ID2019_143

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)

Update of the previous health economic evaluation

09-11-2020

Statens legemiddelverk

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 (NoMA) 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.

NoMA 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).

1 BACKGROUND

This single technology assessment (STA) represents an update of the STA of axicabtagene ciloleucel (axi-cel, Yescarta) for the treatment of second or later relapsed/refractory diffuse large B cell lymphoma (DLBCL) and primary mediastinal large B-cell lymphoma (PMBCL) of 18th June 2019 (1). Two-year follow-up data from the pivotal phase II study (ZUMA-1) were provided in the original submission, and the short follow-up time was an important source of uncertainty in the cost-utility model. Decision Forum (Beslutningsforum) decided not to introduce axi-cel in September 2019, due to uncertainty surrounding the long-term outcomes and the high cost of treatment in relation to its documented effect.

In this updated STA, NoMA has assessed axi-cel based on 3-year OS data from ZUMA-1 according to the request specifications from Ordering Forum (Bestilleforum, request number ID2019_143):

En oppdatering av den opprinnelige analysen med tilhørende modell med nye effektdata og oppdaterte kostnader gjennomføres ved Statens legemiddelverk for axicabtagene ciloleucel (Yescarta) til behandling av diffust storcellet B-celle lymfom, primært mediastinalt B-celle lymfom og transformert follikulært lymfom.

2 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 : *ID2019_143: En oppdatering av den opprinnelige analysen med tilhørende modell med nye effektdata og oppdaterte kostnader gjennomføres ved Statens legemiddelverk for axicabtagene ciloleucel (Yescarta) til 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. 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 (2). 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.

Efficacy results provided in the original submission (1):

At the data cutoff date of 11-Aug-2018 (2-year data), 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 investigator-assessed PFS was 5.9 months (95% CI: 3.3–15.0 months), 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 36% and 48% at 24 months. The median investigator-assessed PFS was 6.3 months (95% CI: 4.0 to 12.4), and the median OS was 17.4 months (95% CI: 11.6 to not estimable).

Efficacy results provided in the updated submission:

In the updated submission, the cost-utility model was updated with 3-year OS data from ZUMA-1 (data cut off 11.08.2019) with a median follow-up of 39.1 months. Median OS in the phase 2 mITT population was 25.8 months (95% CI: 12.8 – not evaluable) and the 3-year OS rate was 47%. Four additional deaths occurred relative to the 2-year data; one of those was due to myelodysplastic syndrome deemed related to prior therapy and 3 were due to lymphoma progression. The ITT population included 10 additional non-infused patients. Median OS in the phase 2 ITT population was 17.4 months (95% CI: 11.6 – NE) and the 3-year OS rate was 44.1%.

Three-year PFS data have not been provided as according to Gilead, the information on progression has not been systematically collected after the primary analysis. Consequently the updated cost-utility model is based on 3-year OS data and 2-year PFS data.

Comparator data

The ZUMA-1 trial was designed as a single arm study. Data for the comparator arm are collected from the SCHOLAR-1 trial (3) , the largest patient-level pooled retrospective meta-analysis that characterized 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 in the original and the updated submission, 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). PFS data were not available in SCHOLAR-1.

No new comparator data were provided in the updated submission. An additional OS analysis for the comparator using a reweighted dataset for SCHOLAR-1 was, however, submitted.

Safety

Safety results provided in the original submission:
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.

No new safety data based on the 3-year data cut off were provided in the updated submission.

Cost effectiveness

In the updated submission, Gilead has updated the cost-effectiveness model used in the original submission with the new 3-year OS data available for axi-cel. Some modeling assumptions were also revised, partly based on the comments that NoMA had during Gilead's original submission for axi-cel. In particular, Gilead used some of NoMA's base case settings for costs and utilities. NoMA has made the following changes to Gilead's updated analysis:

- NoMA considers both the ITT population (enrolled patients) and the modified ITT (mITT) population (infused patients) relevant for decision making. In contrast, Gilead based its updated base case on the mITT population.
- Patients with post-refractory SCT were included in the SCHOLAR-1 dataset, and NoMA's requested PS- adjusted analysis was used to estimate OS for chemotherapy.
- OS for axi-cel is extrapolated with a spline function with 2 knots as opposed to a mixture cure Weibull model. In addition, the modelled mortality rate for long-term survivors on axi-cel has

been set equal to the mortality rate of general population from 84 months and beyond, which represents the time point at which patients are assumed to be "cured" from excess mortality.
- OS for chemotherapy is extrapolated with a spline function with 1 knot as opposed to Gompertz single parametric curve. The modelled mortality rate for long-term survivors on chemotherapy is assumed to be equal to the mortality rate of the general population at 84 months in the model.
- PFS for axi-cel is extrapolated with single parametric Gompertz function in agreement with Gilead. NoMA has adjusted PFS for background mortality, in contrast with Gilead's assumption that patients who remain progression-free for 2 years do not experience any mortality nor progression events for a period of close to 20 years.

NoMA has estimated an incremental cost-effectiveness ratio for axi-cel compared to chemotherapy.
In NoMA's base case analyses, the additional costs for axi-cel compared to chemotherapy, with public list prices excl. VAT for medicines, are:
- 1.04 million NOK per QALY gained in the ITT population (enrolled patients) and 1.06 million NOK per QALY gained 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, as the enrolled patients in ZUMA-1 are highly selected. 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 PS-adjusted SCHOLAR-1 dataset, the proportion of patients who received subsequent SCT increased, and therefore long term survival increased as well. In scenario analyses where patients with 1) subsequent stem cell transplant (SCT) and ECOG 2-4 were removed from the SCHOLAR-1 data, and 2) only ECOG 2-4 were removed, the incremental cost-effectiveness ratios (ICERs) reduced to 0.7 and 0.85 million NOK per quality-adjusted life year (QALY) gained, respectively.

Budget impact
NoMA estimated the budget impact of the total healthcare costs for the specialist health services to be around 68 million NOK (ITT analysis) and 75 million NOK (mITT analysis) 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. The budget impact has not changed much from the original assessment.

NoMA´s overall assessment

The updated submission is based on 3-year OS data as opposed to 2-year data in the original submission. The fact that PFS has not been updated is considered a limitation as different follow-up times lead to inconsistencies in long-term extrapolation of OS and PFS (chapter 4.4).

NoMA notes that the updated 3-year data supports NoMA's critique in the original submission, as the tail of the observed OS has decreased by additional 3% between the 2-year and 3-year data cut-off, thereby invalidating Gilead's original assumption that 50% of all infused patients would be "cured" by month 26. Consequently, NoMA considers the mixture cure model (MCM) approach by Gilead to be too optimistic, and chooses to extrapolate ZUMA-1 OS data with a spline model that provides a good fit to observed OS

data and does not assume that survival returns to general population levels shortly after the ZUMA-1 follow-up time as assumed by the Weibull MCM. At the same time, NoMA does not exclude the possibility of a cure following axi-cel infusion and considers patients that survived for 84 months to be “cured” of excess mortality. At 84 months the mortality in long-term survivors (about 40% of patients) returns to the mortality of the general population. The Norwegian experts contacted by NoMA also believe in a curative potential of axi-cel. They emphasize that, provided that axi-cel performs the same in clinical practice as in ZUMA-1, the projected 40% cure fraction would be an important advance over the currently limited treatment options.

The estimated incremental survival benefit and cost-effectiveness profile for axi-cel has improved on the basis of the updated OS data, compared to the original evaluation. In the ITT population, the QALY gain increased from 1.97 to 2.7, and the ICER decreased from 1.39 million NOK to 1.04 million NOK. In the mITT population, the QALY gain increased from 2.36 to 2.94, and the ICER decreased from 1.28 million NOK to 1.06 million NOK.

Overall, although the updated submission is based on less immature OS data, the limitations identified in the original assessment have not been eliminated. ZUMA-1 study is a single arm study of small size (101 infused patients) which 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 and when 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.

Randomized controlled trials with longer patient follow-up are needed to resolve the uncertainty surrounding the long-term outcomes with axi-cel and the incremental survival benefit compared to standard care.

3 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 *ID2019_143: En oppdatering av den opprinnelige analysen med tilhørende modell med nye effektdata og oppdaterte kostnader gjennomføres ved Statens legemiddelverk for axicabtagene ciloleucel (Yescarta) til 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 (2). 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.

Effektresultater i opprinnelig innsending (1):

Ved datakutt 11-08-2018 (2-års data) 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 endepunkt), og 74 % (54 % CR) basert på vurdering av en uavhengig komité. Utprøver-vurdert median PFS var 5,9 måneder (95% KI: 3,3 – 15,0) 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 36 % og 48 % ved 24 måneder. Utprøver-vurdert median PFS var 6,3 måneder (95 % KI: 4,0 – 12,4) og median OS var 17,4 måneder (95 % KI: 11,6 – ikke oppnådd).

Effektresultater i oppdatert innsending:

I den oppdaterte innsendingen er den helseøkonomiske modellen oppdatert med 3-års OS-data fra ZUMA-1 (datakutt 11.08.2019) med en median oppfølgingstid på 39,1 måneder. Median OS i fase 2 mITT-populasjonen var 25,8 måneder (95% KI: 12,8 - ikke oppnådd) og 3-års OS-rate var 47 %. Fire ekstra dødsfall skjedde i forhold til 2-års dataene; en av disse skyldtes myelodysplastisk syndrom som ble ansett relatert til tidligere behandling, og 3 skyldtes progresjon av lymfom. ITT-populasjonen inkluderte 10 ekstra pasienter som ikke fikk infusjon. Median OS i fase 2 ITT-populasjonen var 17,4 måneder (95 % KI: 11,6 – ikke oppnådd) og 3-års OS-rate var 44,1 %.

Tre-års PFS-data er ikke rapportert. Ifølge Gilead har informasjon om progresjon ikke blitt samlet inn systematisk etter den primære analysen. Følgelig er den oppdaterte helseøkonomiske modellen basert på 3-års OS-data og 2-års PFS-data.

Komparatordata:

ZUMA-1 har enkeltarmet studiedesign. Data for komparator er hentet fra studien SCHOLAR-1 (3), 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, både i opprinnelig og oppdatert 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). PFS-data var ikke tilgjengelig i SCHOLAR-1.

Det er ikke levert nye komparatordata i den oppdaterte innsendingen. En tilleggsanalyse av OS for komparator ved bruk av et nytt vektet datasett fra SCHOLAR-1 ble imidlertid levert.

Sikkerhet

Sikkerhetsresultater i opprinnelig innsending:
De fleste får bivirkninger etter infusjon av axi-cel. Etter hvert som de aktiverte CAR-T cellene proliferer 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 bivirkningene 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.

