunn. Blant annet uttaler Schuster at vi begynner å se "the emergence of plateaus in curves", hvilket betyr at Kaplan-Meier kurvene flater ut hvilket igjen indikerer at de som er overlevere utover en viss minimumstid kan ansés som kurert, med dødelighet og livskvalitet tilnærmet bakgrunnsbefolkningen;

[2] *www.thelancet.com/oncology Published online December 2, 2018 http://dx.doi.org/10.1016/S1470-2045(18)30900-8

"*...what is remarkable across anti-CD19 CAR T-cell trials in relapsed or refractory diffuse large B-cell lymphoma is the consistent durability of responses, with ongoing responses in 39 (39%) of 101 patients at a median of 27,1 months' follow-up in ZUMA-1[5] and 35 (35%) of 99 patients at a median of 19,3 months' follow-up in JULIET;[3] the emergence of plateaus in curves for response duration and progression-free survival beyond 6 months; the absence of late or unexpected gene-therapy-related events; and the unique but manageable toxicities (ie, cytokine release syndrome and neurotoxicity[1,3,5,7]). Investigators at the University of Pennsylvania previously reported a cohort of 14 patients with relapsed or refractory diffuse large B-cell lymphoma (NCT02030834), with a median follow up of 28,6 months, who were treated with a 4-1BB-driven CAR T-cell product. For seven (50%) of the 14 patients who were responders (six complete responses and one partial response), median follow up is now 46,8 months, with the longest follow-upreaching 54,6 months. Of the six patients with complete responses, only one had a relapse (after 32,2 months in continuous remission). In addition to long-term safety, evidence of B-cell recovery during these sustained remissions was also noted (as in Locke and colleagues' study), with evidence of immunoglobulin recovery in some patients too.*"

Gilead har valgt en modell som karakteriseres ved platåer i de modellerte overlevelseskurvene. Legemiddelverket avslår en slik tilnærming, til tross for nevnte kommentarartikkel basert på datautviklingen.

Tilnærmingen til Yescarta er slående ulik mellom TLV og SLV. TLV sier bla. følgende om Yescarta[3]:

"These new, advanced gene therapies show great potential and will have a significant impact on cancer treatment. Nevertheless, these substantial uncertainties must be addressed through follow up of Yescarta in order to establish how the treatment is used in clinical practice. This observation should be continuous and will help reduce uncertainties associated with the treatment effect."

Legemiddelverket uttaler til sammenligning følgende i rapporten:

"The clinical studies of axi-cel are considered to have considerable shortcomings to inform the STA. The ZUMA-1 trial has a single arm study design, is small (101 infused patients), and with short median follow-up time (27.1 months). The study lacks a control arm, and it is therefore not possible to compare outcomes from this trial with outcomes from the comparator trials without a high degree of uncertainty. Long-term outcomes, both in terms of efficacy and safety, are currently not known. Since CAR-T cell therapy is a new treatment principle, which involves genetic modification of the patient's own T cells, there is a particular uncertainty about long-term effects, including overall survival. Thus far, none of the trials for CAR-T therapy have followed patients long enough to ascertain whether adult patients with r/r DLBCL or r/r PMBCL who have an ongoing response could be considered cured. Additional follow-up data would be needed to evaluate the long-term outcomes with axi-cel and reduce the large amount of uncertainty in the

[3] https://www.tlv.se/download/18.6c394216710055f26d12bd/1542882905184/yescarta_english_webbtext.pdf

analysis. New and ongoing studies are expected to report in the coming years (described in section 2.1.3), and data from these studies will likely improve decision making."

Det er mange enkeltheter i Legemiddelverkets vurdering vi finner overraskende. Blant annet at langtidsoverlevelsen for Yescarta i Legemiddelverkets tilnærming baseres på overlevelsen ved dagens behandling/komparator. Det blir ikke overraskende at forskjellen mot komparator blir lav når en legger dette til grunn. Legemiddelverket tar i dette resonnementet heller ikke hensyn til de dataene som ble presentert i desember 2018 med en medianoppfølging for Yescarta på 27,1 måneder, der man ved 24 måneder ser at 50.5% av pasientene fremdeles lever. Medianoverlevelsen for dagens standardbehandling er 6,3 måneder ihht. SCHOLAR-1 studien.

Det har også fremkommet konkrete innspill fra OUS som tydeliggjør at det er direkte feil og mangler i rapporten, som setter spørsmål ved beslutningsgrunnlagets kvalitet. Både med hensyn til kostnadsberegninger og overlevelse.

Gilead har merket seg at to kliniske eksperter på Dagens Medisin sitt åpne prioriteringsmøte 21.3.2019 uttalte at de oppfattet at Legemiddelverket systematisk valgte de dårligste forutsetningene for nye legemidler ved gjennomføring av metodevurderinger. I Gilead føler vi det på samme måte når vi sammenligner metodevurderingene som er gjennomført i mange europeiske land med utgangspunkt i samme modell.

Yescarta er et orphan drug, og Yescarta tilfredsstiller to av tre kriterier i retningslinjene for evaluering av legemidler med særskilt små pasientgrupper med svært alvorlig tilstand. Yescarta tilfredsstiller kravet om særskilt liten pasientgruppe og stor forventet nytte Det tredje kriteriet om antall tapte QALYS er ikke fullt oppfylt da antall tapte QALYS for disse pasientene er 17-18 og ikke 30 tapte gode leveår. Likevel er 17-18 taptegode leveår betydelig i alvorlighetssammenheng. Legemiddelverket tar ikke hensyn tll dette ved evalueringen av Yescarta.

[redacted]

Med vennlig hilsen

Erik Stene (sign)

Gilead Sciences Norway AS

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