Single Technology assessment

Tisagenlecleucel (Kymriah) for the treatment of second or later relapsed/refractory diffuse large B cell lymphoma (DLBCL)

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Norwegian Medicines Agency

PREFACE

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

The Norwegian Medicines Agency has been assigned the responsibility to evaluate Single Technology Assessments (STA) 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. The cost-effectiveness ratio will be weighed against the severity of the relevant condition/disease. NoMA does not assess the benefit risk balance already assessed under the market-authorisation procedure. Information about this is provided by EMA (SmPC Kymriah).

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

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

EXECUTIVE SUMMARY

Rationale

Single technology assessment (STA) of tisagenlecleucel (Kymriah) for the treatment of adult patients with relapsed or refractory (r/r) diffuse large B-cell lymphoma (DLBCL) after two or more lines of systemic therapy. The benefits and risk of tisagenlecleucel in r/r DLBCL have been documented through the approval of marketing authorisation. In this STA, NoMA has assessed tisagenlecleucel treatment against the prioritisation criteria – the benefit criterion, the resource criterion and the severity criterion, according to the Summary of product characteristics (SmPC) for tisagenlecleucel, and the request specifications from Ordering Forum (request number ID2017_116: Tisagenlecleucel (Kymriah). Indikasjon II. Behandling av diffust storcellet B-cellelymfom). Request from Ordering Forum can be found at www.nyemetoder.no. NoMA´s assessment is mainly, but not exclusively, based on the documentation presented by Novartis.

Background

Tisagenlecleucel 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. When tisagenlecleucel 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 lentiviruses 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.

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

According to Novartis, the manufacture and release of the tisagenlecleucel product usually takes about 3-4 weeks. Some patients require bridging chemotherapy to stabilize the cancer while waiting for the tisagenlecleucel infusion. During this waiting period, some of the 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 for infusion.

Patient population

In Norway, approximately 20 r/r DLBCL 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 is poor. In Norway, the degree of severity affects whether the costs are considered reasonable relative to the benefit of the treatment. NoMA has estimated that adult patients with r/r DLBCL have an absolute shortfall of approximately 15-16 Quality Adjusted Life Years (QALYs).

Treatment in the Norwegian setting

Treatment of DLBCL is described in national guidelines from The Norwegian Directorate of Health (1). With current frontline standard of care (R-CHOP, rituximab with cyclophosphamide, doxorubicin, vincristine, and prednisolone) the overall cure rate of adult patients with DLBCL is around 50 – 60%. Patients who relapse will be offered a new treatment regimen 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 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 tisagenlecleucel was demonstrated in one pivotal phase II study (JULIET) in adult patients with r/r DLBCL. The primary endpoint was the best overall response rate, defined as the combined rates of complete response (CR) and partial response (PR). Secondary endpoints included progression free survival (PFS) and overall survival (OS). The JULIET study is ongoing. At the data cut-off date (DCO) of 21-May-2018, the median time from infusion to last follow-up was 19.3 months (range: 0.4 to 28.9). Data from the latest DCO of 11-Dec-2018 were also assessed but remain confidential. Among the 167 patients enrolled in JULIET, 115 patients (69%) received infusion with tisagenlecleucel. The reasons for discontinuation prior to tisagenlecleucel infusion included: death (n=16), physician decision (n=16), tisagenlecleucel manufacturing failure (n=13), adverse events (n=4), patient decision (n=2), and protocol deviation (n=1). The median time from enrolment to CAR-T administration was 54 days (range: 30 to 357 days).

Among the 99 patients who received tisagenlecleucel at least 3 months prior to DCO, the best overall response rate was 54%. In total, 40% of these patients achieved CR. In the intention-to-treat (ITT) analyses of the enrolled patient population (167 patients), the rates of PFS and OS were 35% and 57%, respectively, at 6 months, and 31% and 40% at 12 months. The median PFS was 4.6 months (95% CI: 3.7 to 5.2), and the median OS was 10.6 months (95% CI: 8.3 to 16.1).

The JULIET trial was designed as a single arm study. Novartis has conducted matching-adjusted indirect comparisons (MAIC) with historical controls in order to document the relative efficacy of tisagenlecleucel compared to chemotherapy regimens. The CORAL study is a phase III, multicenter, randomised trial that compared two different second-line salvage regimens, followed by ASCT, in patients with relapsed DLBCL. Patients in the CORAL study who relapsed after ASCT (n=75), and patients who failed to proceed to ASCT (n=203) were prospectively recorded in the CORAL observational follow-up phase. NoMA considers these CORAL extension studies as being an acceptable source of a historical control. However, as the MAIC approach failed to address important differences between the arms, there is little difference between unadjusted and MAIC-adjusted comparisons. The key issue with the comparison vs. CORAL extension studies is the pronounced lead time bias favouring JULIET which would not be present if JULIET was a randomised controlled trial. Consequently, the magnitude of the benefit of tisagenlecleucel is unclear as it

is largely impacted by the early deaths in the CORAL extension studies. NoMA's base case is built on a "lead time"-adjusted analysis which aligns the starting time of the survival analysis in both arms to the JULIET trial, and where the CORAL patients who would not be eligible for JULIET are removed.

Safety
Serious side effects occur in most patients. As the activated CAR-T cells proliferate in the patient and kill tumor B cells, they release inflammatory cytokines. This can cause cytokine release syndrome (CRS) with symptoms like high fevers, low blood pressure, and respiratory distress. Another common and serious side effect is neurotoxicity. The most common neurologic side effects include encephalopathy, headache, delirium, aphasia, anxiety, and tremors. 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 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 tisagenlecleucel is present.

The most common non-haematological adverse reactions in the clinical studies with patients with DLBCL were CRS (57%), infections (54%), pyrexia (35%), diarrhoea (32%), nausea (29%), hypotension (26%) and fatigue (26%). Grade 3 and 4 adverse reactions were reported in 89% of the patients. The most common Grade 3 and 4 non-haematological adverse reactions were infections (32%) and CRS (23%). The most common (>25%) Grade 3 and 4 haematological laboratory abnormalities were lymphocyte count decreased (95%), neutrophil count decreased (81%), white blood cell count decreased (77%), haemoglobin decreased (59%) and platelet count decreased (55%).

Cost effectiveness
NoMA has assessed the submitted health economic analyses from Novartis received on 02-July-2018. Novartis has on 01-Apr-2019 provided an updated model based on data from the latest DCO of JULIET and used that opportunity to also update some of the assumptions in their base case in line with the assumptions in NoMA's base case.

The main difference between NoMA's base case and Novartis's updated base case is the comparison of JULIET vs. CORAL extension studies. NoMA's base case is built on a "lead time"-adjusted analysis where the CORAL patients who died early, and hence would not be eligible for JULIET, are removed. This adjustment increased the subsequent SCT rate and survival in the comparator arm. Please refer to section 4.2 for a detailed description of the changes NoMA has made to the Novartis analysis.

NoMA has estimated an incremental cost-effectiveness ratio (ICER) for tisagenlecleucel compared to chemotherapy. NoMA considers both the ITT population (enrolled patients) and the modified ITT (mITT) population (infused patients) relevant for decision making. Patients that remain progression-free are considered "cured" in the analyses. Spline models with two knots are used to extrapolate PFS and OS for tisagenlecleucel. The tisagenlecleucel OS curve is constrained by the PFS curve, and from the point of convergence the mortality rate as modelled for the comparator arm is applied. For the comparator arm NoMA selected the Gompertz function for OS extrapolation and PFS survival function is based on the

OS:PFS ratio as modelled for tisagenlecleucel. Multiple important limitations and uncertainties in the analysis were identified and remained.

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

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

A scenario analysis where the survival analysis started from enrolment (ITT) in JULIET and from last relapse in the comparator arm resulted in an ICER of 1.4 million NOK per QALY gained.

Budget impact
NoMA estimated the budget impact of the total healthcare costs for the specialist health services to be around 53 - 76 million NOK including VAT in the fifth year after introduction, provided that all eliglible adult patients with r/r DLBCL are treated with tisagenlecleucel.

NoMA´s overall assessment
NoMA identified multiple important limitations and uncertainties in the analysis that remained. The JULIET study was a single arm study of small size (115 infused patients), and with a median follow-up time just above 2 years. The study lacks a control arm, and it is therefore not possible to compare outcomes from this trial with outcomes from comparator trials without a high degree of uncertainty. Long-term outcomes - both in terms of efficacy and safety - are currently not known. Thus far, none of the trials for CAR-T therapy have followed patients for a sufficient time to ascertain whether adult patients with r/r DLBCL who have an ongoing response could be considered cured. NoMA considers the estimated gain in overall and quality adjusted survival for tisagenlecleucel compared to chemotherapy to be highly uncertain. Additional follow-up data are needed to evaluate the long-term outcomes with tisagenlecleucel and reduce the large amount of uncertainty in the analysis. New and ongoing studies are expected to report in the coming years, and data from these studies will likely improve decision making.

OPPSUMMERING

Formål

Hurtig metodevurdering av legemiddelet Kymriah (tisagenlekleucel) i henhold til godkjent preparatomtale og bestilling ID2017_116: «Tisagenlecleucel (Kymriah). Indikasjon II. Behandling av diffust storcellet B-cellelymfom». Legemiddelverket har vurdert prioriteringskriteriene knyttet til alvorlighet, nytte og ressursbruk. Vurderingen tar utgangspunkt i dokumentasjon innsendt av Novartis.

Bakgrunn

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

Kymriah er godkjent til behandling av voksne pasienter med residivert eller refraktært diffust storcellet B-cellelymfom (DLBCL) etter to eller flere systemiske behandlinger. Om lag 20 pasienter med DLBCL er aktuelle for behandling med CAR-T celleterapi hvert år i Norge.

Alvorlighet og helsetap

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

Effekt

Av totalt 167 pasienter som ble inkludert i hovedstudien JULIET, var det 52 pasienter som ikke fikk infusjon med Kymriah, enten fordi Kymriah ikke kunne lages, eller fordi pasienten døde, fikk sykdomsprogresjon eller bivirkninger i ventetiden. Av 99 pasienter som fikk infusjon med Kymriah, og som er fulgt i minst 3 måneder, var det 54 % som fikk respons. Etter ett år var sannsynligheten for å være i live ca. 48 % for de pasientene som hadde fått infusjon. Det var ingen kontrollgruppe i studien og oppfølgingstiden er foreløpig kort. Behandlingsalternativet i dag er kjemoterapi kombinert med rituksimab, som hos noen pasienter blir etterfulgt av stamcelletransplantasjon. Vi har ikke pålitelige data for effektforskjellen mellom Kymriah og dagens behandling.

Sikkerhet

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

Kostnadseffektivitet

Legemiddelverket har vurdert om kostnadene ved bruk av Kymriah står i et rimelig forhold til den nytten behandlingen gir. To pasientgrupper er analysert: Innrullerte pasienter (alle pasienter i studien, både

pasienter som fikk infusjon med Kymriah og pasienter som falt fra i ventetiden) og Infuserte pasienter (kun pasienter som fikk infusjon med Kymriah). I de analysene Legemiddelverket mener kan være sannsynlige, med dagens maksimalpriser for legemidlene, er merkostnad for Kymriah sammenlignet med kjemoterapi:

- 1,8 millioner NOK per vunnet kvalitetsjusterte leveår (QALY) for innrullerte pasienter.
- 2,4 millioner NOK per vunnet kvalitetsjusterte leveår (QALY) for infuserte pasienter.

I et scenario der analysen av overlevelse starter fra innrullering i JULIET og fra siste tilbakefall i kjemoterapi-armen, var merkostnaden for Kymriah 1,4 millioner NOK per vunnet QALY.

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

Budsjettkonsekvenser
Legemiddelverket har estimert at budsjettvirkningen for sykehusene vil være om lag 53 - 76 millioner NOK per år i år fem, hvis Kymriah innføres til behandling av voksne med residivert/refraktært DLBCL.

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

SAMMENDRAG

Metode

Hurtig metodevurdering av legemiddelet tisagenlekleucel (Kymriah) til behandling av voksne pasienter med residivert eller refraktært (r/r) diffust storcellet B-cellelymfom (DLBCL) etter to eller flere systemiske behandlinger. Vurderingen er i henhold til godkjent preparatomtale og bestilling ID2017_116: «Tisagenlecleucel (Kymriah). Indikasjon II. Behandling av diffust storcellet B-cellelymfom». Legemiddelverket har vurdert prioriteringskriteriene knyttet til alvorlighet, nytte og ressursbruk. Vurderingen tar utgangspunkt i dokumentasjon innsendt av Novartis.

Bakgrunn

Tisagenlekleucel 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 ved f.eks. DLBCL. Når tisagenlekleucel 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 lentivirus 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.

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

Ifølge Novartis, vil produksjon og frigiving av ferdig tisagenlekleucel vanligvis ta 3-4 uker. Noen pasienter vil trenge kjemoterapi for å stabilisere kreftsykdommen mens de venter på infusjon med tisagenlekleucel. 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 er aktuelle for behandling med CAR-T celleterapi hvert år i Norge.

Alvorlighet og prognosetap

Pasienter med r/r DLBCL 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 er beskrevet i "Nasjonalt handlingsprogram med retningslinjer for diagnostikk behandling og oppfølging av maligne lymfomer" fra Helsedirektoratet (1). I dag blir ca. 50 – 60 % av pasientene kurert ved standard førstelinjebehandling med R-CHOP (rituksimab med syklofosfamid, doksorubicin, vinkristin og prednisolon). 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 kjemoterapikombinasjoner med rituksimab. 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 tisagenlekleucel er vist i en åpen, enarmet, fase 2 studie (JULIET) hos voksne pasienter med residivert eller refraktært DLBCL. Primært endepunkt var beste totale responsrate, som inkluderte komplett respons (CR) og partiell respons (PR). Totaloverlevelse (OS) og progresjonsfri overlevelse (PFS) var sekundære endepunkter. JULIET pågår fortsatt. Ved datakutt 21-05-2018 var median oppfølgingstid 19,3 måneder (fra 0,4 til 28,9 måneder) etter infusjon. Data fra siste datakutt 11-12-2018 er også vurdert, men er foreløpig konfidensielle. Av 167 pasienter som ble innrullert i JULIET, fikk 115 (69 %) infusjon med tisagenlekleucel. Årsaker til frafall før infusjon var død (n=16), legens beslutning (n=16), at tisagenlekleucel ikke kunne produseres (n=13), bivirkninger (n=4), pasientens beslutning (n=2) og protokollavvik (n=1). Median tid fra innrullering til CAR-T infusjon var 54 dager (fra 30 til 357 dager).

Beste totale responsrate var 54 % hos pasienter som hadde fått tisagenlekleucel minst 3 måneder før datakutt (99 pasienter). Totalt 40 % av pasientene oppnådde CR. I intention-to-treat (ITT) analysen av alle innrullerte pasienter (167 pasienter), var sannsynligheten for PFS og OS henholdsvis 35 % og 57 % ved 6 måneder og 31 % og 40 % ved 12 måneder. Median PFS var 4,6 måneder (95 % KI: 3,7 – 5.2) og median OS var 10,6 måneder (95 % KI: 8,3 – 16,1).