Ingen nye sikkerhetsdata basert på 3-års datakutt ble levert i oppdatert innsending.

Kostnadseffektivitet

Gilead har oppdatert den helseøkonomiske modellen som ble brukt i opprinnelig innsending med nye 3-års OS-data for axi-cel. Noen av antagelsene i modellen er også justert, delvis basert på kommentarene Legemiddelverket hadde i forrige metodevurdering av axi-cel. Dette gjelder særlig kostnader og nyttevekter, der Gilead har brukt de samme forutsetningene som Legemiddelverket brukte i forrige metodevurdering. Legemiddelverket har gjort følgende endringer i Gileads oppdaterte analyse:

- Legemiddelverket anser både ITT-populasjonen (innrullerte pasienter) og den modifiserte ITT (mITT) -populasjonen (infuserte pasienter) som relevante for beslutningstaking. Gilead baserer sin oppdaterte base case på mITT-populasjonen.
- Pasienter som fikk etterfølgende SCT ble beholdt i SCHOLAR-1 datasettet, og PS-justert analyse ble brukt til å estimere OS.
- OS for axi-cel er ekstrapolert med en spline funksjon med 2 knots, og ikke med en Weibull mixture cure modell. I tillegg er modellert dødelighet for langtidsoverlevere i axi-cel-armen satt lik dødeligheten for den generelle befolkningen fra 84 måneder og utover. 84 måneder representerer tidspunktet da pasienter antas å bli "kurert" fra overdødelighet.

- OS for kjemoterapi er ekstrapolert med en spline funksjon med 1 knot, og ikke med en Gompertz parametrisk kurve. Modellert dødelighet for langtidsoverlevere i kjemoterapi-armen antas å være lik dødeligheten for den generelle befolkningen etter 84 måneder.
- PFS for axi-cel er ekstrapolert med en parametrisk Gompertz funksjon i samsvar med Gileads modellering. Legemiddelverket har deretter justert PFS for bakgrunnsdødelighet, i motsetning til Gileads antagelse om at pasienter som er progresjonsfrie i 2 år, deretter ikke dør eller progredierer i en periode på nærmere 20 år.

Legemiddelverket har estimert en inkrementell kostnad-effektbrøk for axi-cel sammenlignet med kjemoterapi. I Legemiddelverkets analyser, med dagens maksimalpriser for legemidlene, er merkostnad for axi-cel sammenlignet med kjemoterapi:

- 1,04 millioner NOK per vunnet kvalitetsjusterte leveår (QALY) for innrullerte pasienter (ITT).
- 1,06 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. 0,7 og 0,85 millioner NOK per vunnet QALY.

Budsjettkonsekvenser
Legemiddelverket har estimert at budsjettvirkningen for sykehusenes totale budsjett vil være om lag 68 millioner NOK (ITT-analyse) og 75 millioner NOK (mITT-analyse) per år i år fem, hvis axi-cel innføres til behandling av voksne pasienter med r/r DLBCL og r/r PMBCL.

Legemiddelverkets totalvurdering
Den oppdaterte metodevurderingen er basert på 3-års OS-data, mens den opprinnelige metodevurderingen var basert på 2-årsdata. Det at PFS ikke er oppdatert anses som en svakhet da forskjellige oppfølgingstider fører til inkonsekvenser i langsiktig ekstrapolering av OS og PFS (kapittel 4.4).

Legemiddelverket bemerker at de oppdaterte 3-årsdataene støtter vår innvending til Gileads antagelse om kurasjon i den opprinnelige innsendingen. Observert OS er redusert med ytterligere 3 % mellom 2-års- og 3-års datakutt, og gjør dermed Gileads opprinnelige antagelse om at 50 % av alle infuserte pasienter er "kurert" etter 26 måneder for høy. Følgelig anser Legemiddelverket at Gileads bruk av *mixture cure modell* (MCM) er optimistisk og velger å ekstrapolere ZUMA-1 OS data med en spline modell som gir god tilpasning til OS-data og som ikke innebærer at en andel pasienter er kurert etter oppfølgingstiden i ZUMA-1. Legemiddelverket utelukker likevel ikke muligheten for kurasjon, og antar i modellen at pasienter som overlever i 84 måneder etter axi-cel-infusjon er "kurert". Etter 84 måneder går dødeligheten hos langtidsoverlevere (ca. 40 % av pasientene) tilbake til samme dødelighet som i den generelle befolkningen. De norske kliniske ekspertene som Legemiddelverket har konferert, tror også at axi-cel har kurativt potensial. De understreker at hvis behandling med axi-cel gir samme resultater i klinisk praksis som i ZUMA-1, er den estimerte kurasjonsraten på 40 % et viktig fremskritt for en pasientgruppe som har få behandlingsalternativer i dag.

Beregnet overlevelsesgevinst og kostnadseffektivitet basert på de oppdaterte OS-dataene for axi-cel er forbedret, sammenlignet med den opprinnelige metodevurderingen. I ITT-populasjonen økte QALY-gevinsten fra 1,97 til 2,7, og IKER ble redusert fra 1,39 millioner kroner til 1,04 millioner kroner. I mITT-populasjonen økte QALY-gevinsten fra 2,36 til 2,94, og IKER ble redusert fra 1,28 millioner kroner til 1,06 millioner kroner.

Samlet sett, selv om den oppdaterte innsendingen er basert på mer modne OS-data, er begrensningene identifisert i den opprinnelige vurderingen fortsatt tilstede. ZUMA-1-studien er en enkeltarmet studie av liten størrelse (101 infuserte pasienter) som mangler en kontrollarm, og det er derfor ikke mulig å sammenligne resultatene fra denne studien med resultater fra komparatorstudiene uten høy 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.

Randomiserte kontrollerte studier med lengre oppfølgingstid er nødvendig for å redusere usikkerheten om langtidsvirkning av axi-cel og størrelsen på overlevelsesgevinsten sammenlignet med dagens standardbehandling.

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LOG

Bestilling:	ID2019_143: En oppdatering av den opprinnelige analysen med tilhørende modell med nye effektdata og oppdaterte kostnader gjennomføres ved Statens legemiddelverk for axicabtagene ciloleucel (Yescarta) til behandling av diffust storcellet B-celle lymfom, primært mediastinalt B-celle lymfom og transformert follikulært lymfom
Forslagstiller:	Leverandør, Gilead Sciences
Legemiddelfirma:	Gilead Sciences
Preparat:	Yescarta
Virkestoff:	Axicabtagene cilolecleucel (axi-cel)
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:	L01XX70

Prosess

Dokumentasjon bestilt av Legemiddelverket	03-03-2020
Fullstendig dokumentasjon mottatt hos Legemiddelverket	28-04-2020
Klinikere kontaktet for første gang	09-09-2020
LIS kontaktet for første gang av Legemiddelverket.	20-08-2020
Legemiddelverket bedt om ytterligere dokumentasjon	30-06-2020. Svar mottatt: 17-07-2020 11-09-2020. Svar mottatt: 18-09-2020 09-10-2020. Svar mottatt: 15-10-2020
Rapport ferdigstilt:	09-11-2020
Saksbehandlingstid:	195 dager hvorav 30 dager i påvente av ytterligere opplysninger fra legemiddelfirma. Dette innebærer en reell saksbehandlingstid hos Legemiddelverket på 165 dager.
Saksutredere:	Ania Urbaniak Mathyn Vervaart
Kliniske eksperter:	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.

4 UPDATED HEALTH ECONOMIC ANALYSIS

In the updated submission, Gilead has updated the cost-utility model with the following inputs/options:

- Axi-cel parametrization based on the 3-year OS data, as opposed to 2-year OS data in the original submission
- An additional reweighted SCHOLAR-1 dataset
- Costs and utility assumptions according to NoMA's preferences from the original evaluation

4.1 ZUMA-1 DATA

Efficacy results provided in the original submission

ZUMA-1 is a pivotal, ongoing, single-arm, phase 1/2 study which provided evidence supporting the regulatory approval of axi-cel. Two-year follow-up data of enrolled (intention-to-treat, ITT) population (N=111) and infused (modified (m) ITT) population (N=101) with a median follow-up time of 27.1 months and data cut off (DCO) 11.08.2018 were provided in the original submission (1). In the cost-utility model progression was defined per investigator assessment of response as defined by IWG criteria (4). Investigator-assessed PFS rates were 40.0% at 18 months and 38.9% at 24 months in the mITT population. Median PFS was 5.9 months (95% CI: 3.3–15.0 months) (5) (Figure 1). Forty patients were censored, 39 due to ongoing response or stable disease and 1 due to starting a new anti-cancer therapy. This one patient, who started new pharmacotherapy before progression and was censored, had partial response as best overall response to the axi-cel therapy. In the ITT population, PFS was defined as time from leukapheresis to the date of disease progression or death from any cause. Forty two patients were censored, 41 due to ongoing response or stable disease and 1 due to starting a new anti-cancer therapy. Median PFS in the ITT population was 6.3 months (95% CI: 4.0- 12.4 months) and 36.1% (27.1%, 45.1%) of patients remained progression-free at 24 months.

Median OS was not reached in the mITT population, with an estimated 2-year survival rate of 50.5% (95% CI: 40.2–59.7%) (Figure 2). An estimated 2-year survival in the ITT population was 48%.

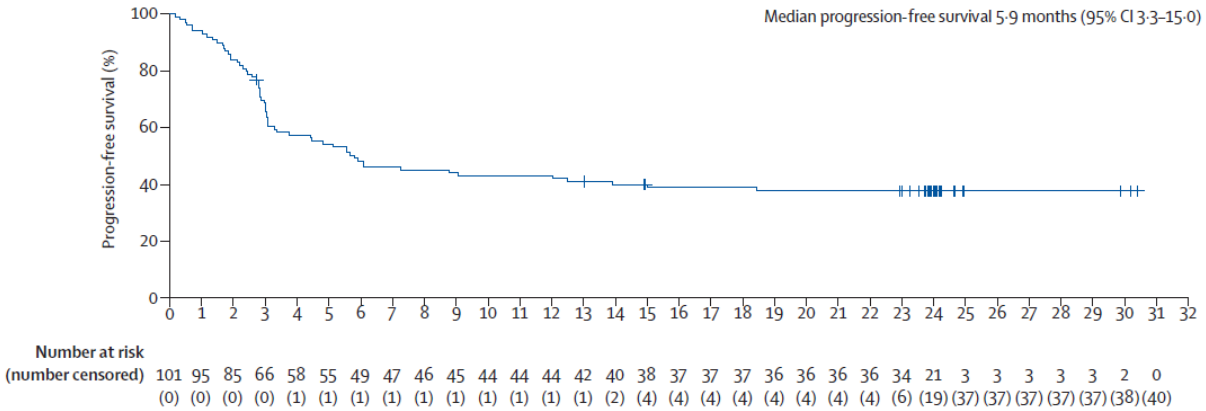

Figure 1 Investigator-assessed PFS in the ZUMA-1 phase 2 mITT population after a median follow-up of 27.1 months (5). PFS defined as time from infusion to disease progression or death.