JULIET har enkeltarmet studiedesign, og Novartis har gjort justerte indirekte sammenligninger (matching-adjusted indirect comparisons, MAIC) med historiske kontroller for å estimere relativ effekt av tisagenlekleucel sammenlignet med kjemoterapi. CORAL er en randomisert, fase 3 studie som sammenlignet to kjemoterapiregimer, etterfulgt av ASCT, i andrelinjebehandling av pasienter med residivert DLBCL. Pasienter i CORAL som fikk tilbakefall etter ASCT (n=75) eller som feilet på kjemoterapi og ikke gikk videre til ASCT (n=203), er fulgt opp i observasjonsstudier. Legemiddelverket vurderer at disse CORAL forlengelsesstudiene kan aksepteres som kilde for historisk kontroll. Det var imidlertid ikke mulig å justere for viktige forskjeller mellom armene i MAIC-analysen, og resultatene fra denne skiller seg lite fra en ujustert sammenligning. Hovedutfordringen i sammenligningen, er en betydelig «lead time»-bias i favør av JULIET, som ikke ville vært tilstede hvis JULIET var en randomisert kontrollert studie. Størrelsen på mereffekten av tisagenlekleucel er derfor usikker siden sammenligningen er påvirket av de mange tidlige dødsfallene i CORAL forlengelsesstudiene. Legemiddelverkets base case er bygget på en «lead

time»-justert analyse hvor startpunkt for analysen av overlevelse er samkjørt mellom armene og hvor CORAL pasienter som ikke ville være kvalifisert for innrullering i JULIET er fjernet.

Sikkerhet

De fleste får bivirkninger etter infusjon av tisagenlekleucel. Etter hvert som de aktiverte CAR-T cellene prolifererer i pasienten og dreper kreftceller, vil inflammatoriske cytokiner frisettes. Dette kan forårsake cytokinfrigjøringssyndrom (CRS) med symptomer som høy feber, lavt blodtrykk og pustevansker. En annen vanlig og alvorlig bivirkning er nevrotoksisitet. De vanligste nevrologiske bivirkningenen er encefalopati, hodepine, delirium, afasi, angst og tremor. 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 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 tisagenlekleucel er tilstede i pasienten.

De vanligste ikke-hematologiske bivirkningene i kliniske studier hos pasienter med DLBCL var CRS (57 %), infeksjoner (54 %), feber (35 %), diaré (32 %), kvalme (29 %), hypotensjon (26 %) og fatigue (26 %). Bivirkinger av grad 3 og 4 ble rapportert hos 89 % av pasientene. De vanligste grad 3 og 4 ikke-hematologiske bivirkningene var infeksjoner (32 %) og CRS (23 %). De vanligste grad 3 og 4 avvikende hematologiske laboratoriefunnene var redusert antall lymfocytter (95 %), redusert antall nøytrofile (81 %), redusert antall hvite blodceller (77 %), redusert hemoglobinnivå (59 %) og redusert antall blodplater (55 %).

Kostnadseffektivitet

Legemiddelverket har vurdert innsendt helseøkonomisk analyse fra Novartis mottatt 02-07-2019. Novartis sendte inn en oppdatert modell 01-04-2019, som er basert på data fra siste datakutt i JULIET, og har i den anledning også oppdatert noen av forutsetningene i sitt basecase i tråd med forutsetningene i Legemiddelverkets basecase.

Den viktigste forskjellen mellom Legemiddelverkets basecase og Novartis' basecase, er sammenligningen av JULIET vs. CORAL forlengelsesstudier. Legemiddelverkets basecase er bygget på en «lead time»-justert analyse hvor CORAL-pasienter som døde tidlig, og som dermed ikke ville vært kvalifisert for innrullering i JULIET, er fjernet. Denne justeringen øker andel pasienter som får etterfølgende SCT og overlevelse i komparatorarmen.

Legemiddelverket har estimert en inkrementell kostnad-effektbrøk (IKER) for tisagenlekleucel sammenlignet med kjemoterapi. Legemiddelverket mener at både ITT populasjonen (innrullerte pasienter) og mITT populasjonen (infuserte pasienter) er relevante for beslutningstaking. I analysene antas pasienter som forblir progresjonsfrie å være «kurert». PFS og OS for tisagenlekleucel ekstrapoleres med spline modeller med to knots. OS-kurven for tisagenlekleucel begrenses av PFS-kurven, og fra det tidspunktet kurvene sammenfaller settes mortalitetsraten lik den modellerte mortalitetsraten i

komparatorarmen. I komparatorarmen velger Legemiddelverket en Gompertz funksjon for ekstrapolering av OS, og PFS er ekstrapolert basert på OS:PFS ratioen som modellert for tisagenlekleucel. Analysene har en rekke viktige begrensninger og usikkerheter. Legemiddelverket anser derfor at estimatene for kostnadseffektivitet er svært usikre.

I Legemiddelverkets analyser, med dagens maksimalpriser for legemidlene, er merkostnad for tisagenlekleucel sammenlignet med kjemoterapi:

- 1,8 millioner NOK per vunnet kvalitetsjusterte leveår (QALY) for innrullerte pasienter.
- 2,4 millioner NOK per vunnet kvalitetsjusterte leveår (QALY) for infuserte pasienter.

I et scenario der analysen av overlevelse starter fra innrullering i JULIET og fra siste tilbakefall i kjemoterapi-armen, var merkostnad for tisagenlekleucel 1,4 millioner NOK per vunnet QALY.

Budsjettkonsekvenser
Legemiddelverket har estimert at budsjettvirkningen for sykehusene vil være om lag 53 – 76 millioner NOK per år i år fem, hvis tidsagenlekleucel innføres til behandling av voksne med r/r DLBCL.

Legemiddelverkets totalvurdering
Legemiddelverket har identifisert en rekke viktige begrensninger og usikkerheter i analysene, og disse er fortsatt tilstede. Studien JULIET har enkeltarmet studiedesign, er relativt liten (167 innrullerte pasienter, 115 infuserte pasienter) og median oppfølgingstid er foreløpig vel 2 år. JULIET mangler kontrollarm, og det er derfor ikke mulig å sammenligne resultater fra denne studien med resultater fra komparatorstudiene uten stor grad av usikkerhet. Langtidsvirkninger – både når det gjelder effekt og bivirkninger – er foreløpig ikke kjent. Så langt har ingen studier av CAR-T celleterapi fulgt pasientene lenge nok til å fastslå om pasienter med vedvarende respons kan anses å være kurert. Legemiddelverket vurderer at estimert gevinst i totaloverlevelse og kvalitetsjustert overlevelse, for tisagenlekleucel sammenlignet med kjemoterapi, er svært usikker.

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Logg

Bestilling:	ID2017_116: Tisagenlecleucel (Kymriah). Indikasjon II. Behandling av diffust storcellet B-cellelymfom
Forslagstiller:	Metodevarsel fra Legemiddelverket
Legemiddelfirma:	Novartis
Preparat:	Kymriah
Virkestoff:	tisagenlekleucel
Indikasjon:	Behandling av voksne med residivert eller refraktært diffust storcellet B-cellelymfom (DLBCL) etter to eller flere systemiske behandlinger.
ATC-nr:	L01

Prosess

Dokumentasjon bestilt av Legemiddelverket	30-10-2017
Fullstendig dokumentasjon mottatt hos Legemiddelverket	02-07-2018
Klinikere kontaktet for første gang	29-06-2018
LIS kontaktet for første gang av Legemiddelverket	28-02-2018
Legemiddelverket bedt om ytterligere dokumentasjon	05-07-18 og 14-08-18. Svar mottatt: 28-09-18 og 13-10-18 22-10-18. Svar mottatt: 24-10-18 og 04-11-18 06-11-18. Svar mottatt: 26-11-18 12-11-18. Svar mottatt: 25-11-18, 06-12-18 og 10-12-18 28-11-18. Svar mottatt: 06-12-18 21-01-19 (draft report). Svar mottatt: 14-03-19, 29-03-19 og 01-04-19 (Novartis's updated base case)
Rapport ferdigstilt:	11-06-2019
Saksbehandlingstid:	344 dager hvorav 164 dager i påvente av ytterligere opplysninger fra legemiddelfirma.
Saksutredere:	Ania Urbaniak Einar Andreassen Kirsti Hjelme Maria Elisabeth Kalland Mathyn Vervaart Terry Vrinzen
Kliniske eksperter:	Alexander Fosså Fredrik Sund Bjørn Østenstad Unn Merete Fagerli
Kliniske eksperter har bidratt med avklaringer av sentrale forutsetninger i analysen (bl.a. sammenlignende behandling, pasientgrunnlag og overførbarhet av studiedata til norsk klinisk praksis). Legemiddelverket er ansvarlig for rapportens innhold. Kliniske eksperter har ikke vært involvert i noen konsensusprosess eller hatt noen «peer-review» funksjon ved utarbeidelse av rapporten.	

GLOSSARY

alloSCT	Allogenic Stem Cell Transplantation
AE	Adverse event
ASCT	Autologous Stem Cell Transplantation
BOR	Best overall response
CAR	Chimeric Antigen Receptor
CNS	Central Nervous System
Cohort A	Patients treated with tisagenlecleucel from the EU manufacturing facility, Fraunhofer Institut für Zelltherapie, Leipzig, Germany
CR	Complete Response
CRS	Cytokine Releasing Syndrome
DCO	Data-cut off
DHAP	Dexamethasone, cytarabine, cisplatin
DLBCL	Diffuse large B-cell lymphoma
DoR	Duration of overall response
DRG	Diagnosis Related group
EAS	All patients who receive tisagenlecleucel infusion at least 3 months prior to DCO date
ECOG	Eastern Cooperative Oncology Group
EFS	Event-Free Survival
EMA	European Medicines Agency
EPOCH	etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin
EQ-5D	European Quality of Life-5 Dimensions
ESHAP	Etoposide, methylprednisolone, cytarabine, cisplatin
FACT-Lym	Functional Assessment of Cancer Therapy-Lymphoma
GDP	Gemcitabine, dexamethasone, cisplatin
Gem-OX	Gemcitabine, oxaliplatin
HRQoL	Health related quality of life
ICE	Ifosfamide, carboplatin, etoposide
ICU	Intensive care unit
IME	Ifosfamide, methotrexate, etoposide
IPI	International Prognostic Index
IRC	Independent Review Committee

IV	Intravenous
IVE	ifosfamide, etoposide, epirubicin
IVIG	Intravenous immunoglobulins
KM	Kaplan-Meier
MAIC	Matching-Adjusted Indirect Comparison
Main Cohort	Patients treated with tisagenlecleucel from US manufacturing facility, Morris Plains
MCM	Mixture Cure Model
MRD	Minimal Residual Disease
NHL	Non-Hodgkin lymphoma
NoMA	Norwegian Medicines Agency
ORR	Overall Response Rate
OS	Overall Survival
OUS	Oslo University Hospital
PFS	Progression-free survival
PR	Partial Response
QALY	Quality Adjusted Life Year
r/r	Relapsed or refractory
SF-36	Short-Form 36
SmPC	Summary of product characteristics
STA	Single Technology Assessment
TFL	Transformed follicular lymphoma
TTR	Time to response

1 BACKGROUND

1.1 SCOPE

This single technology assessment (STA) concerns the treatment of adult patients with relapsed or refractory (r/r) DLBCL in second or later relapse with the CAR-T cell therapy tisagenlecleucel (Kymriah) in Norway.

Health service interventions are evaluated against the three prioritisation criteria in Norway – the benefit criterion, the resource criterion and the severity criterion. Tisagenlecleucel is compared to chemotherapy in cost-utility analyses (CUA). The priority-setting criteria are evaluated together and weighed against each other. NoMA´s assessment is primarily, but not exclusively, based on the documentation presented by Novartis.

NoMA received documentation for STA from Novartis 02-July-2018. A draft STA report from NoMA was shared with Novartis 21-Jan-2019. On the request from Novartis, it was agreed to put the STA process on hold until Novartis provided the results from the latest data cut-off (DCO) date of 11-Dec-2018 from the JULIET trial. Novartis has on 01-Apr-2019 provided an updated model based on data from the latest DCO of JULIET and used that opportunity to also update some of the assumptions in their base case.

NoMA's assessment is based on Novartis's original base case. In addition, Novartis's updated base case of 01-Apr-2019 is presented in this report.

1.2 RELAPSED/REFRACTORY (R/R) DIFFUSE LARGE B CELL LYMPHOMA (DLBCL)

DLBCL is a fast growing, aggressive lymphoma of B-cells and is the most common subtype of non-Hodgkin's lymphomas (NHL). The clinical manifestations of DLBCL vary and depend on the site of disease involvement. Rapidly growing tumours may present as masses, causing symptoms when they infiltrate tissues or organs. Pain may occur due to rapid or invasive tumour growth, and is often the first sign of this illness, sometimes associated with "B-symptoms" of fever, drenching night sweats, and weight loss. Generalized pruritus may also be present.

Patients with DLBCL constitute around 30-35% of all NHL cases (2). Around 340 people are diagnosed with DLBCL each year in Norway. Although DLBCL can occur in childhood, the incidence generally increases with age, with a median age of 70 years at the time of diagnosis.

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

1.3 SEVERITY AND SHORTFALL

The prognosis in patients with r/r DLBCL is poor.

The degree of severity affects whether the costs are considered to be reasonable relative to the benefit of the treatment. NoMA uses a quantitative method (see Appendix 1) for estimating the level of severity based on absolute shortfall.

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

1.4 TREATMENT OF R/R DLBCL

1.4.1   Treatment with tisagenlecleucel

Therapeutic indication
Tisagenlecleucel is indicated for the treatment of:
  – Paediatric and young adult patients up to 25 years of age with B-cell acute lymphoblastic leukaemia (ALL) that is refractory, in relapse post-transplant or in second or later relapse.
  – Adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) after two or more lines of systemic therapy.

This STA applies to adult patients with r/r DLBCL. The assessment of paediatric B-cell ALL is presented in a separate report (3).

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

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

The CAR is comprised of a murine single chain antibody fragment that recognises CD19 and is fused to two intracellular signalling domains, the T cell receptor associated CD3 zeta complex and the costimulatory receptor 4-1BB (CD137). The CD3 zeta component is critical for initiating T cell activation and anti-tumour activity, while 4-1BB enhances the activation, expansion, persistence and function of tisagenlecleucel. Upon binding to CD19-expressing cells, the CAR transmits a signal promoting T cell activation, expansion, inflammatory cytokine production, and acquisition of effector functions, such as cytotoxicity, of tisagenlecleucel. This in turn leads to apoptosis and necrosis of CD19 expressing target cells.

Posology

Manufacturing of tisagenlecleucel occurs at a central facility and must be coordinated closely with the treatment center to ensure timely management of each patient leading up to infusion.
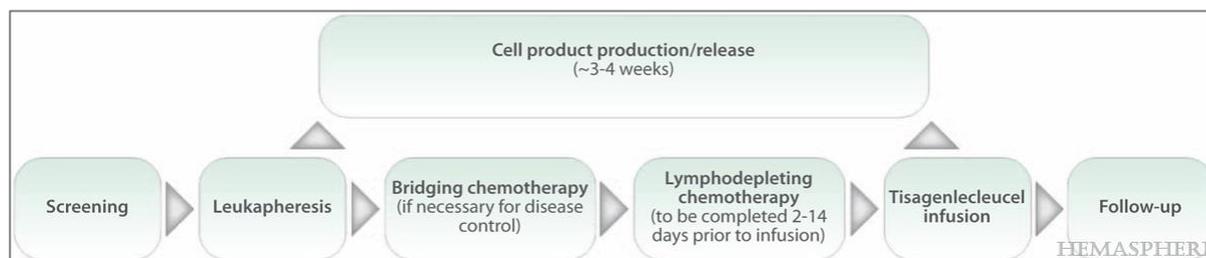

Figure 1: Clinical process flow of tisagenlecleucel therapy. Source: Buechner et al 2018 (4)

Step 1: Leukapheresis

The patient's own peripheral blood mononuclear cells (PBMC) containing T cells are collected by leukapheresis. The cells are then cryopreserved and shipped to a central manufacturing facility in Europe or in the United States.