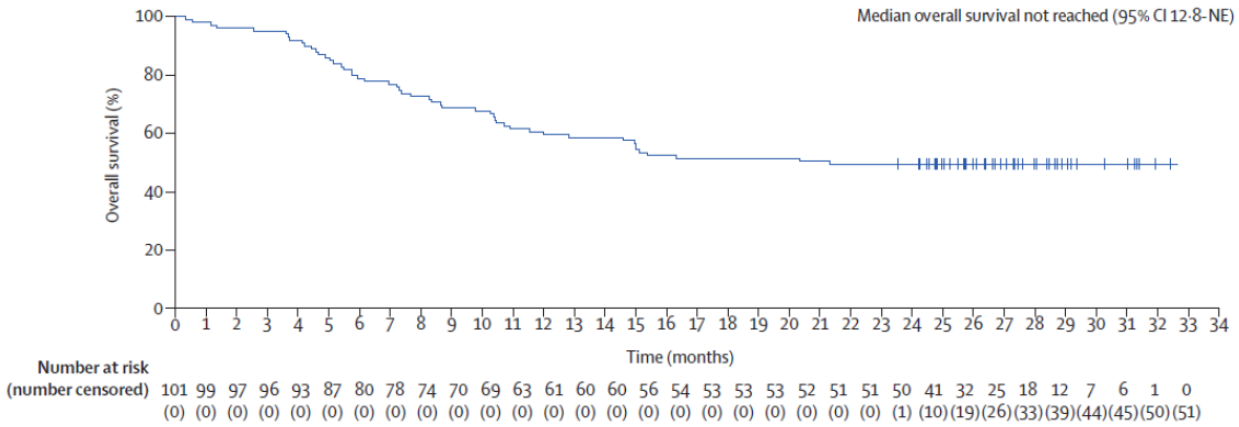

Figure 2 OS in the ZUMA-1 phase 2 mITT population after a median follow-up of 27.1 months (5), as used in the original submission

Efficacy results provided in the updated submission

In the updated submission, the cost-utility model is based on the three-year survival data (DCO 11.08.2019) with a median follow-up of 39.1 months (Gilead's data on file). Median OS in the phase 2 mITT population was 25.8 months (95% CI: 12.8 – not evaluable), the 2-year OS rate was 50% and the 3-year OS rate was 47% (6) (Figure 3). Forty seven patients were censored due to being alive. Four additional deaths occurred relative the 2-year data; one of those was due to myelodysplastic syndrome deemed related to prior therapy and 3 were due to lymphoma progression. The ITT population included 10 additional non-infused patients. Median OS in the ITT population was 17.4 months (11.6 - NE), the 2-year OS rate was 48% and the 3-year OS rate was 44%. All of the 49 censored patients were alive at the end of follow-up time.

As a part of the study protocol, OS will be collected up to year 15. Updated PFS data were not available after 2 years of follow-up in ZUMA-1 as this information was not collected systematically after the primary analysis. According to the response provided by Gilead, axi-cel treated patients in ZUMA-1 resume normal care after 2-year cut-off date, hence, it is not possible to guarantee that they will have a PET-CT at the regular follow-up intervals. Since the measurement of PFS as it is defined according to ZUMA-1 protocol cannot be replicated with certainty during the regular follow-ups in normal clinical practice, it is therefore not possible to define this measure beyond the 2-year data.

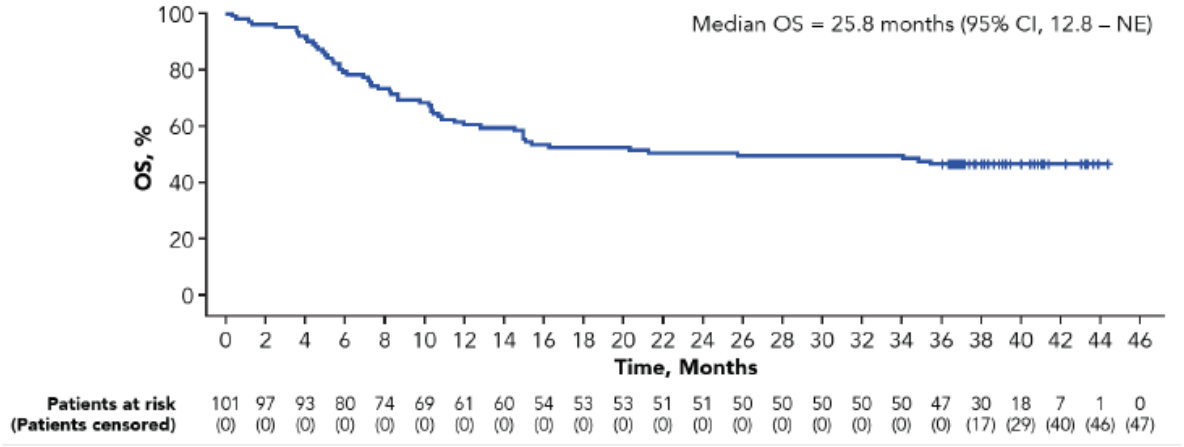

Figure 3 Updated OS in the ZUMA-1 phase 2 mITT population after a median follow-up of 39.1 months (6), used in the updated submission

NoMA has also requested additional data from ZUMA-1 on post-progression survival, which was submitted by Gilead (Figure 4). At the DCO of 11.08.2018, with a maximum follow-up of 28.3 months, 61 out of 101 patients in the mITT population had progressed, and median survival was 4.96 months (95% CI 3.54-8.77 months).

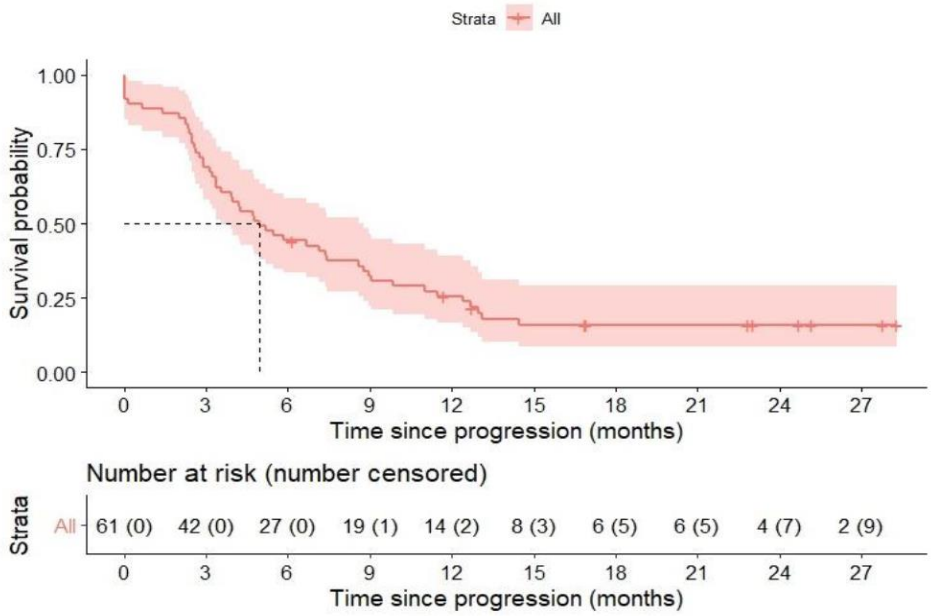

Figure 4 Kaplan-Meier curve for post-progression survival in the mITT population of ZUMA-1, 2-year cut-off (follow-up of 28.3 months)

NoMA's assessment

NoMA welcomes updated OS data from ZUMA-1. A short follow-up of two-years in the original submission was an important source of uncertainty in the cost-utility model. The updated three-year survival data reveal an additional 4 deaths compared to the 2-year data. Out of 101 patients that were

infused with axi-cel, 47 patients were alive and censored between 36 and 45 months of follow-up. No patient was censored before 36 months.

NoMA has also requested post-progression survival data for axi-cel which shows that 8 progressed patients survived for 15 months or longer.

4.2 REAL-WORLD EVIDENCE FOR AXI-CEL

Gilead has identified numerous real-life efficacy and safety data for axi-cel. Three retrospective real-world studies of axi-cel were presented during the 2018 American Society of Hematology Annual Meeting:

- Retrospective analysis of data from all (n=72) r/r large B-cell lymphoma patients treated with axi-cel between 18 June 2015 and 17 September 2018 at the MD Anderson Cancer Center in ZUMA-1 and ZUMA-9 trials as well as outside of a trial (Sano et al, 2018)(7).
- Retrospective analysis of data from 17 US academic centres including all patients leukapherised as of 31 August 2018 with the intention to manufacture commercial axi-cel (Nastoupil, et al. 2018)(8). The updated data show that 275 patients out of 298 leukapherised patients received axi-cel and were included in the mITT population. 53% of patients received bridging therapy (Nastoupil et al 2020)(9).
- Retrospective analysis of data from 104 patients treated with commercially-available axi-cel between December 2017 and October 2018 at 6 US academic centres (Jacobson, et al. 2018)(10). The most recent results show that 45% of patients received bridging therapy (Jacobson et al 2020) (11).

It is not clear if the populations of these studies are completely separate, i.e. it is possible some patients were included in more than one retrospective real-world study as some of the participating institutions overlap.

Two further relevant real-world studies were presented at the 2019 American Society of Hematology Annual Meeting:

- Kuhnl et al. (2020) described the use of commercial axi-cel and tisagenlecleucel (Kymriah) in England between December 2018 and January 2020. 235 patients were leukapherised, and 183 infused with CAR-T therapies (133 with axi-cel and 50 with tisagenlecleucel). Apart from presenting the outcomes of the real-world experience with CAR-Ts in England, the authors highlight the difference between US-based registries and the UK registry. In the US, data collection is retrospective and based on voluntary registry submission. In the UK cohort, data of the entire national cohort are collected prospectively. In the US, patient selection may dependent on the equity of access driven by region, funding and insurance issues as compared to the universally insured UK population. Lastly, the authors point out that in Europe as compared to the US, most patients start infusion in state of active/high tumour burden.
- Prospective US post-marketing safety and efficacy study implemented as part of an US regulatory requirement (Pasquini et al 2019)(12). In the current analysis, 750 patients were infused, 533 with any follow-up reported and 326 with ≥6 months of follow-up.

Finally, results from a real-world cohort of French patients treated with axi-cel within an early access program (Temporary Authorisation for Use) were presented in early 2020 at the 2nd European CAR-T Cell Meeting, jointly organised by the European Hematology Association (EHA) and the European Society for Blood and Marrow Transplantation (EBMT) (Thieblemont et al 2019)(13). Out of 45 requests, 41 patients

were approved for the early access programme, 37 were leukapherised, and 35 received lymphodepleting chemotherapy and axi-cel. 90% of patients with available data received bridging therapy.

A summary of most up to date efficacy and safety data from the six real-world analyses is presented in Table 1 below; 12-month follow-up data from ZUMA-1 are also shown for comparison.

Table 1 Real-world data on the use of axi-cel (Yescarta), compared with 1-year results from the ZUMA-1 study

	Sano, et al. 2018 (7)	**Nastoupil, et al. 2020**	**Jacobson, et al. 2020**(11)	**Pasquini, et al. 2019 (12)**	**Kuhnl, et al. 2020(14)**	**Thieblemont et al. 2019 (13)**	**ZUMA-1**(15, 16) (one-year data)
Country	US	US	US	US	England	France	International
Patients, n	72	275	122	533	183 (of whom 133 received axi-cel and 50 tisagenlecleucel)	35	108 (ITT population for safety outcomes) or 101 (mITT population for efficacy outcomes)
Median follow-up	4.19 months (range: NA, 36.04 months; IQR: 1.7–13.8 months)	12.9 months (3.2-20.7 months)	10.4 months	6.2 months (range: 1–16 months)	9.9 months for infused patients	NR	15.1 months
ORR (investigator/ central review)	82% at Day 30 (n=67)	82% (95% CI, 77% to 86%)	Best ORR 70% (n=85) ITT ORR 65%	74% (n=533) 84% (n=326 in patients with ≥6 months of follow-up data available)	Best response to YESCARTA® at ≥3 months ORR 45% (n=112)	74.2% per investigator assessment (n=31)	83% / 72%
CR (investigator/ central review)	55% at Day 30 (n=67)	64% (95% CI, 58% to 69%)	CR 50%	Exact percentage NR (approx. 55% based on visual inspection of a presented plot)	Best response to YESCARTA® at ≥3 months CR 30% (n=34)	41.9% per investigator assessment (n=31)	58% / 51%
Median PFS (investigator/ central review)	NR	8.3 months (95% CI: 6.0–15.1 months) 12-month PFS: 45% (95% CI, 39% to 51%)	4.5 months (95% CI, 3.2 to 12.1 months),	Exact percentage NR (approx. 6.5 months based on visual inspection of the presented Kaplan-Meier plot)	PFS not reported. Median EFS of 3.2 months (95% CI 3.0–4.6 months) from CAR-T infusion reported for YESCARTA® and tisagenlecleucel combined (n=183), with events defined as radiological or clinical progression, or start of new treatment.	NR	5.9 months (95% CI: 3.3–NE) / 9.1 months (95% CI: 5.8–12.5)

Median OS	15.4 months (95% CI: 13.5–NE)	NR 12-month OS 64% (95% CI, 59% to 70%)	Not reached 12-month OS mITT: 67% (95% CI, 59% to 77%) 12-month OS ITT: 65% (95% CI, 57% to 74%)	Exact percentage NR (not reached based on visual inspection of the presented Kaplan-Meier plot)	13.4 months for infused patients (95% CI: 9.7 NR) Estimated from patient approval for CAR-T treatment, for YESCARTA® and tisagenlecleucel combined (n=183)	NR	Not reached (95% CI: 12.8 months–NE)
CRS, any Grade	88.9%	91%	93%	NR for the entire population, 80% in patients aged <65 years and 84% in those aged ≥65 years	92.5% for YESCARTA®	51%	93%
Grade ≥3 CRS	11.1%	7%	16%	NR for the entire population, 8% in patients aged <65 years and 10% in those aged ≥65 years	9% for YESCARTA®	9%	12%
Neurotoxicity, any Grade	72.2%	69%	70%	NR for the entire population, 55% in patients aged <65 years and 64% in those aged ≥65 years	43.2% for YESCARTA®	29%	67%
Grade ≥3 Neurotoxicity	54.2%	31%	35%	NR for the entire population, 16% in patients aged <65 years and 18% in those aged ≥65 years	18.9% for YESCARTA®	9%	32%

CAR-T: chimeric antigen receptor; CI; confidence interval; CR: complete response; CRS: cytokine release syndrome; EFS: event-free survival; ITT: intention-to-treat; mITT: modified intention-to-treat; NE: not evaluable; NR: not reported; IQR: interquartile range; NHS: National Health Service; ORR: overall response rate; OS: overall survival; PFS: progression-free survival; r/r: relapsed or refractory
Note that due to the short follow-up reported in the real-world studies, 1-year rather than 2-year data are presented for ZUMA-1.

** Note that the criteria for assessing safety outcomes varied between the presentations. Nastoupil et al. 2020 used Lee criteria for grading CRS and CTCAE or CARTOX criteria for grading neurotoxicity. Jacobson, et al. 2020 did not report the grading systems used. Sano et al. 2018 used the CARTOX criteria for grading both CRS and neurotoxicity. Pasquini et al. used the 2014 Lee criteria for grading CRS but it was not clear how neurotoxicity was graded. Kuhnl et al. 2020 used ASTCT 2019 criteria for grading CRS and neurotoxicity. Thieblemont et al. 2020 monitored safety through pharmacovigilance reporting, but the grading scale was not stated. A comprehensive review of the different CRS and neurotoxicity grading systems was published in 2019(17).

NoMA's assessment

The real-world efficacy data for axi-cel have been provided for external validity and are not used in the updated cost-effectiveness model. The median follow-up time of the real-word data is too short to validate long-term OS extrapolation of axi-cel in the model. With the exception of the UK registry (Kuhnl et al 2020), the objective response rate (ORR) of 74%-83% seems consistent across the real-world studies. The lower response rate in the UK registry than the US registries may be driven by the inclusion of the total national cohort as opposed to the voluntary US registry inclusion and the higher disease burden at infusion in the UK registry, as hypothesized by Kuhln et al. The PFS was reported only in 3 studies and

median PFS ranged from 4.5 to 8.3 months. The proportion of patients experiencing cytokine release syndrome (CRS) and neurotoxicity in real-world studies is comparable. The real-world results are also broadly aligned with 1-year data from ZUMA-1. However, as patient characteristics are not consistently published in the real-world studies, it is difficult to draw any strong conclusions about comparability to ZUMA-1. The largest of the three retrospective studies, including 275 axi-cel -treated patients reported that as many as 43% of patients receiving the treatment in the real world would not have met ZUMA-1 eligibility criteria at the time of leukapheresis (Nastoupil, et al. 2020 (9). It also appears that bridging therapy, which was not allowed in ZUMA-1, is commonly used before axi-cel infusion in clinical practice. If this is also the case in Norway, this will increase the total costs of the axi-cel treatment.

4.3 UPDATED COMPARATOR ASSUMPTIONS

The OS comparator data in the cost-utility model are sourced from SCHOLAR-1 (3). SCHOLAR-1 is the largest international, multi-cohort retrospective study that characterized response rates and survival of salvage chemotherapy among patients with refractory DLBCL.

In the original submission (1), the comparator efficacy data were based on a crude SCHOLAR-1 adjustment, excluding patients with ECOG 2-4 and post-SCT. NoMA argued that patients with post-SCT should not be excluded from the comparator dataset, as these patients would potentially have better survival than the average patient in the relevant population. In addition, NoMA preferred a propensity score (PS)- adjusted comparison between SCHOLAR-1 and ZUMA-1 as a method of reducing the bias in estimating a relative treatment effect based on single arm trials or observational studies.

In the current submission, Gilead used the same crude SCHOLAR-1 adjustment in the base case analysis. An additional OS analysis for the comparator using a Reweighted dataset for SCHOLAR-1 has been made available by Gilead. In this additional analysis, the matching between the ZUMA-1 and SCHOLAR-1 data was based on stratifying the SCHOLAR-1 data on covariates considered to be prognostic for response and subsequently weighting the SCHOLAR-1 outcomes across those strata based on the proportions of subjects in the ZUMA-1 study in those strata. Patients with subsequent SCT have been retained in this dataset. Two covariates were pre-specified as covariates to define the strata:

- Refractory subgroup based on Last Refractory Categorization
    - Primary refractory
    - Refractory to second- or later-line therapy
    - Relapse ≤ 1 year of ASCT
- ECOG categorization

Gilead's crude, reweighted and NoMA's PS-adjusted SCHOLAR-1 survival curves are presented in Figure 5. Long-term OS (100 months) with NoMA's PS-analysis for the SCHOLAR-1 population was estimated at around 20% with a post-SCT proportion of 29%. The long-term survival is 7% for the crude adjustment and 17% for the reweighted dataset.

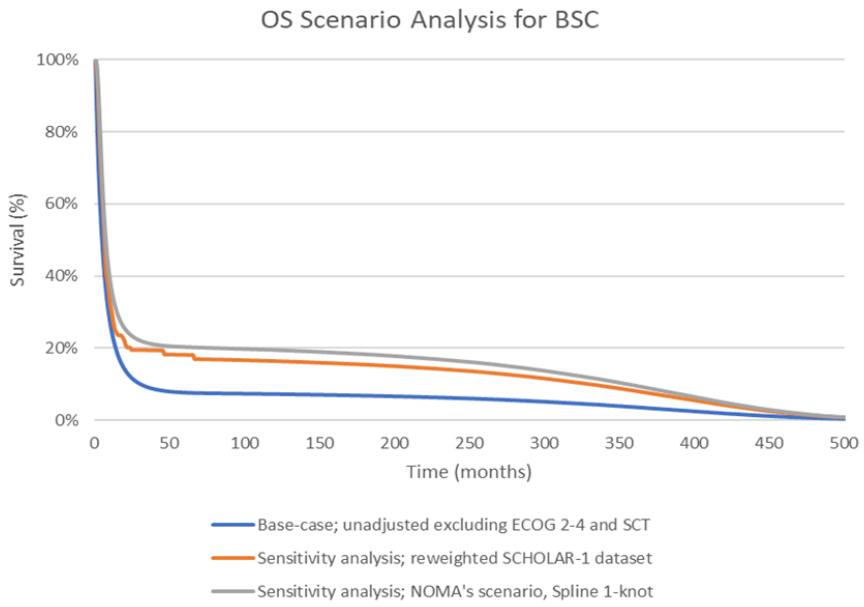

Figure 5 Modelling of the salvage therapy arm; crude and adjusted SCHOLAR-1 data. Gilead's base case in blue, NoMA's base case in grey.