Step 2: Tisagenlecleucel manufacturing

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

Step 3: Pre-treatment conditioning - Lymphodepleting chemotherapy

Lymphodepleting chemotherapy is recommended to be administered before tisagenlecleucel infusion unless the white blood cell count within one week prior to infusion is ≤1,000 cells/µL.

The recommended lymphodepleting chemotherapy regimen for DLBCL is fludarabine (25 mg/m^2 intravenous daily for 3 days) and cyclophosphamide (250 mg/m^2 intravenous daily for 3 days starting with the first dose of fludarabine). If the patient experienced a previous Grade 4 haemorrhagic cystitis with cyclophosphamide, or demonstrated a chemorefractory state to a cyclophosphamide-containing regimen administered shortly before lymphodepleting chemotherapy, then bendamustine (90 mg/m^2 intravenous daily for 2 days) should be used.

Tisagenlecleucel is recommended to be infused 2 to 14 days after completion of the lymphodepleting chemotherapy.

Step 4: Tisagenlecleucel infusion

In adult DLBCL patients, tisagenlecleucel treatment is administered as a single intravenous infusion at a dosage of 0.6 to 6 x 10^8 CAR-positive viable T cells (non-weight based).

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

Adverse reactions
Upon activation in the patients, the CAR-T cells proliferate and subsequently kill tumor cells, and concomitantly release inflammatory cytokines in order to enhance an effective immune response. The release of pro-inflammatory cytokines can cause CRS with symptoms of high fevers, low blood pressure, and respiratory distress. Another common and severe side effect of CAR T-cell therapy is neurotoxicity. The most common neurological side effects observed with tisagenlecleucel in adult patients with DLBCL included agitation, encephalopathy, seizures, tremor, confusional state, delirium, irritability and somnolence.

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

The most common non-haematological adverse reactions in the clinical studies with patients with DLBCL were CRS (57%), infections (54%), pyrexia (35%), diarrhoea (32%), nausea (29%), hypotension (26%), and fatigue (26%). Grade 3 and 4 adverse reactions were reported in 89% of the patients. The most common Grade 3 and 4 non-haematological adverse reactions were infections (32%) and CRS (23%). The most common (>25%) Grade 3 and 4 haematological laboratory abnormalities were lymphocyte count decreased (95%), neutrophil count decreased (81%), white blood cell count decreased (77%), haemoglobin decreased (59%), and platelet count decreased (55%). Grade 3 and 4 adverse reactions were more often observed within the initial 8 weeks post-infusion (85%) compared to the subsequent follow-up phases after 8 weeks post-infusion (49%).

1.4.2   Treatment guidelines

Treatment of adult patients with DLBCL is described in national guidelines from The Norwegian Directorate of Health: "*Nasjonalt handlingsprogram med retningslinjer for diagnostikk behandling og oppfølging av maligne lymfomer*" (1).

The current standard of care for the first-line treatment is a regimen of rituximab in combination with cyclophosphamide, doxorubicin, vincristine, and prednisolone (R-CHOP). For patients <60 years, etoposide can be added (R-CHOEP). Approximately 30% of the DLBCL patients experience a relapse and 20% have refractory disease to first-line therapy.

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

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

1.4.3   Comparator

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

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

2 RELATIVE EFFECTIVENESS

2.1 OVERVIEW OF RELEVANT CLINICAL STUDIES

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

The clinical trial was designed as a single arm study. Novartis has therefore conducted matching-adjusted indirect comparisons (MAIC) with historical controls in order to document the relative efficacy.

2.1.1 Tisagenlecleucel efficacy studies

NoMA considers the ongoing JULIET study (C2201, NCT02445248) as the most relevant clinical evidence to this STA. Supporting evidence is derived from study A2101J (NCT02030834), which is an ongoing phase 2a case-series study initiated by the University of Pennsylvania (5). The A2101J study is small and therefore considered to provide only supporting evidence, but has longer follow-up time than the JULIET study.

Table 1 Methods – The JULIET study and study A2101J

	JULIET (Study C2201)	Study A2101J
Design	Phase II, Single arm Multicenter	Phase IIA case-series, Single arm
Patients	Adult patients with r/r DLBCL (incl. TFL) age ≥18 years having failed ASCT, or being ineligible for or not consenting to ASCT	Patients with r/r CD19$^+$ B-cell NHL (incl. DLBCL and TFL) age ≥18 years ineligibility for ASCT or alloSCT, or relapse after ASCT
Intervention	Tisagenlecleucel; Single IV infusion of 1-5×10^8 CAR$^+$ viable T cells	Tisagenlecleucel; Single IV infusion of 1-5x10^8 CAR$^+$ viable T cells
Comparator	none	none
Primary endpoint	ORR (CR and PR) in patients of the Main Cohort who have had at least 3 months of follow-up after infusion, IRC-assessed based on the Lugano Classification criteria	ORR at 3 months, and response rate according to NHL subtype
Some secondary endpoints	TTR, DoR, EFS, PFS, OS, Safety, FACT-Lym, and SF-36	BOR, DoR, PFS, OS, Safety, *in vivo* expansion, and production feasibility
Data cut-off (DCO) date	Primary analysis - 08 Mar 2017: Enrolled: N = 147 Infused: N = 99 Median follow-up infused patients: 5.6 (range: 0-17.1) months Analysis used for initial MA – 08 Dec 2017 Enrolled: N = 165 Infused: N = 111 Median follow-up infused patients: 13.9 (range: 0.1-26) months DCO of 21 May 2018: Enrolled: N = 167 Infused: N = 115 Median follow-up infused patients: 19.3 (range: 0.4-28.9) months DCO of 11 Dec 2018 were also assessed but remain confidential	07 May 2017: Enrolled: N = 38 Infused: N = 28 (DLBCL: n=14; TFL: n= 14) Median follow-up infused patients: 29.3 months

AlloSCT = allogeneic stem cell transplant. ASCT = autologous stem cell transplantation. BOR = Best overall response. DoR = Duration of overall response. EFS = Event-free survival. FACT-Lym = Functional Assessment of Cancer Therapy-Lymphoma. IRC = Independent Review Committee. IV = Intravenous. NHL = non-Hodgkin lymphoma. ORR = Overall response rate. OS = Overall survival. PFS = Progression-free survival. SF-36 = Short-Form 36. TTR = Time to response.

The JULIET study consisted of the following sequential periods: screening including acceptance of leukapheresis product, enrolment, pre-treatment with bridging- and lymphodepleting (LD) chemotherapy, one single dose of tisagenlecleucel infusion, primary follow-up (1-60 months), secondary follow-up (if applicable, 2-60 months) for patients who progress after CAR-T cell infusion, and long-term follow-up for safety and survival (Figure 2). All patients were allowed to receive bridging chemotherapy constituting standard 3rd or later lines of antineoplastic therapy based on the physicians choice to stabilize the disease while waiting for successful tisagenlecleucel manufacturing and subsequent infusion.

1   Performed prior to Study Entry
2   As indicated per protocol
3   Only for patients who drop out of the Primary Follow-up before Month 60.
4   Patients will be followed for survival until the end of trial, or until they are enrolled in the long-term follow-up.
5   Long term safety follow-up conducted per health authority guidance under a separate protocol
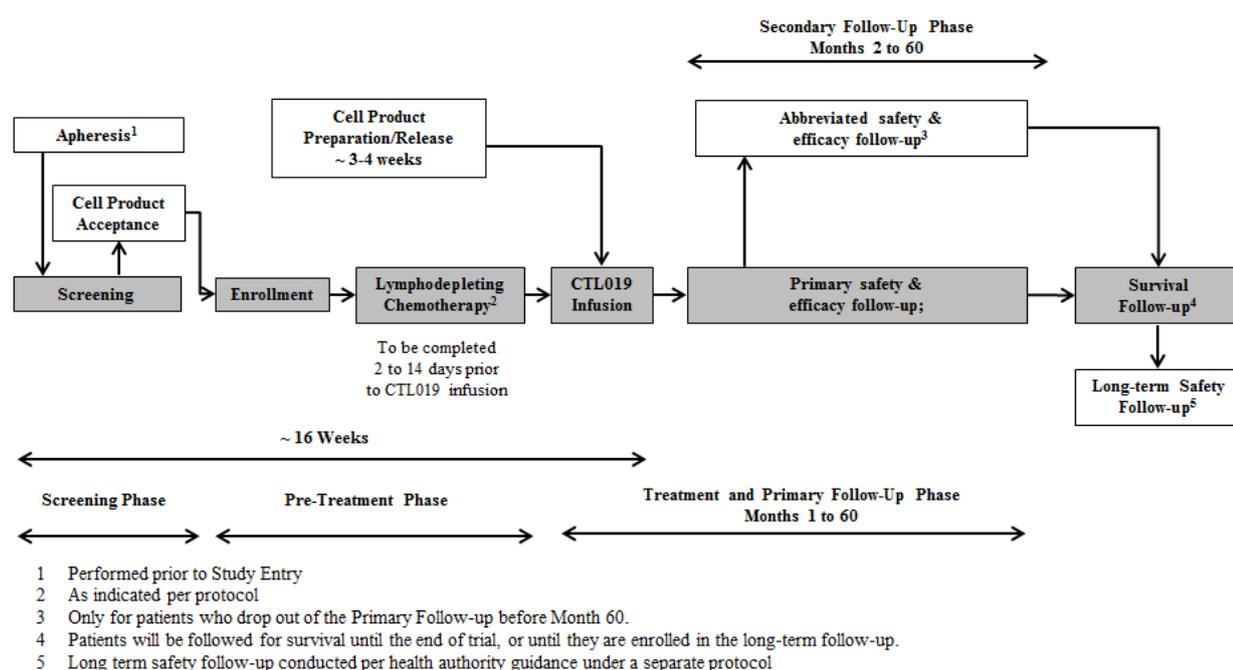
Figure 2: Study periods of the Phase II JULIET study

Primary endpoint

The primary efficacy endpoint in the JULIET study was overall response rate (ORR) post infusion as determined by independent review committee (IRC) assessment. The ORR was defined as the proportion of patients with a best overall response (BOR) of complete response (CR) and partial response (PR) based on the Lugano Classification criteria (6) interpreted by a Novartis Image guideline. BOR was defined as the best disease response recorded from tisagenlecleucel infusion until progressive disease (PD) or start of new anticancer therapy (including SCT), whichever came first. Efficacy of tisagenlecleucel was assessed at Day 28 (±7 days) and at 3, 6, 9, 12, 18, 24 months (±14 days) and then every 12 months for 5 years until documented disease relapse or disease progression.

Secondary endpoints

Progression-free survival (PFS) and overall survival (OS) were secondary endpoints in the JULIET study. PFS was defined as the time from date of tisagenlecleucel infusion to the date of first documented disease

progression or death due to any cause. OS was defined as the time from date of tisagenlecleucel infusion to the date of death due to any cause.

The JULIET study included 27 study sites across 10 countries, including one centre in Norway.

NoMA's assessment of the submitted clinical evidence

The clinical studies of tisagenlecleucel are considered to have considerable shortcomings to inform the STA:

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

- The JULIET study included a relatively small number of patients (167 enrolled patients, of which only 115 received the study drug) with a median follow-up time just above 2 years.

- The primary endpoint was best ORR for patients who received tisagenlecleucel manufactured at the US facility after at least 3 months post-infusion, assessed by an IRC. ORR included the proportion of patients achieving either a CR or PR in response to the treatment. ORR is relevant as it provides a direct measure of the antitumor activity of this CAR-T cell therapy. However, time-to-event results (i.e. PFS, OS) are considered more clinically relevant.

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

2.1.2   Indirect treatment comparisons

Due to the single arm trial design of JULIET, Novartis presented an indirect treatment comparison to a historical control using a matching-adjusted indirect comparison (MAIC). A MAIC uses individual patient data from trials of one treatment to match baseline summary statistics reported from trials of another treatment. After matching, by an approach similar to propensity score weighting, treatment outcomes are compared across balanced trial populations.

Studies included in the MAIC were identified through a Systematic Literature Review (SLR) conducted by Novartis according to the best practices for systematic literature search, including those published by the Cochrane Collaboration. The SLR was comprehensive and transparent. The search criteria, sources, inclusion and exclusion criteria were clearly stated.

Patient-level data from JULIET and published aggregate data from the CORAL extension studies (7, 8) or SCHOLAR-1 (9) were used for MAIC.

Comparison with the CORAL extension studies

CORAL (10) is a phase III, multicenter, randomised trial that compared the efficacy of three cycles of R-ICE or R-DHAP as second-line therapy, followed by ASCT with or without rituximab maintenance, in patients with relapsed DLBCL. Among 477 patients randomised to R-ICE or R-DHAP, 255 patients who achieved CR, PR, or SD after the third cycle of salvage treatment received consolidation with BEAM followed by ASCT. The CORAL extension study 1 (7) includes 75 patients in the CORAL observational follow-up phase who relapsed after ASCT. The CORAL extension study 2 (8) includes 203 patients in the CORAL observational follow-up phase who failed to proceed to ASCT. Patients in the CORAL extension studies were required to fail only two lines of prior therapy.

NoMA considers the CORAL extension studies as being an acceptable source of historical controls in the Norwegian setting. The observed OS rates after second relapse is very similar to the survival of DLBCL patients with two or more relapses or progressions from the Oslo University Hospital (OUS) Lymphoma Register. This registry contains information on 35-40% of all DLBCL cases in Norway (Figure 7, Section 3.1). As in JULIET, the original CORAL randomised study enrolled patients with a better prognosis as these were all considered eligible for ASCT at the time of relapse/refractoriness to 1st line of treatment.

Matching was conducted on four variables only; gender, International Prognostic Index (IPI) risk classification (<3 vs. ≥3), ASCT as the most recent therapy (yes vs. no) and refractory to last line of treatment (yes vs. no). Matching was not performed on histological subgroups. Specifically, all patients in the pooled CORAL extension studies had DLBCL as their primary diagnosis. In JULIET, 80% of the patients who received tisagenlecleucel infusion had DLBCL, 18.3% TFL, and 1.7% (i.e. 2 patients) had other types of lymphoma. The response rates were higher for the TFL population in JULIET compared to the DLBCL population, thus increasing the magnitude of the observed clinical benefit for the total study population compared to the DLBCL population. In addition, there was a between-studies imbalance in the number of previous lines of therapies. Here, patients in JULIET were more heavily pretreated, which could not be adjusted for.

The starting time for the OS analysis in the MAIC presented in the original submission by Novartis was the time from relapse to last treatment both in JULIET and CORAL extension studies (Figure 3 and Figure 4). That means from a time point before enrolment in JULIET. As a consequense, an artificial "lead time" survival is applied from relapse to enrolment in JULIET. Furthermore, only patients with a life expectancy of at least 3 months were included in JULIET. It was therefore a concern that all patients in the CORAL extension studies, who had previously relapsed, were included in the comparison, irrespectively of prognosis. It is clear from Figure 5 that patients who died on day 1 after relapse were included in the CORAL extension studies, reflected by the sharp unusual drop at this time. Instead, in order to enter into analysis in JULIET, patients had to survive from screening and enrolment to administration of tisagenlecleucel infusion. Hence the horizontal survival line from time 0 to enrolment (i.e. 1.88 months), or from time 0 to infusion (i.e. 3.96 months).

1) Inclusion criteria:
-   r/r DLBCL after ≥ 2 lines of systemic therapy
-   Life expectancy ≥ 12 weeks
-   ECOG: 0-1
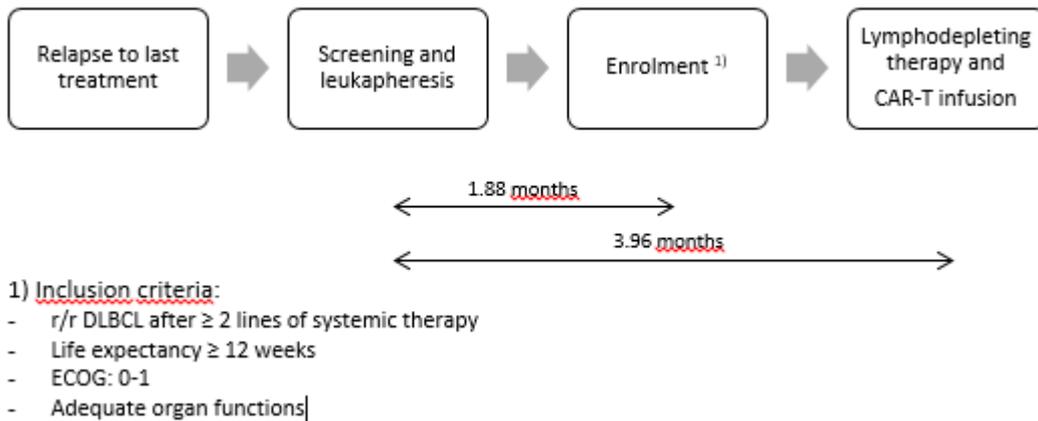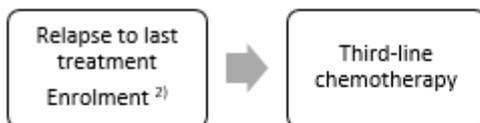-   Adequate organ functions

Figure 3 Steps from last relapse to treatment in JULIET study

2) Included patients:
-   Study 1: relapsed after ASCT in CORAL
-   Study 2: failed to proceed to ASCT in CORAL

Figure 4 Steps from last relapse to treatment in CORAL extension studies
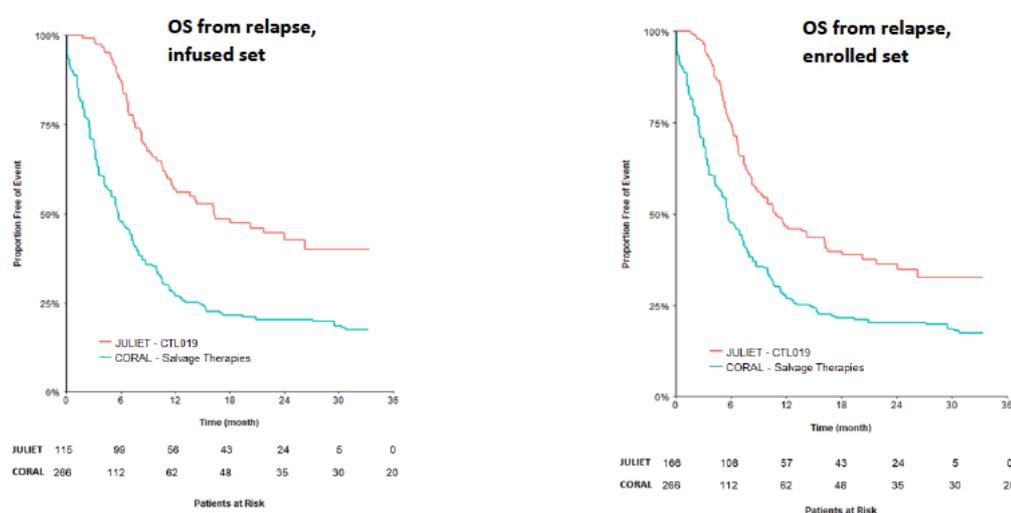
Figure 5 KM Curves of OS comparing JULIET and Pooled CORAL Extension Studies after MAIC. JULIET infused population (left), and JULIET enrolled population (right). OS measured form most recent relapse. Original submission by Novartis.

The JULIET trial included patients that were transplant ineligible. However, no pre-specified criteria for transplant ineligibility were defined in the study protocol. According to the Norwegian, Swedish and European ESMO guidelines patients eligible for transplant would be below 65-70 years old, have a performance status of 0 to 1 and no major organ dysfunction (1, 11, 12). Therefore, contradictory to the targeted «transplant ineligible» population, it appears the inclusion criteria for the JULIET trial define a population that would indeed be transplant eligible. It is therefore understood that patients were defined as transplant ineligible due to being r/r despite having received 2 or more previous treatment lines. Similar to the CORAL extension study population, it is expected that, if achieving a response to their next treatment line, these patients would become transplant eligible.

By including patients from last relapse in the CORAL extension studies the following four patient categories are probably included in the analysis:

1. Patients that relapsed but were not considered medically fit for subsequent treatment lines (would not have been included in the JULIET trial),
2. Patients that relapsed and received subsequent therapy but that had a short life expectancy (would not have been included in the JULIET trial)
3. Patients that received subsequent treatment and had a reasonable life expectancy but were not eligible for a subsequent SCT (if responding)
4. Patients that received subsequent treatment and were fit enough for SCT (if responding) (would have been included in the JULIET trial).

To address this lead time bias and to ensure that patients are as comparable as possible (i.e the first two categories from above are removed), NoMA asked Novartis to conduct a "lead time"-adjusted analysis (Figure 6) where:

1. The artificial survival between relapse and enrolment/infusion in JULIET was removed so that the starting time of the analysis was either time from enrolment or time from infusion as pre-specified in JULIET, AND
2. The initial events after relapse (i.e. events within the first 1.88 months or 3.96 months) were removed from the CORAL extension studies so that the starting time of the analysis was aligned to JULIET.
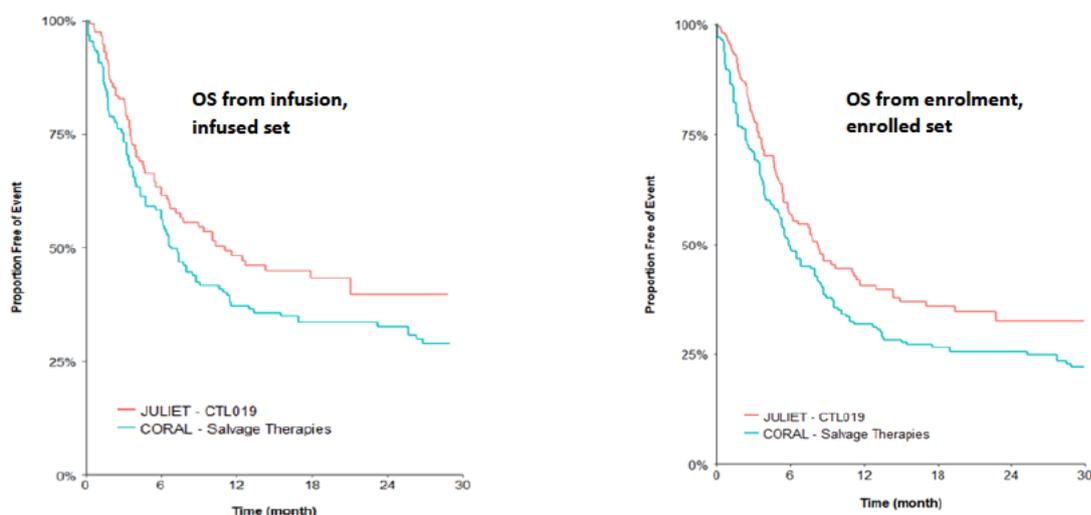
Figure 6 Additional Analyses: OS from infusion (infused set, left) and OS from enrolment (enrolled set, right). "Lead time"-adjusted comparisons of JULIET vs CORAL as requested by NoMA.

NoMA believes that the "lead time"-adjusted analysis is not conservative. The 1.88 months was the time from screening to enrolment in JULIET. If the longer time from last relapse to enrolment from JULIET was used as the threshold to remove early deaths in the CORAL extension studies then more patients would have been removed from the analysis. Such a scenario would negatively affect the incremental survival benefit of tisagenlecleucel.

When compared to the time from relapse analysis (266 patients), 62 patients were removed for the enrolled set analysis and 116 patients were removed for the infused set analysis from the CORAL arm. The subsequent SCT proportion increased from 29% to approximately 38% in the enrolled CORAL set. This approximation is based on an assumption that none of the removed patients would receive a transplant and it does not take censoring events into consideration. This assumption is reasonable given that events within the first 1.88 months were removed. The increase in subsequent SCT rate is difficult to

approximate for the infused population as events within 3.96 months were removed and the CORAL publications do not provide information on the transplant timing. If none of the removed patients received a subsequent transplant, the proportion of SCT in the remaining patients would increase to 51%. Some patients may however initiate SCT within 3.96 months after relapse, which would result in a lower percentage. NoMA therefore assumed an overall transplant rate of 45% in the "lead time"-adjusted mITT CORAL population. The transplant rate of 38% for the ITT and 45% for the mITT "lead time" adjusted CORAL is high but comparable to what would have been expected with JULIET patients if they had not received tisagenlecleucel. The response rate in CORAL extension studies was as high as 40.3% and the subsequent SCT rate was 29%. It's expected that the response rate would increase in the "lead time" adjusted analysis as more non-respondents were likely to be removed. If those remaining patients fulfilled JULIET eligibility criteria (age, no major organ disfunction and PS 0-1) they would potentially be considered for transplant. The increased costs of subsequent SCT in the comparator arm are addressed in the model.

Clinical experts commented that the transplant rate for r/r DLBCL patients in clinical practice is much lower than the 38%-45% transplant rate in the "lead time"-adjusted CORAL population. It is important to emphasise that the provided indirect comparison is based on a single arm JULIET trial and pooled results from the CORAL extension studies. The golden standard for obtaining an unbiased estimate of the relative treatment effect is to conduct a RCT. NoMA therefore believes that the right approach is to approximate the conditions of a controlled trial in order to reduce the bias in the estimate of the relative effect. NoMA therefore intend to select those patients from the CORAL extension studies that could have been included in a theoretical JULIET control arm. It is not appropriate to compare the JULIET clinical trial with a historical control which approximates clinical practice, as they are not comparable. A recent abstract of real-world results on another CAR-T product, axi-cel, shows that patients in the clinical programme were more selected when compared to the clinical practice (13). Interestingly, eligibility for the pivotal phase II trial was a significant predictor of prolonged CR when compared to non-eligible patients in the clinical practice.

In summary, there are many methodological issues underlying the provided MAIC comparison. NoMA recognizes that certain aspects such as fewer prior lines of therapies in the CORAL extension studies might have biased the results in favour of the outcomes observed in the CORAL extension studies but at the same time the histopathological subtype profile likely favours JULIET. The main challenge of the comparison is that patient characteristics were not reported in the same way and there was a high proportion of missing data in the CORAL extension studies. Therefore, matching for all important prognostic factors and effect modifiers could not be conducted. As a result, the comparison vs. CORAL is considered more as a naïve comparison rather than an adjusted comparison. The key issue with the comparison vs. CORAL is the pronounced lead time bias favouring JULIET. Consequently, the magnitude of the benefit of tisagenlecleucel is unclear as it is largely impacted by the early deaths in the CORAL extension studies. In addition, the starting time for the OS analysis in the MAIC analysis was restricted to that reported in the CORAL publications (i.e. from relapse to last treatment). The additional analyses requested by NoMA attempted to address the issue of the lead time bias by removing those patients who died early in the CORAL extension studies and adjusting for patients at risk accordingly. Consequently, the

starting time in JULIET for the OS analysis becomes the time from either enrolment or infusion. NoMA chooses the "lead time"-adjusted analyses as the base case to address the considerable number of deaths on Day 1, to align the starting time of the survival analysis and to ensure that CORAL patients who would not be eligible for JULIET are removed.

In Novartis's updated base case of 01-Apr-2019, survival is measured from enrolment in JULIET (and not from relapse as in the original base case) and relapse in CORAL extension studies. However, Novartis argues that the lead-time adjusted CORAL data, based on manual removal of patients who were dead or censored in the first few months (1.88 months or 3.96 months), is not a fair comparison to JULIET data.

A scenario analysis where OS is measured from enrolment (JULIET) and relapse (CORAL extension studies) (Novartis's preferred option) based on NoMA's selected survival functions, costs and utilities is presented in Section 4.2.4. A respective sensitivity analysis of the infused JULIET set (from infusion) is not conducted as the difference in the starting time of the survival analysis of > 3.96months as compared to the CORAL extension studies (measured from last relapse) is considered too large.

Detailed description of the methodology, results and the assessment can be found in Appendix 2.

Comparison with SCHOLAR-1

SCHOLAR-1 is the largest patient-level pooled retrospective meta-analysis of response rates and survival after salvage chemotherapy among patients with refractory DLBCL.

Patient inclusion and exclusion criteria were not fully aligned between JULIET and SCHOLAR-1. Only patients who met SCHOLAR-1 inclusion criteria (i.e. PD or SD as best response to chemotherapy or relapsed ≤12 months post-ASCT) were selected from JULIET. Consequently, 24 out of 115 patients from the infused population, and 32 out of 167 patients from the enrolled population in JULIET were excluded from the MAIC. Hence, the generalizability of the results in terms of the wider tisagenlecleucel indication is questionable.

Published patient characteristics were generally similar between SCHOLAR-1 and JULIET. However, SCHOLAR-1 included patients with ECOG 0-4, whereas JULIET included only patients with ECOG 0-1. ECOG status is considered an important prognostic factor which could not be adjusted for in the comparison. Moreover, the data were collected at screening for JULIET, while SCHOLAR-1 measured characteristics at diagnosis for observational cohorts and at randomisation for the randomised trials. Consequently, matching based on the IPI score is problematic as the component variables such as age, ECOG performance status, and disease stage change over time. Furthermore, the registries in SCHOLAR-1 included patients who had DLBCL irrespectively of their co-morbidities or life expectancy. In JULIET, patients had to have a life-expectancy of at least 3 months and adequate organ function. In situations where matching for patient characteristics is limited, it is even more important to be able to select the most appropriate patient population based on the inclusion criteria. Overall, NoMA does not believe that SCHOLAR-1 and JULIET have matching patient populations.

The large amount of missing data in SCHOLAR-1 is a concern, both with respect to the matching for baseline characteristics and the comparison in general. An unanchored MAIC assumes that all effect modifiers and prognostic factors are accounted for. This assumption is clearly untenable. Failure of meeting this assumption leads to an unknown amount of bias in the unanchored estimate.

The key advantage of SCHOLAR-1 as a comparator is the large sample size. However, due to the differences in inclusion criteria, timing of patient characteristics assessment, differences in life expectancy, co-morbidities, and the high proportion of missing data, it is deemed inappropriate to accept SCHOLAR-1 as the primary source of historical controls for JULIET.

Detailed description of the methodology, results and the assessment of the MAIC can be found in Appendix 3.

2.1.3   Ongoing and initiated studies

BELINDA is an ongoing, randomised, open-label, phase 3 study (CCTL019H2301) designed to evaluate the efficacy of tisagenlecleucel in 2nd line r/r DLBCL patients, comparing tisagenlecleucel versus standard of care. Oslo University Hospital (OUS) is one of the study sites in this trial.

In order to provide more robust information on the long term outcomes of tisagenlecleucel, Novartis will submit further follow-up data from the JULIET study with DCOs set at Feb-2020 where all infused patients will have been followed for at least 24 months, as well as the final clinical study report corresponding to 5 years of follow-up, when available.