NoMA's assessment

Gilead has chosen to use crude SCHOLAR-1 adjustment, excluding patients with ECOG 2-4 and post-SCT for their base case. NoMA disagrees with the exclusion of patients who received a subsequent SCT as well as with using a comparison method that does not account for differences in patient characteristics. Consequently, NoMA uses the same assumptions for the extrapolation of OS (i.e. based on the PS-adjusted SCHOLAR-1 dataset) and PFS as in the original assessment. NoMA believes that, in the absence of a randomized controlled trial, it is more appropriate to select those patients from the SCHOLAR-1 dataset that could have been included in a theoretical ZUMA-1 control arm. An unadjusted comparison is likely to introduce selection bias as it fails to account for differences in potential prognostic factors such as ECOG, gender, age, disease stage, number of lines of prior chemotherapy, relapse/refractory status. The exclusion criteria (ECOG 2-4 and patients with unknown disease status) and PS-analysis requested by NoMA attempts to reduce the impact of potential selection bias. In the updated submission, Gilead has also provided an additional Reweighted SCHOLAR-1 dataset where two variables were used to match ZUMA-1; Refractory subgroup and ECOG Categorization. NoMA has not explored the use of this dataset further as the preferred PS-analysis accounts for more prognostic factors including refractory subgroup.

4.4 Extrapolation of axi-cel OS and PFS based on updated ZUMA-1 data

4.4.1 Original submission

In the original submission (1), Gilead chose a Weibull mixture cure model (MCM) to extrapolate OS for axi-cel, and a Gompertz single parametric model (SPM) for chemotherapy. PFS for axi-cel was modelled using a Gompertz function without background mortality, and PFS for chemotherapy was based on the modelled ratio between OS and PFS for axi-cel.

The use of a Weibull MCM implied that by month 26, 50% of all patients that were infused with axi-cel would be cured from the disease and have the same mortality as the general population. This was criticized by NoMA as an overly optimistic assumption, as NoMA argued that the cure fraction was likely

overestimated due to the immaturity of the data. Furthermore, evidence from studies with a much longer follow-up suggest the presence of excess mortality in patients with DLBCL up to 10 years after therapy initiation (3, 18-20).

The combination of a Weibull MCM for OS and Gompertz distribution for PFS resulted in a substantial separation between the OS and PFS curves that was sustained over 20 years in the model. This implied that a substantial proportion of patients that had progressed on axi-cel were assumed to be "cured" of excess mortality and have a long-term prognosis. As there are effectively no curative therapies available after progression and the prognosis is very poor, this assumption was deemed clinically implausible by NoMA. The implausibility of this assumption was further supported by additional information submitted by Gilead during the NICE single technology assessment for axi-cel, which revealed that 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.

NoMA therefore used a spline model with 2 knots as opposed to a Weibull MCM to perform a short-term extrapolation of OS for axi-cel until the point where the OS and PFS curves converged (Table 2). At the point of convergence with the PFS curve, NoMA assumed the mortality risk would be equal to mortality as modelled for long-term survivors in SCHOLAR-1.

Table 2 Gilead's base case in the original and updated submission together with NoMA's preferred assumptions.

Parameter	**Gilead's base case in the original submission (1)**	**NoMA's base case in the original submission (1)**	**Gilead's base case in the updated submission**
Based on:	***DCO 11.08.2018***		***DCO 11.08.2019***
Population	Infused set (mITT)	Enrolled (ITT) and infused set (mITT)	Infused set (mITT)
OS axi-cel	Weibull mixture cure model (MCM). General population-based mortality was applied to long-term survivors.	Spline function with 2 knots constrained by the PFS curve. 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.	As in the original submission; Weibull MCM, and general population-based mortality applied to long-term survivors
PFS axi-cel	Gompertz single parametric model (SPM) without background mortality*	Gompertz SPM without background mortality*	As in the original submission; Gompertz SPM without background mortality*
OS chemotherapy	Gompertz SPM	Spline function with 1 knot	As in the original submission; Gompertz SPM
PFS chemotherapy	Based on the modelled ratio between OS and PFS for axi-cel	Based on the modelled ratio between OS and PFS for axi-cel	As in the original submission: based on the modelled ratio between OS and PFS for axi-cel

** If background mortality (i.e. general population mortality adjusted for sex and age) is not applied, the PFS mortality may become lower than the mortality in the general population which may not be plausible in long-term.*

4.4.2 Updated submission

In the current updated submission, Gilead adopts the same approach as previously and chooses a Weibull MCM to extrapolate the updated axi-cel OS data (Table 2). The Weibull MCM was selected based on visual fit and statistical fit (lowest Akaike information criterion, AIC, of 223 in the mITT population). As per original submission, the company assumed that the cured population would be subject to the mortality risk of the general Norwegian population. An excess mortality of 12% is used in a sensitivity analysis. The excess mortality of 12% is based on the lower bound 95% CI of the standardized mortality ratio (SMR) in patients who achieved event-free survival (EFS) at 24 months after first-line treatment (19). According to Gilead, the Weibull distribution was selected based on visual fit, statistical fit and clinical plausibility. Figure 6 shows the overall estimated OS for the selected model (MCM with Weibull distribution), compared to the observed KM curve. PFS was extrapolated with the same Gompertz function as in the original submission. General population mortality was not applied to PFS resulting in a flat tail of the extrapolated curve.

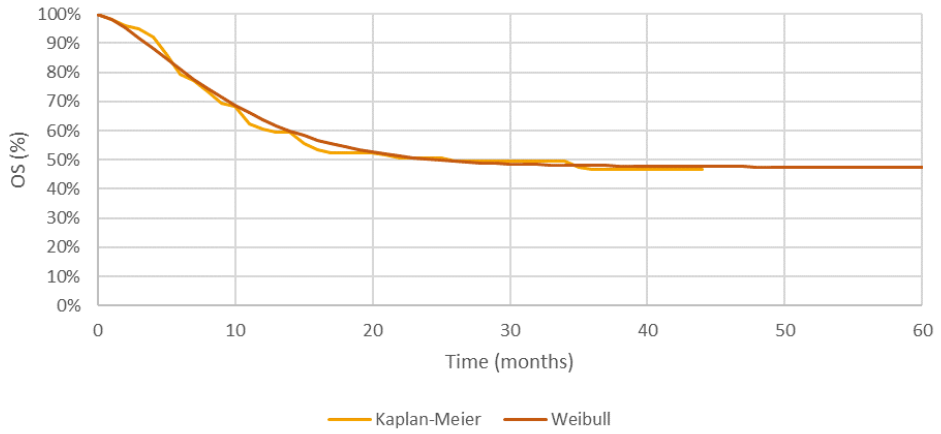

Figure 6 Gilead's base case modelling of axi-cel OS in the mITT population: 3-year KM with fitted Weibull mixture cure model.

Gilead's base case extrapolation of PFS and updated OS is presented in Figure 7. Gilead claims that the optimistic projection of long-term survival post-progression (i.e. the area between the axi-cel OS and PFS curves) is supported by the observed data from ZUMA-1, which shows that 4 progressed patients survived for about 2 years before being censored (Figure 4).

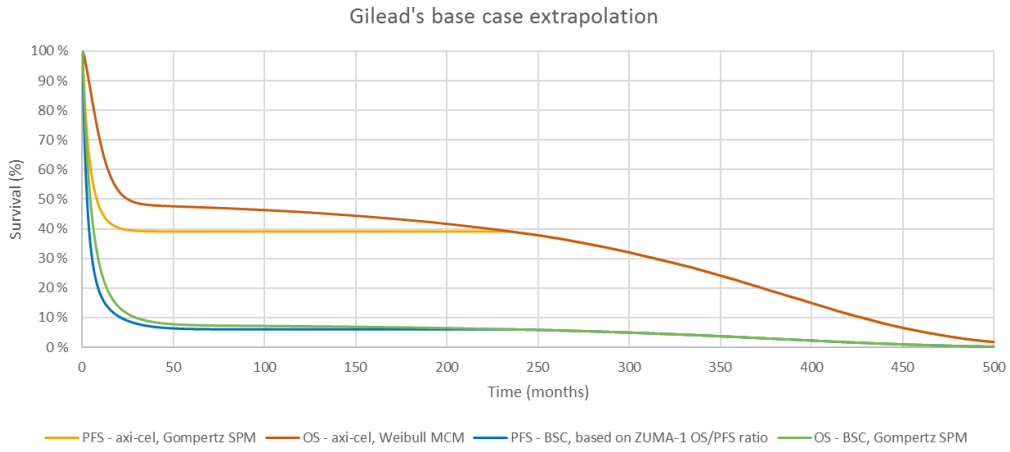

Figure 7 Gilead's base case extrapolation of 2-year PFS and 3-year axi-cel OS in the mITT population and the salvage chemotherapy arm (based on unadjusted SCHOLAR-1 without ECOG 2-4 and post-SCT).

NoMA's assessment

The updated cost-utility model provides an option of fitting mixture cure models (MCM; Weibull, Gamma or lognormal), a spline model with 2 knots and standard parametric functions to the updated axi-cel OS KM data. NoMA notes that extrapolating observed survival data over a time period that is over 10 times larger than the observed time period based on ZUMA-1 introduces substantial uncertainty in the analysis. NoMA considers the mixture cure model approach by Gilead to be overly optimistic as it implies that mortality returns to general population levels shortly after the observed 3-year follow-up period. This assumption is not supported by the 3-year survival data from ZUMA-1, which shows ongoing excess mortality in long-term survivors. In addition, it is noted that the projected cure fraction of 50% in the original submission is higher than 47% estimated with a Weibull MCM in the current submission supporting NoMA's original critique that the data is too immature to reliably predict the cure fraction. Lastly, numerous sources from the literature suggest that the mortality in surviving DLBCL patients is still increased after 3 years compared to the general population. For instance, the conditional survival analysis of relapsed DLBCL after autologous transplant showed that excess mortality is still present in patients who achieved event-free survival at 60 months (EFS 60) (21). Even in DLBCL patients in first complete remission who achieve post-treatment event-free survival for 48 months, the mortality is still increased compared to the general population (19). NoMA considers AIC to be of lesser importance, since likelihood-based measures do not have any bearing on the plausibility of the long-term extrapolations.

Gilead's approach to modelling PFS as a flat curve implies that patients that have not progressed during the first 2 years are "immortal" for a period of close to 20 years, i.e. these patients are assumed to not experience any background mortality nor progression events. As NoMA explained in the appraisal of the original submission, this assumption is highly implausible.