Novartis will also provide real-world data, including details of the manufacturing turnaround time, based on the registry study CCTL019B2401 for enrolled patients with r/r DLBCL who received commercial tisagenlecleucel. The aim of these data is to elucidate the representativeness of the efficacy results observed in the infused patient population (mITT) of the JULIET study.

3 PICO[1]

3.1 PATIENT POPULATION

Norwegian clinical practice

Tisagenlecleucel is intended as a treatment option for adult patients with r/r DLBCL after two or more lines of systemic therapy.

Given the waiting period between leukapheresis and infusion (which usually takes about 3-4 weeks as per SmPC), the need for lymphodepleting chemotherapy, and the risk of serious adverse events (SAEs) associated with tisagenlecleucel, candidates for CAR-T cell treatment need to be sufficiently fit prior to infusion. Hence, CAR-T cell therapy may not be a treatment option for patients with deteriorating clinical status and rapidly progressing DLBCL, patients who experience persistent toxicities from recent chemotherapy, or patients with an active infection.

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

The OUS Lymphoma Register covers 35-40% of all DLBCL cases in Norway. Patients who transformed from other types of lymphoma to DLBCL are not included. In total, 1 194 patients are registered in the OUS Lymphoma Register in the period between 1 May 2006 and 31 December 2016. The mean and median age at diagnosis were 61 and 63 years, respectively. In total, 57 patients included in the register had a second relapse or progression. The median OS was 4.5 months in these patients. When excluding patients with central nervous system (CNS) involvement, as in the JULIET study, the median OS was 5.0 months (n=46).

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[1] Patients, Intervention, Comparator, Outcome.
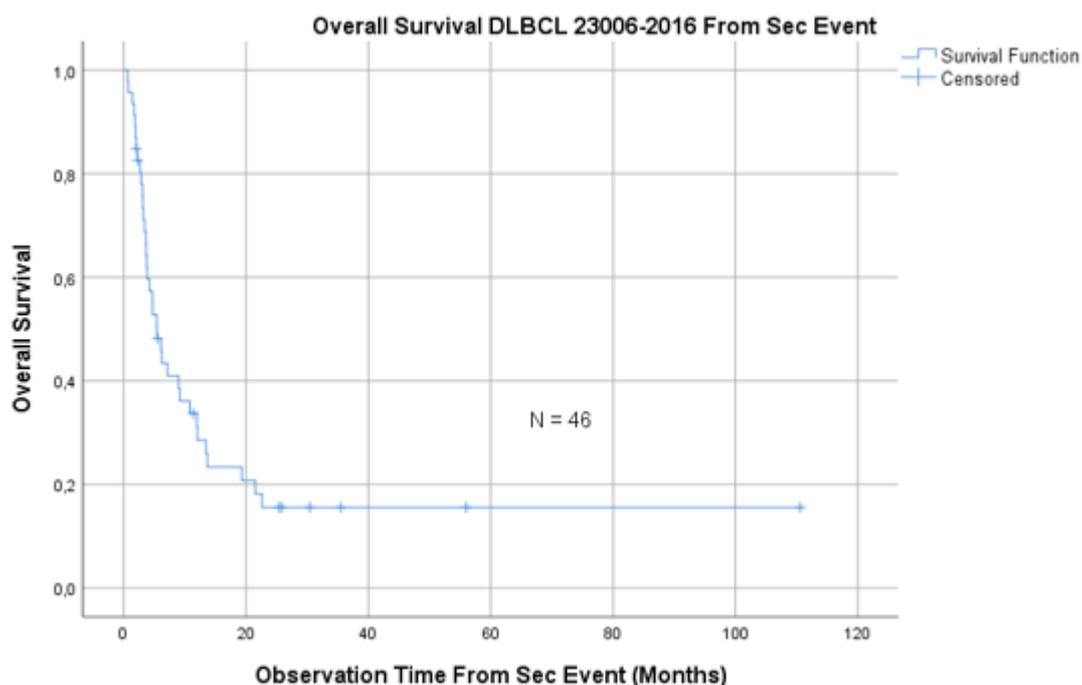
Figure 7 OS after second relapse or progression, patients with any CNS disease involvement excluded (n=46). Source: OUS Lymphoma Register

Submitted clinical studies

The JULIET study included adult patients with DLBCL, including patients with DLBCL transformed from follicular lymphoma (TFL), who had r/r disease after ≥2 previous lines of chemotherapy (including standard treatment with rituximab and an anthracycline [eg, doxorubicin]), and were ineligible for SCT (i.e., had failed SCT, were ineligible for SCT, or did not consent to SCT). To be eligible for participation in the study, patients had to have measurable disease, defined as nodal lesions greater than 20 mm in the long axis and extra-nodal lesions (outside lymph node or nodal mass, but including liver and spleen) greater than 10 mm in both long and short axis, at time of enrolment, adequate organ functions, ECOG performance status (PS) score of 0 or 1, and a life expectancy ≥12 weeks. Patients who had received prior treatment with any anti-CD19/anti-CD3 therapy (e.g. blinatumomab), any adoptive T cell therapy or other gene therapy, had undergone alloSCT, and patients with active CNS involvement by malignancy were excluded from the study.

Among the 167 patients enrolled in the JULIET study at the DCO of 21-May-2018, 115 received infusion with tisagenlecleucel. In total, 52 enrolled patients (31.1%) discontinued prior to tisagenlecleucel infusion due to the following reasons: deaths (9.6%; n=16), physician decision (9.6%; n=16), tisagenlecleucel manufacturing failure (7.8%; n=13), adverse events (2.4%; n=4), patient decision (1.2%; n=2), and protocol deviation (0.6%; n=1). The median time from enrolment to CAR-T cell administration for those patients who received infusion was 54 days (range: 30 to 357 days). None of the patients were pending infusion at the time of DCO.

Table 2 Patient characteristics in the JULIET study (C2201; DCO: 21-May-2018)

	JULIET (C2201)		
	Infused (n=115)	Not infused (n=52)	Enrolled (i.e. all patients) (n=167)
Age (years)			
Mean	53.8	60.3	55.8
Median (min-max)	56.0 (22-76)	63.0 (33-76)	58.0 (22-76)
Age category (years) – n (%)			
<40 years	17 (14.8)	4 (7.7)	21 (12.6)
≥40 and <65 years	72 (62.6)	27 (51.9)	99 (59.3)
≥65 years	26 (22.6)	21 (40.4)	47 (28.1)
Sex - n (%)			
Female	44 (38.3)	18 (34.6)	62 (37.1)
Male	71 (61.7)	34 (65.4)	105 (62.9)
ECOG PS – n (%)			
0	65 (56.5)	14 (26.9)	79 (47.3)
1	50 (43.5)	38 (73.1)	88 (52.7)
IPI at initial diagnosis – n (%)			
<2	27 (23.5)	8 (15.4)	35 (21.0)
≥2	67 (58.3)	37 (71.2)	104 (62.3)
Unknown	21 (18.3)	7 (13.5)	28 (16.8)
IPI at study entry – n (%)			
<2	31 (27.0)	3 (5.8)	34 (20.4)
≥2	84 (73.0)	49 (94.2)	133 (79.6)
Stage at initial diagnosis – n (%)			
Stage I	9 (7.8)	1 (1.9)	10 (6.0)
Stage II	24 (20.9)	8 (15.4)	32 (19.2)
Stage III	19 (16.5)	19 (36.5)	38 (22.8)
Stage IV	58 (50.4)	22 (42.3)	80 (47.9)
Unknown	3 (2.6)	0	3 (1.8)
Missing	2 (1.7)	2 (3.8)	4 (2.4)
Stage at study entry – n (%)			
Stage I	9 (7.8)	1 (1.9)	10 (6.0)
Stage II	18 (15.7)	8 (15.4)	26 (15.6)
Stage III	23 (20.0)	14 (26.9)	37 (22.2)
Stage IV	65 (56.5)	29 (55.8)	94 (56.3)
Predominant histology/cytology – n (%)			
Diffuse large B-cell lymphoma (DLBCL)	92 (80.0)	37 (71.2)	129 (77.2)
Transformed follicular lymphoma (TFL)	21 (18.3)	13 (25.0)	34 (20.4)
Transformed lymphoma - other	1 (0.9)	2 (3.8)	3 (1.8)
Other	1 (0.9)	0	1 (0.6)
Molecular subtype – n(%)			
Germinal center B-cell type	63 (54.8)	31 (59.6)	94 (56.3)
Activated B-cell type	49 (42.6)	17 (32.7)	66 (39.5)
Missing	3 (2.6)	2 (3.8)	5 (3.0)
Can not be determined	0	2 (3.8)	2 (1.2)

Disease status – n (%)			
Refractory to all lines with prior HSCT	6 (5.2)	2 (3.8)	8 (4.8)
Refractory to all lines without prior HSCT	16 (13.9)	6 (11.5)	22 (13.2)
Refractory to last line but not all lines with prior HSCT	19 (16.5)	8 (15.4)	27 (16.2)
Refractory to last line but not all lines without prior HSCT	21 (18.3)	19 (36.5)	40 (24.0)
Relapsed to last line with prior HSCT	31 (27.0)	8 (15.4)	39 (23.4)
Relapsed to last line without prior HSCT	22 (19.1)	9 (17.3)	31 (18.6)
Prior hematopoietic stem-cell transplantation – n (%)			
No	59 (51.3)	34 (65.4)	93 (55.7)
Yes	56 (48.7)	18 (34.6)	74 (44.3)
Time since most recent relapse/ progression prior to infusion – months			
Mean	5.9	-	5.9
Median (min-max)	5.4 (1.6-21.5)	-	5.4 (1.6-21.5)
Number of prior lines of anti-neoplastic therapy – n (%)			
1	5 (4.3)	1 (1.9)	6 (3.6)
2	51 (44.3)	22 (42.3)	73 (43.7)
3	36 (31.3)	16 (30.8)	52 (31.1)
4	14 (12.2)	6 (11.5)	20 (12.0)
5	8 (7.0)	3 (5.8)	11 (6.6)
6	1 (0.9)	1 (1.9)	2 (1.2)
7	-	2 (3.8)	2 (1.2)
8	-	1 (1.9)	1 (0.6)

Submitted health economic analyses

Adult patients with r/r DLBCL after two or more lines of systemic therapy were included in the economic model. The starting age, from which the outcomes are modelled, is 57 years (based on OUS data), the proportion of females 38% (based on OUS data), and average weight 78.5 kg (based on JULIET trial). Novartis included only the mITT population (infused patients only) in the economic analysis. Upon request, Novartis submitted a new model that included the ITT population (enrolled patients).

NoMA´s assessment

The patient population evaluated in the JULIET study has been used to inform the economic analyses.

The mean and median age of the enrolled patients in the clinical study were 56 and 58 years, respectively. The Norwegian patient population expected to be eligible for treatment with tisagenlecleucel is estimated by the Norwegian clinicians to be between 50 and 70 years mainly, with a median age around 60 years. However, the studied patient population in the JULIET study does not fully reflect the variety of DLBCL patients intended for tisagenlecleucel. Both the inclusion and exclusion criteria applied in the study may have introduced a selection bias of patients likely to benefit from the treatment, but unlikely to be at high risk of being harmed by tisagenlecleucel (e.g. ECOG PS 0-1; adequate organ functions, and life expectancy ≥12 weeks). In addition, the prolonged time period from apheresis to CAR-T administration might have further enriched the infused patient population for patients who had a better prognosis. In total, as many

as 31.1% of the patients enrolled into the study dropped out before receiving tisagenlecleucel infusion. A higher proportion of the non-infused patients had unfavourable prognostic factors compared to the infused patients, indicating that patients with a worse prognosis were excluded from the main efficacy analysis (mITT). This may have impacted the results of the efficacy analysis of the JULIET study and introduced bias in the cross study comparison.

In the infused patients (mITT), the Norwegian clinicians who were contacted by NoMA were of the opinion that the prolonged waiting period in the JULIET study could have influenced the efficacy results in two different ways:

1) Enrichment of DLBCL patients with a better prognosis in the infused patient population (mITT), could in turn have given an overly optimistic efficacy results of tisagenlecleucel.
2) The status of patients who received the infusion worsened in the waiting period, which may have reduced the efficacy of tisagenlecleucel compared to what would have been observed if patients had received the infusion earlier and a higher proportion of the enrolled patient population (ITT) had been treated.

It is not possible to conclude which of the scenarios had the highest impact on the study results. Therefore, several uncertainties remain regarding the true magnitude of the efficacy estimates for tisagenlecleucel.

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

In the ITT population, the efficacy of tisagenlecleucel is measured from the time of enrolment to account for the time period required to manufacture the CAR-T cells and the treatment patients received while waiting for the infusion. It is considered important to include these aspects in the analysis for several reasons, as listed below:

•   Patients would have received the comparator treatment at the time of enrolment if they had not waited for infusion with tisagenlecleucel.
•   A substantial proportion of the patients who underwent leukapheresis, i.e. 31.1% of all the enrolled patients, did not receive tisagenlecleucel infusion in the JULIET study. This should be reflected in the economic analysis.
•   The median time from enrolment to infusion of 54 days (range: 30 to 357) in the primary analysis is markedly longer than the manufacturing time of 3-4 weeks specified in the SmPC. Thus, only patients surviving the waiting period and who were able to receive infusion were included in the mITT analysis. As mentioned above, this delay in administration may have led to the inclusion of healthier patients in the mITT population. Consequently it is difficult to separate the impact of patient characteristics and (unobserved) prognostic factors from the treatment effect of tisagenlecleucel in the infused set. The mITT population is likely to introduce important selection bias and it is difficult to rule out significant overestimation of the treatment effect.

- Most of the patients in the JULIET study received bridging chemotherapy (88.7%; 102/115) to stabilize the disease while waiting for the tisagenlecleucel infusion. Costs and disutility associated with bridging therapy should be included in the economic analysis.
- The ITT analysis evaluates the efficacy of all the sequential treatment phases associated with this CAR-T cell product, including the bridging and lymphodepleting regimens patients received prior to infusion, and not only tisagenlecleucel alone. Although the impact of bridging chemotherapy on the efficacy outcomes is likely to be small and of short duration, bridging therapy along with lymphodepleting chemotherapy should be considered essential elements of the treatment strategy. A potential carry-over effect from the bridging chemotherapy cannot be excluded. Among patients who received bridging therapy in the JULIET study and had two available disease assessments pre-infusion, 20.6% (95% CI: 13.2 to 29.7%) already had a BOR of CR (5.9%) or PR (14.7%) to their last treatment when they were given tisagenlecleucel.

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

- The historical control studies included only patients who received treatment (i.e. mITT population).
- The ITT analysis may be too conservative compared to clinical practice. According to Novartis, both manufacturing time and capacity have been improved in the commercial setting for paediatric and young adult patients with acute lymphoblastic leukaemia, ALL, and is now closer to the 3-4 weeks which are specified in the SmPC. It is therefore likely that a higher proportion of patients may receive successful infusion of CAR-T cells within acceptable timelines with improved manufacturing experience in the future.
- The ITT analysis is affected by the timing of enrolment in the clinical trial. In the JULIET study, enrolment started from the acceptance of the leukapheresis products by the manufacturing site for production. The cells were then cryopreserved until a production slot was available. The timing of enrolment and leukapheresis in various CAR-T cell trials might differ and are likely to affect both the waiting time and dropout rates observed in the period from leukapheresis to infusion, and might have a considerable impact on the efficacy results observed in the ITT population. Thus, in order to assess CAR-T products on equal terms, NoMA considers the mITT analysis to be useful.