As in the original submission, the combination of a Weibull MCM for OS and Gompertz distribution for PFS results in a substantial separation between the OS and PFS curves that is sustained over 20 years in the model. This implies that a substantial proportion of patients that has progressed on axi-cel are assumed to have a long-term prognosis. As there are effectively no curative therapies available after progression, and ZUMA-1 trial data on post-progression survival demonstrates a very poor prognosis in progressed patients (median survival of 5 months), this assumption is deemed clinically implausible by NoMA. In addition, Norwegian clinical experts contacted by NoMA do not believe that axi-cel will improve post-progression survival compared to the current standard of care.

As per original submission, NoMA has evaluated the fit of spline models to the updated axi-cel OS KM data. The spline model with 2 knots had the best mathematical fit (AIC of 278 in the mITT population) among spline models and good visual fit to KM data. The projected 3-year survival with the spline model with 2 knots is 47% in the mITT population and 45% in the ITT population, which is fully aligned with the observed KM curve from ZUMA-1. During the original assessment, NoMA chose to model PFS with the Gompertz function without applying general population mortality. Consequently, the extrapolated portion of the PFS curve was flat implying progression-free patients are assumed not to experience any mortality of progression events. This was not plausible, but because the PFS and OS curves merged relatively early at 37 months, this would not affect the results much. At the point of crossing of PFS and OS at 37 months in the axi-cel arm, the mortality of SCHOLAR-1 was used for both arms. If the same approach was taken for PFS with the updated OS extrapolation, a substantial proportion of patients would remain in the post-progression health state until about month 200, which NoMA considers implausible (Figure 8, left). On the other hand, when background mortality is applied to PFS, PFS and OS never merge and there is a relatively high proportion of patients in the post-progression health state during the full model time horizon (Figure 8, right).

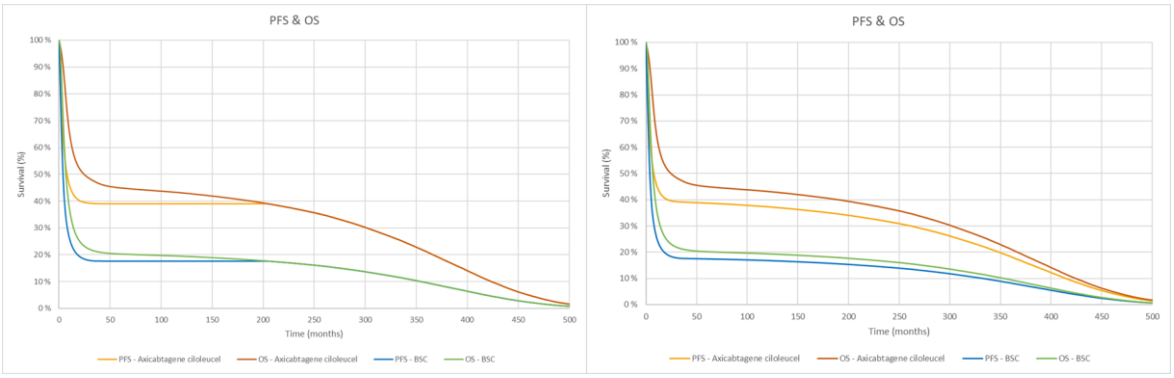

Figure 8 Scenario where spline2k model is applied to axi-cel OS + SCHOLAR-1 mortality from Month 37. Based on mITT population in ZUMA-1, 3-year OS data. PFS extrapolated with Gompertz; no background mortality applied to PFS curve (left), background mortality applied (right).

Because of the implausibility of both of the above scenarios, NoMA has chosen to extrapolate OS with a spline 2k model until month 84, rather than month 37. After that, the general population mortality is applied (Figure 9). This approach relies more on the ZUMA-1 empirical data than in the original NoMA's base case, as the extrapolated OS is used until month 84, rather than month 37 as used in the original submission. This is more appropriate as the updated ZUMA-1 data is more mature and there are no censoring events until month 36 (mITT population), implying that the observed data is more informative for the extrapolation. The turning point of month 84 was chosen as the potential "cure point". In the model, the mortality rate in SCHOLAR-1 converges towards general population mortality rate at 84 months, at which point general population mortality is used for the rest of the time horizon. If the spline model with 2k is used to extrapolate OS for the axi-cel for the full model time horizon, the mortality rate at 84 months becomes larger than for SCHOLAR-1. As there is no evidence suggesting higher mortality for axi-cel vs best supportive care in the long-term, NoMA has chosen to use general population mortality for both arms at month 84.

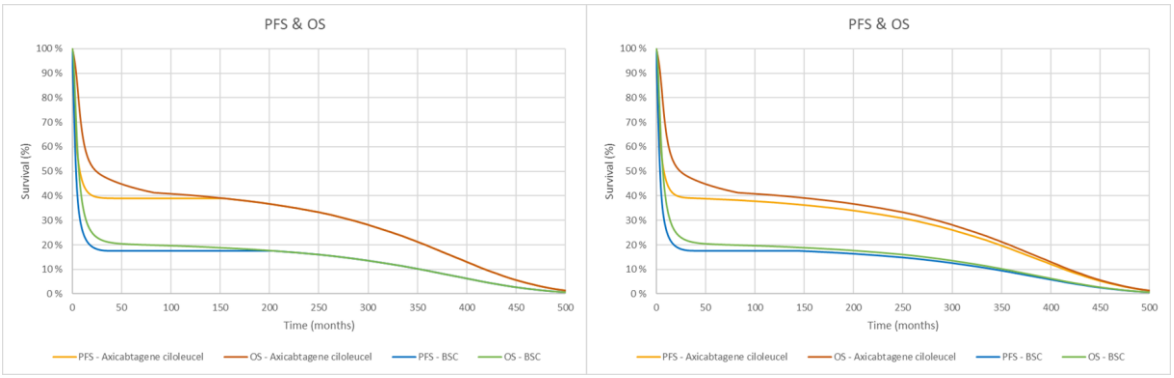

Figure 9 Scenario where spline2k model is applied to axi-cel OS + general population mortality from Month 84. Based on mITT population in ZUMA-1, 3-year OS data. PFS extrapolated with Gompertz; no background mortality applied to PFS curve (left), background mortality applied (right, NoMA's base case).

For PFS, NoMA accepts the choice of the Gompertz function as per original assessment. However, NoMA applied general population mortality to the PFS curve (Figure 9, right) to avoid that progression-free patients remain "immortal" between month 50 to month 160 (i.e. a flat PFS curve), which would be the case if general population mortality would not be applied (Figure 9, left). With the updated NoMA's base case, there is still a modest proportion of patients in the post-progression health state over a longer time horizon, but this proportion is smaller than in other scenarios, and importantly the assumption that progression-free patients do not experience any mortality nor progression events during a substantial time period is removed. NoMA acknowledges that the updated axi-cel extrapolations are not free from limitations. Any inconsistencies in the longer term extrapolations will however not be resolved as long as there is a misalignment between the follow-up time between PFS (two-year data) and OS (three-year data), and without longer follow-up data.

4.5 UPDATED UTILITY ASSUMPTIONS

Health-related quality of life (HRQoL) data were not collected in ZUMA-1 phase 2. In the original submission, Gilead used health state utilities based on EQ-5D data collected in Cohort 3 (safety management cohort) of ZUMA-1. The calculated utility was 0.72 for the progression-free disease and 0.65 for the progressed disease.

In addition, Gilead assumed 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. The company has 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 (22).

In the current submission, Gilead updated these assumptions in agreement with NoMA's original assessment (1):

- Health state utilities sourced from the CAR-T study JULIET (0.83 for progression-free disease, 0.71 for progressed disease) (23) as opposed to ZUMA-1 safety cohort.
- Disutility for AEs sourced from the CAR-T study JULIET as opposed to ZUMA-1 safety cohort.
- No reduction in long term quality of life, compared to 5% reduction in Gilead's base case.
- Age adjustment of health state utility values in line with NoMA guidelines.

NoMA's assessment

NoMA agrees with the utility inputs used in the updated submission.

The Cohort 3 of ZUMA-1 is not the same population as the Phase 2 ZUMA-1 population, the source of input data for efficacy and safety. Furthermore, utility scores were only available for 34 patients. The progressed disease health state was informed by very few observations (5 observations), and only 49 observations informed the PFS health state. For consistency with another CAR-T cell therapy STA; tisagenlecleucel (Kymriah) for the treatment of second or later r/r DLBCL (23), NoMA supports the use of utilities based on data collected in the tisagenlecleucel study JULIET.

4.6 UPDATED COST ASSUMPTIONS

In the updated submission, Gilead used cost inputs as preferred by NoMA in the original submission:

- Leukapheresis costs of 50 845 NOK were based on data from Oslo University Hospital, as opposed to 9 728 NOK (source: Helsedirektoratet, 2*DRG 816P).
- Hospitalization for 14.7 days for the comparator treatment (source: clinical expert opinion) as opposed to outpatient treatment.
- Hospitalization for 21.6 days for axi-cel treatments (source: ZUMA-1 clinical study report) as opposed to 7 days (source: Gilead assumption).
- Rituximab included in the costs of comparator treatment.
- Hospitalization and ICU costs derived from Lindemark (24, 25)
- Costs of subsequent SCT (both alloSCT and ASCT) included in the comparator arm
- Terminal care costs 57 820 NOK based on Wang (26), as opposed to 169 371 NOK based on Moger (27)
- IVIG treatment due to B-cell aplasia included.
- Excluded pharmacy mark-up of 77 780 NOK in the list price for axi-cel

Since the previous STA submission to NoMA, all costs were inflated to 2019 NOK prices.

NoMA's assessment

NoMA agrees with the cost inputs used in the updated submission.

Alternative assumptions are tested in scenario analyses (chapter 4.3). Since the original submission, new US real-world data emerged for axi-cel suggesting that hospitalization at infusion is shorter (i.e. 16 days) than in ZUMA-1 (21.6 days) (28). The methodology in the source has however not been well described nor peer reviewed. In addition, the real-world axi-cel population seem different from the one in ZUMA-1 as 53% of the patients would not be eligible for ZUMA-1 inclusion. NoMA has also done a sensitivity analysis of Gilead's original assumption of using 7 days of hospitalization but this change does not seem to impact the ICER substantially. NOMA has therefore not assessed this in more detail.

5 UPDATED HEALTH ECONOMICS RESULTS

5.1 GILEAD'S UPDATED BASE CASE

Results for axi-cel versus chemotherapy from Gilead's base case analysis is presented in Table 3. Results are reported per patient and discounted at a discount rate of 4% per year. 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 without background mortality, and PFS for chemotherapy was based on the modelled ratio between OS and PFS for axi-cel.

Table 3 Results from Gilead's updated base case. mITT population (infused patients). List price for axi-cel and chemotherapy excl. VAT.