3.2 INTERVENTION

Norwegian clinical practice

The SmPC states that tisagenlecleucel must be administered in a qualified treatment centre. It is assumed that the posology in the SmPC for lymphodepleting chemotherapy, and the tisagenlecleucel infusion will be followed in clinical practice (see section 1.4.1).

Treatment with bridging chemotherapy during the waiting period from apheresis to CAR-T administration will presumably be needed to stabilise the clinical state for some of the patients while waiting for infusion.

Submitted clinical studies

Tisagenlecleucel:
The planned dosage of tisagenlecleucel in the JULIET study (dose range: 1 to 5 x 10^8) was similar to the dosage that is now recommended in the SmPC (dose range: 0.6 to 6 x 10^8). In total, 1 patient (0.9%) in the JULIET study received a lower dose of CAR-positive viable T-cells (0.1×10^8 viable CAR-T cells), whereas 5 patients (4.3%) received a higher dose than the range specified in the study protocol. All these patients had similar response rates as patients who reived doses within the protocol-specified minimum and maximum of the target dose.

Lymphodepleting chemotherapy:
A standard fludarabin/cyclophosphamide based regimen was used in the clinical study, except for patients who had previously experienced grade IV haemorrhagic cystitis with cyclophosphamide or were chemorefractory to a prior cyclophosphamide-containing regimen.

Among the 111 patients who received tisagenlecleucel infusion in the JULIET study (DCO: 8-Dec-2017), 103 (92.8%) patients received lymphodepleting chemotherapy after enrolment and prior to tisagenlecleucel infusion. In total, 73.0% (81/111) of the patients received the fludarabine/cyclophosphamide regimen and 19.8% (22/111) received bendamustine. The remaining 7.2% (8/111) of the patients did not receive lymphodepleting chemotherapy.

Bridging chemotherapy:
The protocol allowed the patients to receive bridging chemotherapies per investigator choice to stabilise the patient's disease during the waiting period from apheresis to manufacturing of tisagenlecleucel and infusion. Among the 115 patients who received tisagenlecleucel infusion in the JULIET study (DCO: 21-May-2018), 102 patients (88.7%) had received antineoplastic therapy after enrolment and prior to tisagenlecleucel infusion.

The most frequently used bridging therapies (in ≥ 15% of patients) registered at the DCO of 8-Dec-2017 were rituximab (61.3%), gemcitabine (38.4%), dexamethasone (25.3%), etoposide (26.1%), cytarabine (19.2%), cisplatin (18.2%), and cyclophosphamide (15.2%). Ninety-two patients had at least one multi-agent regimen, and 31 patients had at least one single agent regimen. The median number of bridging regimens each patient received was 1 (range 1-5) and the mean number was 1.7 regimen. In total, 83% of

the patients who received bridging chemotherapy prior to tisagenlecleucel infusion did not receive more than two treatment regimens. The treatment duration of bridging chemotherapy had a median of 40 days and a mean of 48.8 days. See Table 3 for an overview of the duration of bridging chemotherapy based on weeks treated patients received prior to infusion.

Table 3: Duration of bridging chemotherapy prior to infusion with tisagenlecleucel in the JULIET study (DCO: 8-Dec-2017)

Duration of bridging chemotherapy[1]	N (%)
<3 weeks	24 (23.8%)
3 to <6 weeks	30 (29.7%)
6 to <9 weeks	18 (17.8%)
9 to <12 weeks	11 (10.9%)
>= 12 weeks	18 (17.8%)
[1]Duration of bridging chemotherapy is calculated as the sum of the durations of each bridging chemotherapy regimen taken by the patient.	

Table 4 gives an overview of the best overall responses patients who received bridging chemotherapy obtained to this treatment before they were given tisagenlecleucel.

Table 4: Bridging therapy ORR prior to tisagenlecleucel infusion in the JULIET study (DCO: 21-May-2018)

	mITT N=115
Patients who received bridging therapy – n (%)	102 (88.7)
Response to bridging therapy* - n (%)	
CR	6 (5.9)
PR	15 (14.7)
SD	22 (21.6)
PD	39 (38.2)
Unknown	20 (19.6)
Bridging therapy ORR (CR+PR) – n (%)	21 (20.6)
95% CI	(13.2, 29.7)
*The percentages are based on number of patients who were treated with bridging therapy while waiting for infusion with tisagenlecleucel. CI: confidence interval. CR: complete response. mITT = All patients who received an infusion of tisagenlecleucel. ORR: overall response rate. PD: progressive disease, PR: partial response. SD: stable disease. The 95% CIs were exact Clopper-Pearson CIs.	

Submitted health economic analyses

Tisagenlecleucel:
Tisagenlecleucel infusion is given once as a single infusion.

In the mITT analysis all patients received tisagenlecleucel infusion.

In the ITT analysis (enrolled patients), the proportion of patients who received infusion was 68.9% derived from the JULIET trial (DCO: 21-May-2018). For the non-infused patients, cost inputs were based on the cost of comparator treatment (i.e. treatment, administration, and hospitalisation).

Lymphodepleting chemotherapy:
The dosing schedule, number of doses and distribution of patients receiving each lymphodepleting regimen are obtained from the JULIET trial (DCO: 8-Mar-2017):

- Fludarabine + cyclophosphamide – 73.91% of patients:
    - Fludarabine: 25 mg/m^2 IV daily for 3 days
    - Cyclophosphamide: 250 mg/m^2 IV daily for 3 days
- Bendamustine – 19.13% of patients:
    - Bendamustine: 90 mg/m^2 IV daily for 2 days

Bridging chemotherapy:
Novartis has included bridging chemotherapy in the ITT analysis (enrolled patients), but not in the mITT analysis (infused patients). In the ITT analysis, bridging treatment costs were added to both infused and non-infused patients (see section 4.1.3).

NoMA´s assessment

The intervention arm for the economic analysis is in line with the SmPC for tisagenlecleucel and corresponds to the intervention in the tisagenlecleucel clinical trials, except for the cost of bridging chemotherapy. In NoMA's base case, the cost of bridging therapy has been adjusted according to Norwegian clinical practice, please refer to section 4.1.3 for more information.

3.3 COMPARATOR

Norwegian clinical practice

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

The various combinations of salvage chemotherapy used in Norwegian practice varies with the patients' characteristics and aim of the treatment. The most common treatments would be:
- R-GDP (rituximab, gemcitabine, dexamethasone, cisplatin),
- R-EPOCH (rituximab, etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin),
- R-DHAP (rituximab, dexamethasone, cytarabine, cisplatin),
- R-Gem-OX (rituximab, gemcitabine, oxaliplatin), and

- R-ICE (rituximab, ifosfamide, carboplatin, etoposide) in rare cases

Submitted clinical studies

The tisagenlecleucel studies (JULIET and study A2101J) are single-arm studies and hence lack comparators.

Novartis presented indirect treatment comparisons using a MAIC of tisagenlecleucel versus historical controls. Patient-level data from JULIET and published aggregate data from CORAL extension studies (Appendix 2) and SCHOLAR-1 (Appendix 3) were used for the MAIC.

In the CORAL extension study 1 (n = 75; patients who relapsed after ASCT), third line therapy (+/- rituximab) consisted of ICE-type (17.3%), DHAP-type (24%), gemcitabine-containing (28%), CHOP-like (13.3%) and miscellaneous regimens (26.1%). No significant differences in response rate were observed between the various salvage regimens used as third-lines. Among the 75 patients, 16 patients (21.6 %) could eventually undergo a second transplantation, three patients received an ASCT and 13 patients an alloSCT.

In the CORAL extension study 2 (n = 203; patients who failed to proceed to per-protocol ASCT), salvage therapy (+/- rituximab) consisted of ICE-like (15.3%), DHAP-like (14.8%), gemcitabine-containing (11.3%), dexa-BEAM (7.4%), CHOP-like (6.9%) and miscellaneous regimens (31.9%). Miscellaneous treatments were a heterogeneous group of various chemotherapies including lenalidomide, vincritstine, bleomycin, fludarabine, bendamustine, in monotherapy or in different combinations. For 18.2% of the patients the regimen they received were unknown. OS was not significantly different according to the type of treatment. Among the 203 patients, 64 patients (31.5%) were eventually transplanted, the majority with ASCT (n=56), but some patients with alloSCT (n=8).

In SCHOLAR-1, the specific chemotherapy regimens used by the patients were not reported. In this study 30% of the patients received ASCT or alloSCT at any time after determination of refractory status.

Submitted health economic analyses

Combination chemotherapy regimens +/- rituximab is the comparator in the submitted health economic analysis. The comparator treatment cost was estimated as the average of four different chemotherapy regimens:
- (R)-Gem-Ox (rituximab, gemcitabine, oxaliplatin)
- (R)-IVE (rituximab, ifosfamide, etoposide, epirubicin)
- (R)-ESHAP (rituximab, etoposide, methylprednisolone, cytarabine, cisplatin)
- (R)-DHAP (rituximab, dexamethasone, cytarabine, cisplatin)

The model assumes that patients can receive subsequent alloSCT or autoSCT after the initial treatment.

NoMA´s assessment

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

Various combination chemoterapy regimens were used in the historical controls, and no significant differences in response rate were observed between the various chemotherapy regimens used as third-line therapy.

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

NoMA considers CORAL extension studies as being an acceptable source of a historical control in the Norwegian setting. The OS after second relapse in these studies is very similar to the survival of DLBCL patients with a second relapse or progression from the OUS Lymphoma Register. However, the registry could not be used as a comparator due to unavailability of patient characteristics. In NoMAs opionion, the survival in the "lead time"-adjusted CORAL population (see figure 17, section 3.4.2) is comparable to the observed survival in the OUS Lymphoma Register (see figure 7, section 3.1).

Both the tisagenlecleucel trials and the comparator trials lack control arms, and it is therefore not possible to compare outcomes from these trials without a high degree of uncertainty.

3.4 OUTCOMES

3.4.1 Efficacy

Submitted clinical studies

The median follow-up time from tisagenlecleucel infusion to the DCO of 21-May-2018 of the JULIET study was 19.3 months, with a maximum of 28.9 months. Results from the latest DCO of 11-Dec-2018 were also assessed but remain confidential. Among a total of 238 patients screened for r/r DLBCL, 181 patients fulfilled the eligibility criteria, 167 patients were enrolled (one of these did not satisfy at least one clinical eligibility criteria), and 115 patients were infused. All 167 patients who met clinical eligibility criteria and underwent leukapheresis were enrolled into the JULIET study. This means that no leukapheresis product sent to the manufacturing facility was rejected for manufacture before patient enrolment.

The results of the JULIET study demonstrate a best overall response rate of ORR (CR or PR) of 54% (95% CI: 43 to 64) in those patients who received tisagenlecleucel at least 3 months prior to the DCO (n=99). In total, 40 % of these patients achieved a CR, and 13% obtained a PR (*Table 5*). Further, the median progression-free survival (PFS) in the mITT population (n=115) was 2.9 months (95% CI: 2.3 to 4.2) and the median overall survival (OS) was 11.1 months (95% CI: 6.6, upper range not yet estimable).

In the ITT population (n=167), the PFS and OS probabilities were 35% (95% CI: 26 to 43) and 57% (95% CI: 48 to 64), respectively, at 6 months, 31% (95% CI: 23 to 39) and 40% (95% CI: 32 to 49) at 12 months, and 29% (95% CI: 21 to 37) and 36% (28 to 44) at 18 months after enrolment (*Table 5*).

Table 5 Efficacy results in the mITT (infused) and ITT (enrolled) patient populations in the JULIET study (DCO: 21-May-2018)

	JULIET (study C2201)	
	Infused (n=115)	Enrolled (i.e. all patients) (n=167)
Progression-free survival (PFS)*		
Events – n (%)	68 (59.1)	97 (58.1)
Median (months) (95% CI)	2.9 (2.3, 4.2)	4.6 (3.7, 5.2)
% event free probability at 6 months	38.3 (28.9, 47.6)	34.5 (26.4, 42.7)
% event free probability at 12 months	34.9 (25.7, 44.2)	30.9 (23.1, 39.1)
% event free probability at 18 months	34.9 (25.7, 44.2)	28.8 (21.0, 36.9)
Overall survival (OS)*		
Events – n (%)	61 (53.0)	92 (55.1)
Median (months) (95% CI)	11.1 (6.6, NE)	8.2 (5.8, 11.7)
% event free probability at 6 months	61.5 (51.8, 69.8)	56.6 (48.2, 64.2)
% event free probability at 12 months	48.3 (38.4, 57.4)	40.4 (32.2, 48.5)
% event free probability at 18 months	43.2 (33.3, 52.7)	35.9 (27.8, 44.1)

*PFS and OS from the time of infusion in the mITT (infused) patient population, and from the time of enrolment in the ITT (enrolled) patient population.

The Kaplan-Meier (KM) plots of PFS per IRC assessment and OS in the mITT population is presented in Figure 8 and Figure 9, respectively.
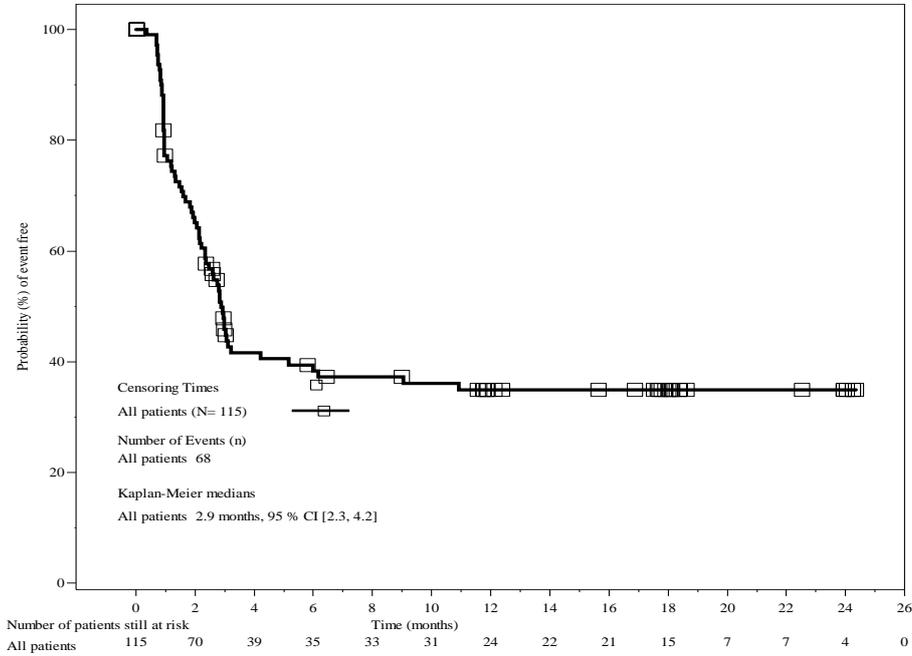
Figure 8: KM plot of PFS in the mITT population censoring HSCT by IRC assessment (DCO: 21-May-2018)
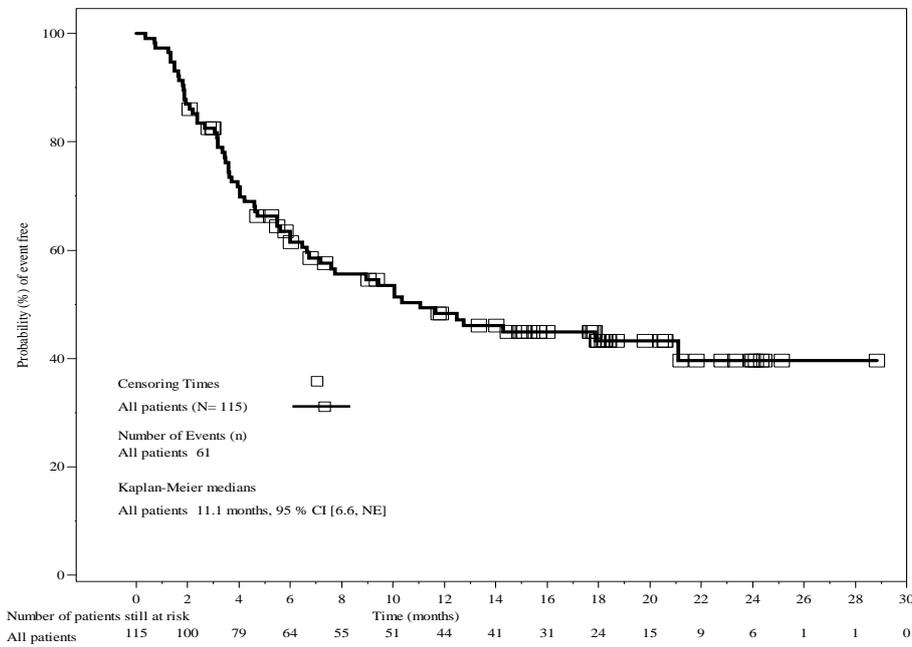
Figure 9: KM plot of OS in the mITT population (DCO: 21-May-2018)

The KM plots of PFS and OS per IRC assessment in the ITT population are presented in Figure 10 and Figure 11, respectively.
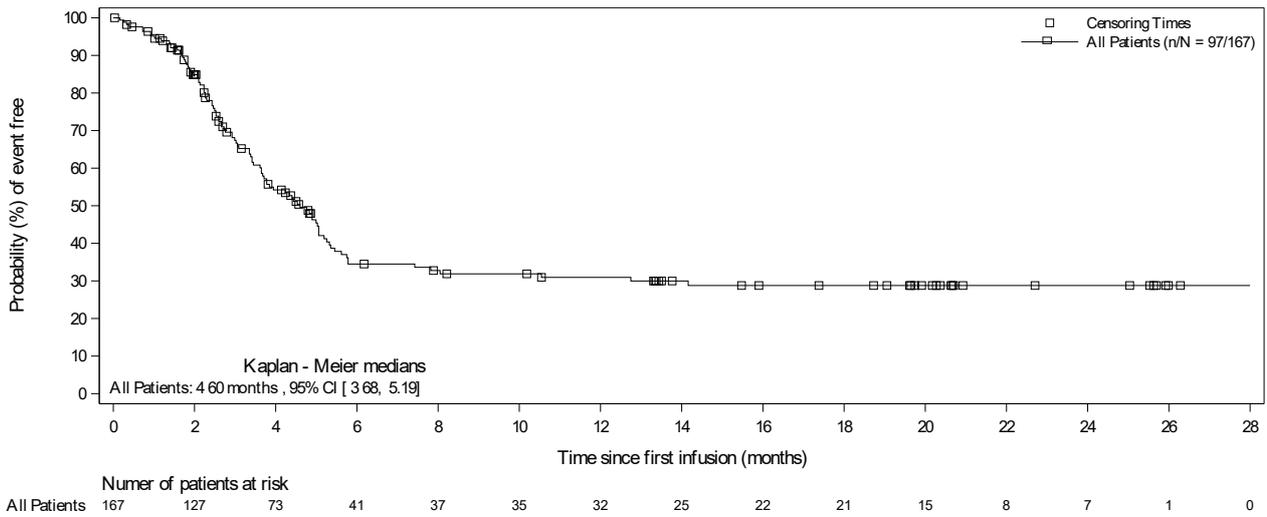
Figure 10: KM plot of PFS from enrolment in the ITT population (Enrolled set; DCO: 21-May-2018)
Time is relative to enrolment, 1 month=30.4375 days. PFS censoring HSCT based on IRC assessment was used for all infused patients. For non-infused patients, PFS was approximated by defining PFS event as discontinuation either due to death or due to physician/subject decision where the detailed reason mentioned disease progression; other discontinued patients were censored at the date of discontinuation.
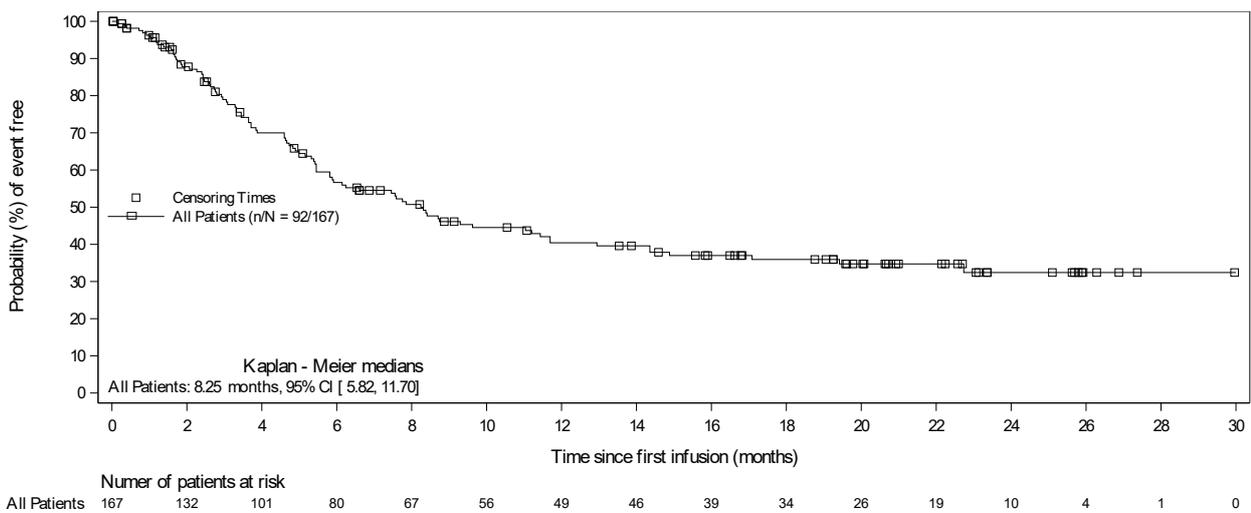
Figure 11: KM plot of OS from enrolment in the ITT population (Enrolled set; DCO: 21-May-2018)
Time is relative to enrolment, 1 month=30.4375 days.

The duration of responses (DoR) in patients obtaining a best disease control rate of CR or PR in the JULIET study indicates that sustained responses can be achieved in these patients, predominantly in patients who obtained a CR. A large proportion of patients who achieve a CR obtained sustained clinically meaningful responses. However, this does not seem to apply to the low number of patients who achieved a PR, with the exception of 1 patient. The KM plot of DoR per IRC assessment among the 53 responding patients who received tisagenlecleucel at least 3 months prior to DCO and who achieved a best overall response rate of CR or PR is presented in Figure 12.

The responses were ongoing and censored at the DCO of 21-may-2018 in 31 patients of the mITT population. Among the 60 responding patients (ORR of CR or PR by IRC), 23 patients had relapsed. The relapses occurred between 1 and 10 months after onset of the responses. No patients who achieved a BOR of CR or PR after the tisagenlecleucel infusion in the JULIET study proceeded to alloSCT or ASCT while they responded to the treatment. However, one of the patients underwent ASCT, while six patients underwent alloSCT post-tisagenlecleucel infusion.
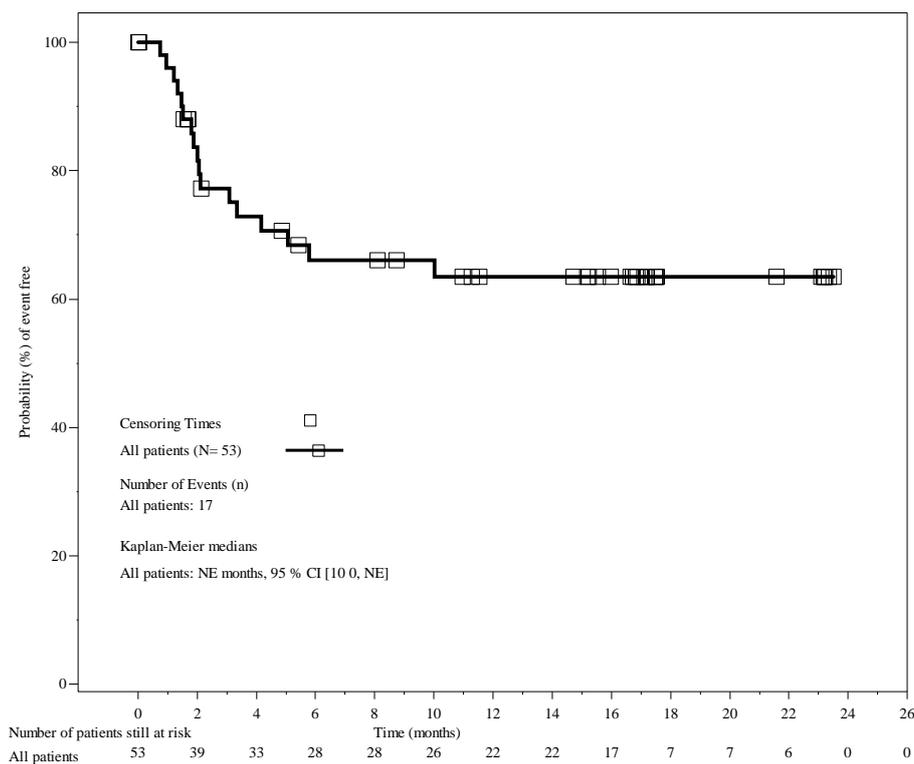
Figure 12: KM plot of the DOR in patients who achieved a BOR of CR or PR censoring HSCT by IRC assessment (EAS)
Time is relative to onset of response, 1 month=30.4375 days.

Submitted health economic analyses

Efficacy inputs for tisagenlecleucel are sourced from JULIET. Novartis originally submitted a model based on the DCO of 21-May-2018. In the recent update, Novartis presented a model based on a DCO of 11-Dec-2018. The survival functions were similar and no new assessment of the fit of different survival models was presented nor evaluated. Consequently the assessment below is based on the DCO of 21-May-2018. Patient data for PFS and OS for the mITT (infused patients from infusion) and ITT (enrolled patients from enrolment) populations were used separately to estimate the number of patients in each respective health state in the model.

Efficacy inputs for comparator were based on the pooled CORAL extension studies (7, 8). Only aggregate OS data were available in these publications. Published data on PFS were not available for salvage chemotherapy. OS data were extracted from the published KM curves using the digitization software Engauge. Pseudo-patient level data were then derived based on the KM data using algorithm outlined in Guyot et al, 2012 (14). The PFS curves were based on the ratio of PFS to OS assessed from the literature (as explained below).

NoMA´s assessment

NoMA chose to use the "lead time"-adjusted comparison of JULIET vs. CORAL extension studies as the source of efficacy data in the economic model in order to align the starting time of the survival analysis between JULIET and CORAL and to ensure that CORAL patients who would not be eligible for JULIET are removed. For a full discussion on the "lead time"-adjusted analysis refer to Section 2.1.2 and Appendix 2. The results from the base case by Novartis are presented in Section 4.2.

3.4.2 Extrapolation of efficacy

Extrapolation of efficacy described in this section is based on the "lead time"-adjusted analysis.

Submitted health economic analyses - projection of overall survival (OS)

Novartis proposed three approaches for projecting long-term survival:

1. Use of KM data plus a standardised mortality ratio (SMR)-adjusted survival. After the end of the observed period (30 month for the ITT population (survival measured from enrolment) and 29 month for the mITT population (survival measured from infusion), the same mortality rate was applied for both tisagenlecleucel and salvage chemotherapy arm. The SMR of 3.56 up to year 8 and the SMR of 3.07 from year 8 onwards was based on SMR-adjusted mortality for DLBCL survivors as reported in Hill et al. 2011 and applied to Norwegian general population mortality (15).
2. Use of standard parametric or flexible spline-survival models instead of SMR-adjusted mortality to extrapolate OS and PFS for tisagenlecleucel and CORAL separately beyond the observation period (Figure 13).

3. Use of a mixture cure model (MCM) to extrapolate OS and PFS for tisagenlecleucel and salvage therapy separately beyond the observation period (Figure 13).

The fit of standard parametric functions as well as a series of one-, two-, three-, and four-knot spline models to the KM data is presented in Table 6-Table 7 and Figure 13. To account for the uncertainty of choosing specific survival distribution, Novartis used a model averaging approach following the recommendations of the NICE mock appraisal (16) and using the methods described in Jackson et al 2009 (17). This technique includes all plausible survival functions as part of a weighted distribution to estimate the joint distribution of uncertainty around the parameter estimates and the choice of survival function. The weights were calculated based on AIC score using the following equation: Weight = $A_k/(\sum A_k)$, where $A_k = e^{-(0.5\times AIC)}$. The weighted distribution was then applied in the base case analysis.

Table 6 Distributions used to estimate overall survival for tisagenlecleucel (JULIET); ITT population (survival from enrolment) and mITT population (survival from infusion).

	mITT population			ITT population		
	AIC[2]	BIC[2]	AIC based weight[3]	AIC[2]	BIC[2]	AIC based weight[3]
Exponential	471,52	477,01	0,4%	699,66	702,78	0,0%
Weibull	468,97	477,20	1,5%	698,57	704,81	0,0%
Gompertz	473,10	481,33	0,2%	683,69	689,92	0,3%
Log-Normal	463,30	471,54	24,7%	681,74	687,98	0,9%
Log-Logistic	464,11	472,34	16,5%	684,85	691,09	0,2%
Gamma	465,25	476,23	9,3%	680,83	690,19	1,4%
Spline with single knot[1]	462,87	471,11	30,6%	674,67	684,02	30,3%
Spline with two knots[1]	464,92	475,90	11,0%	673,94	686,41	43,6%
Spline with three knots[1]	466,85	480,58	4,2%	675,87	691,46	16,6%
Spline with four knots[1]	468,68	485,15	1,7%	677,66	696,37	6,8%

[1]Cubic spline models with one, two, three, and four knots expressed on the proportional hazard scale are fitted based on the method developed by Royston and Parmar (18) [2] The knot locations were chosen at quantiles of the log uncensored death times in the study, per the default settings for the FlexSurv package in R.   AIC - Akaike information criterion. A smaller AIC value represents a better goodness of fit; BIC - Bayesian information criterion. A smaller BIC value represents a better goodness of fit. [3]The weights are calculated based on AIC scores using the method outlined in Jackson 2009. The weights represent the adequacy of each distribution in predicting the efficacy and are used in the calculation for the weighted distribution.