	Axi-cel	Chemotherapy	Difference
Total costs	3 799 967 NOK	323 216 NOK	3 476 751 NOK
Total QALYs	6.41	1.30	5.11
Total life years	8.24	1.72	6.52
Incremental cost per QALY gained			**680 581 NOK**
Incremental cost per life year gained			**533 115 NOK**

The estimated incremental survival benefit and cost-effectiveness profile for axi-cel in Gilead's updated base case is similar to Gilead's original submission. The QALY gain decreased from 5.22 to 5.11, and the ICER increased from 0.64 million NOK to 0.68 million NOK.

5.2 NOMA'S UPDATED BASE CASE

In the updated assessment, NoMA has used the original cost-utility model but updated the efficacy data for axi-cel. This was to ensure consistency between the original and the updated assessments for parameters for which no new data was available.

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 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. The summary of NoMA's remaining changes to Gilead's updated base case are presented in Table 4. NoMA's updated base case results based on list prices are presented in Tables 5 and 6.

Table 4 NoMA's changes to Gilead's updated base case

Parameter	Gilead's updated base case	NoMA's updated base case (only changes presented)
Population	Infused (mITT)	Infused (mITT) and enrolled (ITT)
Comparator	Crude SCHOLAR-1 adjustment, excluding patients with ECOG 2-4 and post-SCT	PS-adjusted SCHOLAR-1 where patients with post-SCT were retained
Chemotherapy OS extrapolation	Gompertz single parametric model (SPM)	Spline model with 1 knot
Axi-cel OS extrapolation	Weibull mixture cure model (MCM)	Spline model with 2 knots. General population mortality applied at month 84.
PFS axi-cel	Gompertz SPM without background mortality	Gompertz SPM with background mortality
Mortality in long-term survivors	General population mortality at ~ month 36.	General population mortality applied at month 84.

NoMA agrees with the cost and utility inputs used in the updated submission.

Table 5 NoMA´s updated base case (ITT population) per patient, discounted. List price for axi-cel and chemotherapy excl. VAT.

	Axi-cel	Chemotherapy	Difference
Total costs	3 422 397 NOK	607 748 NOK	2 814 649 NOK
Total QALYs	5,64	2,93	2,70
Total life years	7,24	3,82	3,42
Incremental cost per QALY gained			**1 041 280 NOK**
Incremental cost per life year gained			**822 703 NOK**

Table 6 NoMA´s updated base case (mITT population) per patient, discounted. List price for axi-cel and chemotherapy excl. VAT.

	Axi-cel	Chemotherapy	Difference
Total costs	3 714 698 NOK	609 763 NOK	3 104 935 NOK
Total QALYs	5,87	2,93	2,94
Total life years	7,54	3,82	3,72
Incremental cost per QALY gained			**1 055 456 NOK**
Incremental cost per life year gained			**833 687 NOK**

The estimated incremental survival benefit and cost-effectiveness profile for axi-cel has improved on the basis of the updated OS data, compared to the original assessment. In the ITT population, the QALY gain increased from 1.97 to 2.7, and the ICER decreased from 1.39 million NOK to 1.04 million NOK. In the mITT population, the QALY gain increased from 2.36 to 2.94, and the ICER decreased from 1.28 million NOK to 1.06 million NOK.

When the list price (AIP, excl. VAT) is used for axi-cel and the discounted prices (LIS, excl. VAT) are used in the cost-utility model, the ICER increases minimally to [redacted] in the ITT population and [redacted] in the mITT population.

5.3 SCENARIO ANALYSES

NoMA has explored an impact of alternative long-term extrapolation, relative effect and costs in a number of sensitivity analyses (Table 7).

Only one parameter is changed in each scenario and NoMA's base case settings are used for the remaining parameters in the cost-utility model.

Table 7 Scenario analyses performed by NoMA. List price for axi-cel and chemotherapy excl. VAT.

Parameter	NoMA's base case	Scenario analyses	ICER (NOK)
NoMA's base case (ITT population)	**See 4.2 for all changes**	-	**1 041 280**
OS extrapolation for axi-cel	Spline model with 2 knots. General population mortality applied at month 84.	Spline model with 2 knots for the full model time horizon.	1 074 278
OS extrapolation for axi-cel	Spline model with 2 knots. General population mortality applied at month 84.	Weibull MCM, standardized mortality ratio of 1.12 (based on (19) applied to general population mortality	914 644
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	705 133
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% of the SCHOLAR-1 population receiving post-SCT. OS and PFS for axi-cel are identical to NoMA's base case.	850 237
Hospitalisation length of stay	21.6 days, incl. lymphodepleting therapy, infusion, and monitoring Source: ZUMA-1, assumption	16 days, incl. lymphodepleting therapy, infusion, and monitoring Source: real world data (28)	1 023 201

Hospitalisation length of stay	21.6 days, incl. lymphodepleting therapy, infusion, and monitoring Source: ZUMA-1, assumption	7 days Source: Gilead's original submission.	994 146
Bridging therapy	Not included as this was not permitted in ZUMA-1	Bridging therapy costs of kr 79 980 assumed for 55% of axi-cel patients. Source: real world evidence (8, 10, 13) and Kymriah DLBCL STA (ID2017_116).	1 070 872
Model time horizon	44 years	5 years	3 278 863
Model time horizon	44 years	15 years	1 481 392
Model time horizon	44 years	25 years	1 143 755

The length of hospital stay in clinical practice is uncertain and may turn out to be less than what was observed in ZUMA-1, which was driven by a strict clinical trial protocol. One source of real world data suggests the length of hospital stay could be around 16 days, although the patient population this is based on differs substantially from the patient population in ZUMA-1 (29). Alternative durations of hospitalization did not have a large impact on the ICER, which reduced by about 47 000 NOK in an optimistic scenario where 7 days of hospitalization was assumed.

6 BUDGET IMPACT

NoMA has used the same underlying assumptions to compute the budget impact as in the original assessment. Differences in budget impact between the original and updated assessment are driven solely by updated OS and PFS data and extrapolations.

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.

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 8. The number of patients expected to be treated if Yescarta is not recommended is presented in Table 9.

Table 8 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

	Year 1	Year 2	Year 3	Year 4	Year 5
Yescarta (axi-cel)	20	20	20	20	20
Chemotherapy	0	0	0	0	0
Total	20	20	20	20	20

Table 9 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

	Year 1	Year 2	Year 3	Year 4	Year 5
Yescarta (axi-cel)	0	0	0	0	0
Chemotherapy	20	20	20	20	20
Total	20	20	20	20	20

NoMA has calculated the budget impact for two scenarios:

1. Drug costs for Yescarta and 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.

In both scenarios, costs have been calculated for the ITT and the mITT population and all changes by NoMA as described in section 5.2 are incorporated.

The estimated budget impact in NOK as a result of drug costs only (scenario 1) for the eligible patient population is presented in Table 10 (ITT population) and Table 11 (mITT population).

Table 10 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 11 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 12 (ITT population) and Table 13 (mITT population).

Table 12 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	78 521 681	79 207 835	79 661 388	80 046 732	80 363 696
Yescarta (axi-cel) not recommended for use	11 809 298	12 207 628	12 433 216	12 613 983	12 769 347
Budget impact of recommendation	66 712 382	67 000 206	67 228 172	67 432 748	67 594 349

Table 13 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	86 068 139	86 907 650	87 398 700	87 772 896	88 066 327
Yescarta (axi-cel) not recommended for use	12 026 445	12 494 817	12 727 564	12 895 531	13 036 815
Budget impact of recommendation	74 041 694	74 412 833	74 671 136	74 877 365	75 029 512

The budget impact with the approval of public funding for Yescarta for the eligible patient population as described in this STA is estimated to be around 68 million NOK (ITT analysis) and 75 million NOK (mITT analysis) including VAT in the fifth year after introduction. The calculations are uncertain and based on simplifications. The budget impact has not changed much from the original assessment.

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.

7 SUMMARY AND CONCLUSIONS

Health service interventions are to be evaluated against three prioritisation criteria – the benefit criterion, the resource criterion and the severity criterion. The priority-setting criteria are to be assessed and weighed against one another. The more severe the condition or the more extensive the benefit of the intervention, the 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 updated 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. The updated submission is based on 3-year OS data as opposed to 2-year OS data provided in the original submission. PFS and safety data have not been updated and is based on 2-year data.

In the mITT population, four additional deaths occurred relative to the 2-year data; one of those was due to myelodysplastic syndrome deemed related to prior therapy and 3 were due to lymphoma progression. Median OS was not reached at the 2-year data cut and was 25.8 months (95% CI: 12.8 – not evaluable) at the 3-year data cut. The 2-year OS estimates remained the same with longer follow-up, whereas the 3-year OS rate was 47%. Forty seven patients were censored due to being alive. The ITT population included 10 additional non-infused patients. Median OS in the ITT population was 17.4 months (11.6 - NE), the 2-year OS rate was 48% and the 3-year OS rate was 44%. All of the 49 censored patients were alive at the end of follow-up time.

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, although the 3 years of observed follow up in ZUMA-1 is not short for this patient population, it is still short for assessing a curative potential, and compared to the model time horizon of 44 years. Consequently, there is large uncertainty surrounding long-term outcomes, particularly overall survival, and the relative effect of axi-cel vs. chemotherapy cannot be reliably established.

NoMA's updated 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 3 110 000 excluding pharmacy markup and VAT. The expected (discounted) total healthcare cost was approximately 3.4 million NOK per patient for axi-cel and 0.6 million NOK per patient for chemotherapy in NoMA's base case (ITT population), resulting in a mean incremental healthcare cost of about 2.8 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 updated 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 (1). The estimated absolute shortfall has not changed from the original assessment.

NoMA's updated assessment of budget impact:
NoMA estimated the budget impact of the total healthcare costs for the specialist health services to be around 68 million NOK (ITT analysis) and 75 million NOK (mITT analysis) 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 updated assessment of quality and uncertainty associated with documentation:
The pivotal ZUMA-1 study is considered to have considerable shortcomings to inform this STA as it is a single arm study with a small sample size (101 infused patients). The updated 3-year OS data are welcome as they decrease some uncertainty surrounding OS for axi-cel, which is an important input in the cost-effectiveness model. The updated OS data do not, however, resolve the uncertainty surrounding the incremental treatment effect of axi-cel compared to standard care due to the absence of randomized data. ZUMA-1 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. Furthermore, the fact that PFS data has not been updated is considered a limitation as different follow-up times lead to inconsistencies in the long-term extrapolation of OS and PFS.

NoMA does not exclude the possibility of a curative potential, but doesn't consider Gilead's assumption that the mortality in axi-cel infused patients returns to general population levels at the end of the ZUMA-1 follow-up time supported by any data nor clinical plausibility arguments. Evidence from the literature suggests that the mortality is still increased in patients with relapsed DLBCL after autologous transplant who achieved event-free survival at 60 months (21). Gilead has also provided real-world evidence for axi-cel but the follow-up in those studies is too short to support the long-term survival predictions in the model.

Since CAR-T cell therapy is a new treatment principle, which involves genetic modification of the patient's own T cells, there is uncertainty surrounding long-term outcomes, including overall survival. Randomized controlled trials with longer patient follow-up are needed to resolve the uncertainty surrounding the long-term outcomes with axi-cel and the incremental survival benefit compared to standard care. New and ongoing studies are expected to report in the coming years, and data from these studies will likely improve decision making.

Statens legemiddelverk, 09-11-2020

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ATTACHMENT 1 COMMENTS FROM THE MANUFACTURER

Gilead Sciences would like to give our comment to NOMAs revised/updated Yescarta report:

1. The updated analysis shows an ICER having gone down substantially, to just above 1 mill. NOK per QALY, down from 1,3 mill NOK and 1,4 mill NOK respectively. This substantially improved cost-effectiveness is mainly due to survival data for Yescarta being clearly better than NOMA assumed in 2019, at the same time corresponding well with Gilead´s previous model.
2. NOMA´s first analysis of Yescarta based on the two years survival data underestimated survival for the patients significantly. In their first analysis, NOMAs calculations showed a survival at three years at approximately 38%. The follow up data from the study (Kaplan-Meier) shows a three years survival at 47%, 9 percentage points higher.
3. In the revised/updated report NOMA continues to use a very conservative methodological approach as regards modelling of future survival. Clinical experts have given inputs to NOMA that Yescarta has a curative potential, and NOMA follows this up by assuming “cure”, but only after 84 months. This is also a very conservative approach, only partially following inputs from clinical experts. Furthermore, NOMA has used a two-knot spline model as their preferred model for survival extrapolation. Very little information has been supplied on the statistical justification of this model including; the fit to the underlying hazard function and the determination of knot points. These should be considered before implementing the model. It should also be noted in the report that, unlike cure models, spline models do not explicitly model the uncured and cured populations, which is contrary to clinical expert opinion.
4. We have provided to NOMA a revised model on the comparator survival, i.e. the standard of care today. We have also provided real life survival data for the actual patients from OUS/Radiumhospitalet. NOMA has not revised their conservative approach for the comparator survival.
5. NOMA highlights uncertainty in their report. We think that it is clear that the data is maturing, and we are confident that future survival data of Yescarta will be showing a trend of improved long term Overall Survival, in line with what we have seen this far and congruent with our original prediction.
6. There are many new technologies onwards that are developed with protocols similar to the Yescarta ZUMA-1 study, with few enrolled patients and without an active comparator arm. We are afraid that because of a conservative approach towards such studies in Norway, the HTA appraisals will continue to underestimate real value to patients and society, limiting access to such technologies for Norwegian patients.

REFERENCES

1. Norwegian Medicines Agency. 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). Assessment report.; 2019.
2. Nasjonalt handlingsprogram med retningslinjer for diagnostikk, behandling og oppfølging av pasienter med maligne lymfomer: The Norwegian Directorate of Health; 2019 [Available from: https://helsedirektoratet.no/Lists/Publikasjoner/Attachments/1492/IS-2747%20Handlingsprogram%20lymfom%20090119.pdf.
3. Crump M, Neelapu SS, Farooq U, Van Den Neste E, Kuruvilla J, Westin J, et al. Outcomes in refractory diffuse large B-cell lymphoma: results from the international SCHOLAR-1 study. Blood. 2017.
4. Cheson BD, Pfistner B, Juweid ME, Gascoyne RD, Specht L, Horning SJ, et al. Revised response criteria for malignant lymphoma. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2007;25(5):579-86.
5. Kite Pharma Inc. KTE-C19-101 A phase 1/2 multicenter study evaluating the safety and efficacy of KTE-C19 in subjects with refractory aggressive nonhodgkin lymphoma (ZUMA-1). (Clinical Study Report: KTE-C19-101). Data on file 28 July 2017.
6. Neelapu SS RJ, Jacobson CA, et al. CD19-Loss With Preservation of Other B Cell Lineage Features in Patients With Large B Cell Lymphoma Who Relapsed Post–Axi-Cel. 61st American Society of Hematology Annual Meeting; December 7-10, 2019; Orlando, FL, US.
7. Sano D, Nastoupil LJ, Fowler NH, et al. 96: Safety of Axicabtagene Ciloleucel CD19 CAR T-Cell Therapy in Elderly Patients with Relapsed or Refractory Large B-Cell Lymphoma. 60th Annual Meeting of the American Society of Hematology; December 1-4, 2018; San Diego, CA, US.
8. Nastoupil LJ, Jain MD, Spiegel JY, et al. 91: Axicabtagene Ciloleucel (Axi-cel) CD19 Chimeric Antigen Receptor (CAR) T-cell Therapy for Relapsed/Refractory Large B-cell Lymphoma: Real World Experience. 60th Annual Meeting of the American Society of Hematology; December 1-4, 2018; San Diego, CA, US.
9. Nastoupil LJ, Jain MD, Feng L, Spiegel JY, Ghobadi A, Lin Y, et al. Standard-of-Care Axicabtagene Ciloleucel for Relapsed or Refractory Large B-Cell Lymphoma: Results From the US Lymphoma CAR T Consortium. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2020;38(27):3119-28.
10. Jacobson CA, Hunter B, Armand P, et al. 92: Axicabtagene Ciloleucel in the Real World: Outcomes and Predictors of Response, Resistance & Toxicity. 60th Annual Meeting of the American Society of Hematology; December 1-4, 2018; San Diego, CA, US.
11. Jacobson CA, Hunter BD, Redd R, Rodig SJ, Chen PH, Wright K, et al. Axicabtagene Ciloleucel in the Non-Trial Setting: Outcomes and Correlates of Response, Resistance, and Toxicity. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2020;38(27):3095-106.
12. Pasquini MC, Locke F, Herrera A, et al. Post-Marketing Use Outcomes of an Anti-CD19 Chimeric Antigen Receptor (CAR) T Cell Therapy, Axicabtagene Ciloleucel (Axi-Cel), for the Treatment of Large B Cell Lymphoma (LBCL) in the United States (US). 61st Annual Meeting of the American Society of Hematology; December 7-10, 2019; Orlando, FL, US.
13. Thieblemont C, Le Gouill S, Di Blasi R, et al. Real-world results of an anti-CD19 CAR T-cell axicabtagene ciloleucel for patients with relapsed/refractory large B-cell lymphoma included in a French early access program EHA-EBMT 2nd European CAR T Cell Meeting; January 30 – February 1, 2020; Sitges, Spain.
14. Kuhnl A, Roddie C, Kirkwood AA, et al. OUTCOME OF HIGH GRADE LYMPHOMA PATIENTS TREATED WITH CD19 CAR T UPDATED REAL WORLD EXPERIENCE IN THE UK. EHA Annual Meeting 2020; June, 2020; Orlando, FL, US.

15. Kite Pharma EU B.V. YESCARTA (axicabtagene ciloleucel) Summary of Product Characteristics January 2020 [Available from: https://www.ema.europa.eu/en/documents/product-information/yescarta-epar-product-information_en.pdf.
16. European Medicines Agency. Yescarta (axicabtagene ciloleucel) Committee for Medicinal Products for Human Use (CHMP) Assessment Report Procedure No. EMEA/H/C/004480/0000 June 28, 2018 [Available from: https://www.ema.europa.eu/documents/assessment-report/yescarta-epar-public-assessment-report_en.pdf.
17. Lee DW, Santomasso BD, Locke FL, Ghobadi A, Turtle CJ, Brudno JN, et al. ASTCT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells. Biology of Blood and Marrow Transplantation. 2019;25(4):625-38.
18. Howlader N, Mariotto AB, Besson C, Suneja G, Robien K, Younes N, et al. Cancer-specific mortality, cure fraction, and noncancer causes of death among diffuse large B-cell lymphoma patients in the immunochemotherapy era. Cancer. 2017;123(17):3326-34.
19. Jakobsen LH, Bøgsted M, Brown PdN, Arboe B, Jørgensen J, Larsen TS, et al. Minimal loss of lifetime for patients with diffuse large B-cell lymphoma in remission and event free 24 months after treatment: a Danish population-based study. Journal of Clinical Oncology. 2017;35(7):778-84.
20. Smeland KB, Kiserud CE, Lauritzsen GF, Blystad AK, Fagerli UM, Falk RS, et al. A national study on conditional survival, excess mortality and second cancer after high dose therapy with autologous stem cell transplantation for non-Hodgkin lymphoma. Br J Haematol. 2016;173(3):432-43.
21. Assouline S, Li S, Gisselbrecht C, Fogarty P, Hay A, van den Neste E, et al. The conditional survival analysis of relapsed DLBCL after autologous transplant: a subgroup analysis of LY.12 and CORAL. Blood Adv. 2020;4(9):2011-7.
22. Burström K, Johannesson M, Diderichsen F. Swedish population health-related quality of life results using the EQ-5D. Quality of life research. 2001;10(7):621-35.
23. Norwegian Medicines Agency. Single Technology assessment -Tisagenlecleucel (Kymriah) for the treatment of second or later relapsed/refractory diffuse large B cell lymphoma (DLBCL). 2019.
24. Lindemark F, Haaland ØA, Kvåle R, Flaatten H, Norheim OF, Johansson KA. Costs and expected gain in lifetime health from intensive care versus general ward care of 30,712 individual patients: a distribution-weighted cost-effectiveness analysis. Critical Care. 2017;21(1):220.
25. Lindemark F, Haaland ØA, Kvåle R, Flaatten H, Norheim OF, Johansson KA. Additional File - Costs and expected gain in lifetime health from intensive care versus general ward care of 30,712 individual patients: a distribution-weighted cost-effectiveness analysis. Critical Care. 2017;21(1).
26. Wang H-I, Smith A, Aas E, Roman E, Crouch S, Burton C, et al. Treatment cost and life expectancy of diffuse large B-cell lymphoma (DLBCL): a discrete event simulation model on a UK population-based observational cohort. The European Journal of Health Economics. 2017;18(2):255-67.
27. Moger TA, Bjørnelv GM, Aas EJTEJoHE. Expected 10-year treatment cost of breast cancer detected within and outside a public screening program in Norway. 2016;17(6):745-54.
28. Riedel P A et al. A multicenter retrospective analysis of outcomes and toxicities with commercial axicabtagene ciloleucel and tisagenleucleucel for relapsed/refractory aggressive B-cell lymphomas. Poster ASH 2019, more updated data presented at TCT.