Table 7 Distributions used to estimate overall survival for salvage therapy (CORAL extension studies); ITT and mITT populations*

	mITT population			ITT population		
	AIC[2]	BIC[2]	AIC based weight[3]	AIC[2]	BIC[2]	AIC based weight[3]
Exponential	817,07	823,09	0,0%	1175,59	3659,92	0,0%
Weibull	812,00	821,03	0,0%	1123,63	3707,51	0,0%
Gompertz	805,09	814,12	0,3%	1097,57	4145,56	1,8%
Log-Normal	798,20	807,23	9,5%	1098,34	3729,74	1,3%
Log-Logistic	798,48	807,51	8,2%	1097,31	3935,05	2,1%
Gamma	799,63	811,68	4,6%	1099,39	3617,06	0,7%
Spline with single knot[1]	795,00	3549,25	46,7%	1093,04	3549,25	17,8%
Spline with two knots[1]	796,75	3555,65	19,5%	1091,07	3555,65	47,7%
Spline with three knots[1]	798,71	3562,00	7,3%	1092,74	3562,00	20,7%
Spline with four knots[1]	800,02	3564,17	3,8%	1094,69	3564,17	7,8%

*ITT represents CORAL extension without accounting for deaths within the first 1.88 months to match JULIET's ITT (enrolled) population. mITT represents CORAL extension without accounting for deaths within the first 3.96 months to match JULIET's mITT (infused) population.
[1]Cubic spline models with one, two, three, and four knots expressed on the proportional hazard scale are fitted based on the method developed by Royston and Parmar (18). [2] The knot locations were chosen at quantiles of the log uncensored death times in the study, per the default settings for the FlexSurv package in R.   AIC - Akaike information criterion. A smaller AIC value represents a better goodness of fit; BIC - Bayesian information criterion. A smaller BIC value represents a better goodness of fit. [3]The weights are calculated based on AIC scores using the method outlined in Jackson 2009. The weights represent the adequacy of each distribution in predicting the efficacy and are used in the calculation for the weighted distribution.

*In JULIET, ITT represents JULIET enrolled population with survival measured from enrolment, mITT represents JULIET infused patients with survival measured from infusion. ITT represents CORAL extension without accounting for deaths within the first 1.88 months to match JULIET's ITT (enrolled) population. mITT represents CORAL extension without accounting for deaths within the first 3.96 months to match JULIET's mITT (infused) population.

Figure 13 OS KM with weighted AIC curves; ITT population* (left) and mITT population (right).

Novartis discouraged the use of standard parametric models or flexible spline models due to crossing of the OS and PFS curves. Instead, Novartis prefers to use either the SMR applied to the end of KM data (not shown) or mixture cure models (Figure 14, Figure 13).

The cure model is based on the assumption that the patient population consists of a mix of patients who wind up cured and patients who are bound to die (19-22). The probability of a cure was estimated based on a logistic regression, and the survival of these "cured" patients were assumed to follow the general population mortality. The survival of patients who were not cured was estimated through standard parametric survival distributions. The probability of a patient being cured and the parameters in the survival functions were estimated simultaneously within one model using the R package *flexsurvcure*. Novartis believes that the mixture cure model more accurately reflects the impact of the flat tail of the tisagenlecleucel OS curve after month 23. There was also no additional progression event observed from month 12 to month 24 with the updated data from the DCO of 21-May-2018. In addition, Novartis obtained clinical feedbacks from the UK experts who confirmed that the consideration of mixture cure model would be reasonable for tisagenlecleucel. In the ITT population log-logistic MCM had the best fit to the OS for tisagenlecleucel and comparator. The corresponding cure fractions were 29.1% and 11.6% respectively. In the mITT population, log-normal MCM was suggested for OS in both arms with resulting cure fractions of 38.2% for tisagenlecleucel and 16.1% for comparator. OS curves and the applied MCM are presented in Figure 14.
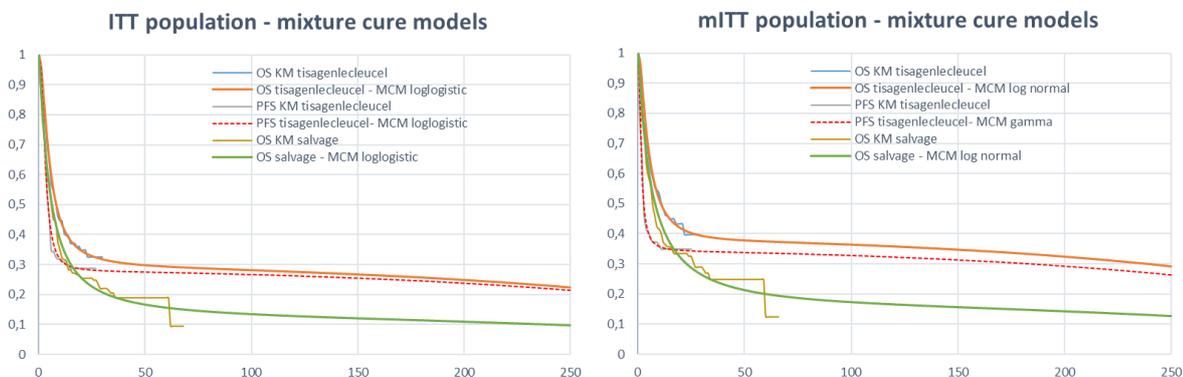

In JULIET, ITT represents JULIET enrolled population with survival measured from enrolment, mITT represents JULIET infused patients with survival measured from infusion. ITT represents CORAL extension without accounting for deaths within the first 1.88 months to match JULIET's ITT (enrolled) population. mITT represents CORAL extension without accounting for deaths within the first 3.96 months to match JULIET's mITT (infused) population.

Figure 14 OS KM with mixture cure model parametric curves based on the best AIC fit; ITT population* (left) and mITT population (right).

NoMA's assessment of OS

For OS extrapolation, Novartis chose to use the SMR applied to the end of KM data or a mixture cure model (MCM). The application of both approaches implies the beginning of a survival plateau after 28.9 months. Meanwhile, the examination of long term survival curves in r/r DLBCL as observed in the CORAL extension studies or the SCHOLAR-1 study shows that additional deaths can be observed beyond 29 months (Figure 15). Although both the CORAL extension studies and SCHOLAR-1 (9) provide support for a long-term prognosis for a proportion of the patients in this disease setting, a survival plateau is not observed as early as after 28.9 months as assumed in the analysis by Novartis. Therefore, NoMA does not consider Novartis's assumption of a long-term survival plateau after 29 months (either by applying the SMR or a mixture cure model) to be supported by evidence.
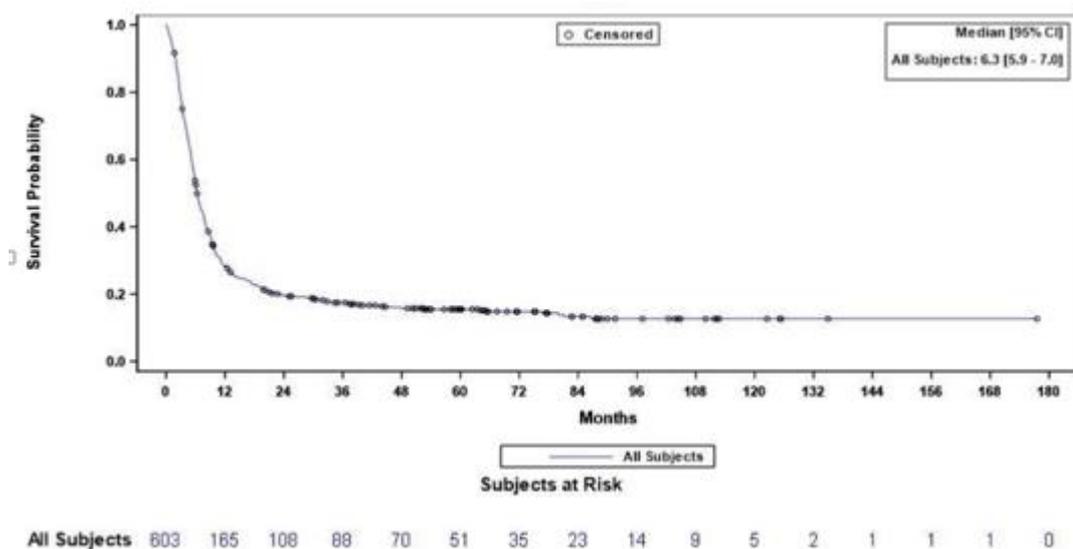
Figure 15 Overall survival from commencement of salvage therapy in SCHOLAR-1 (9)

The support for a long-term survival plateau in the tisagenlecleucel's clinical development programme is very limited. The efficacy results from the supportive case-series study Schuster et al 2017 (5) with median follow-up of 29.3 months (max about 38 months) showed the estimated proportion of patients alive at 38 months of about 45-50%. The study is, however, small with 7/14 DLBCL patients dying during the follow up. In addition, the majority of the long-term responders in this study had TFL. In JULIET, TFL patients had much better response than DLBCL patients. According to Farewell (1986) (23), the mixture cure model generally requires long-term follow-up, the presence of a survival plateau and large samples, and censoring from loss to follow-up during the period when events can occur must not be excessive. The required long-term survival plateau could not be observed in the short follow up time (max follow up 28.9 months for the mITT population in JULIET). Furthermore, additional deaths and progression events were observed at each new DCO. Consequently, although NoMA acknowledges that a proportion of patients may have a long-term prognosis, the JULIET data is not mature enough to robustly estimate a cure fraction or the timing of a cure. The application of a mixture cure model or the SMR to the current JULIET data most likely overestimates the cure fraction resulting in an overly optimistic estimate of survival

benefit. Furthermore, the application of the general population mortality to the "cured" fraction is implausible given the evidence from the literature, which suggests the presence of excess mortality for at least 5 years after therapy initiation (15, 24). This is supported by the Norwegian clinical experts who claim that although patients who achieved CR and are alive at 2 years can be considered a success, it is incorrect to assume that their mortality rate returns to normal.

Novartis proposed the use of a weighted AIC curve as opposed to a specific function. NoMA acknowledges that weighted AIC curves can account for the uncertainty resulting from choosing a specific survival distribution. However, the position of the weighted AIC curve is dependent on the number and type of parametric functions considered, and the plausibility of individual functions has not been discussed. Furthermore, Novartis has averaged survival probabilities as opposed to averaging expected costs and effects resulting from each parametric function in its submission. Choosing a specific parametric model does not only affect survival outcomes, but also for example quality of life and costs. As the model outcomes are highly non-linear functions of the survival parameters, NoMA considers that the approach taken by Novartis introduces bias. This is also explained in the literature, where it is described that the correct approach for model-averaging is to weigh model outcomes in terms of costs and effects (15, 23, 24).

In order to address some of the limitations of a mixture cure function but also to allow for a possibility of a long term survival, NoMA explored alternative approaches to model OS and PFS. The selection of a spline model with two knots resulted in the best mathematical and visual fit to both arms in the ITT population. It also provided the 2nd best fit in the mITT population. In order to be consistent between the populations the spline model with two knots was selected for tisagenlecleucel. The tail of the spline model was closely aligned with the weighed AIC curve. Flexible cubic spline models are recommended when the log-cumulative hazard plots are not straight lines (25), which is clearly the case for tisagenlecleucel (Figure 16).
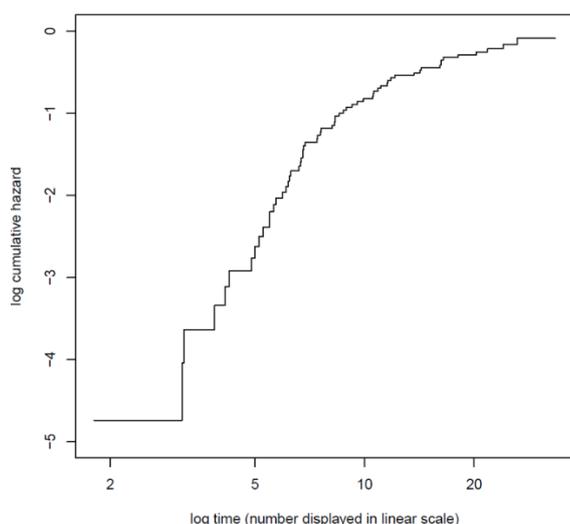
Figure 16 Log cumulative hazard plot vs log time of tisagenlecleucel

NoMA notes that when spline models are applied to the KM data, the PFS for tisagenlecleucel crosses the OS curve. This is due to different shapes of PFS and OS KM curves as observed in the incomplete follow-up; the PFS curve has a more stable plateau at the tail compared to OS which results in more optimistic long-term projection of PFS. A standard approach of limiting PFS survival with the OS curve (i.e. applying the same mortality rate) would result in an implausible increase in the mortality rate of progression-free patients. Therefore, NoMA modified the long-term OS and PFS in the model so that extrapolations result in more plausible outcomes (Figure 17). The mortality from the comparator arm was applied to the tisagenlecleucel arm at the end of follow up time in JULIET which approximately was aligned with the change in survival in CORAL. The application of the same mortality rate from the comparator arm relies on the extrapolated survival beyond the CORAL extension studies follow up period of about 5 years. The Gompertz function was selected as this is the only function that reflects a mortality rate that converges to the mortality rate in the general population over a longer time horizon as observed in the literature (9, 15, 25). The maximum between the mortality rate as predicted by the Gompertz function and the general Norwegian population was selected. The predicted mortality in JULIET is higher than in CORAL which is likely due to the extrapolation of immature JULIET data. The CORAL extension studies have a longer follow-up time and the results of the extrapolation are more aligned with the literature. The use of salvage therapy's mortality for the long-term extrapolation in the tisagenlecleucel arm was proposed by Novartis in previous versions of the model.
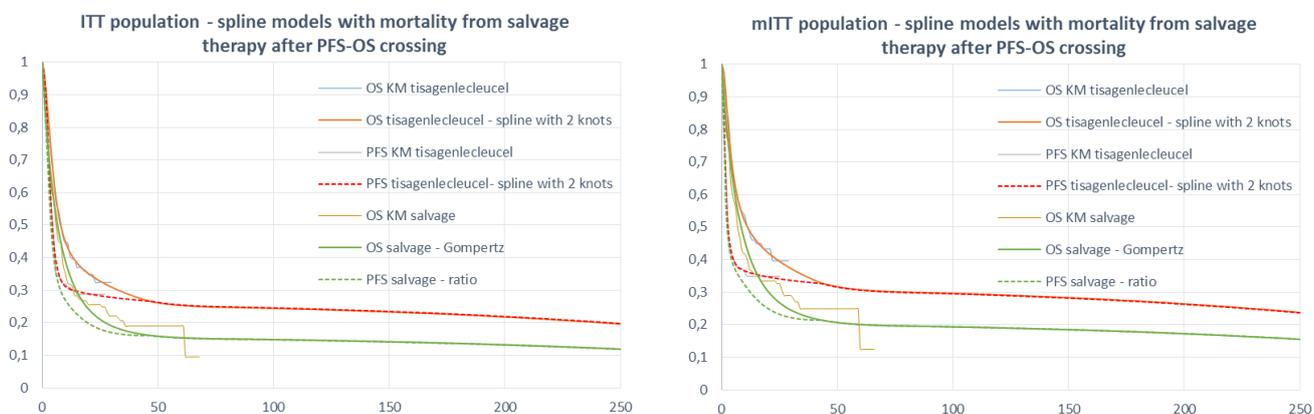
In JULIET, ITT represents JULIET enrolled population with survival measured from enrolment, mITT represents JULIET infused patients with survival measured from infusion. ITT represents CORAL extension without accounting for deaths within the first 1.88 months to match JULIET's ITT (enrolled) population. mITT represents CORAL extension without accounting for deaths within the first 3.96 months to match JULIET's mITT (infused) population.

Figure 17 OS KM with cubic spline models with two knots with common mortality from salvage therapy applied after PFS-OS crossing in JULIET; ITT population (left), mITT population (right). The PFS curve for the salvage therapy arm is based on the PFS:OS ratio from JULIET. NoMA's base case.*

The choice of a survival function is a key driver in the health economic model. Survival extrapolation by means of cure models relies on an assumption that a fraction of the population can be cured from the disease, and that this fraction of cured patients can be identified from the data. The position of the tail of

a KM curve drives the shape of the extrapolated curve in a mixture cure model by setting the survival close to that level. Judgment is needed to ascertain whether follow-up time is long enough and whether a clear survival plateau has been observed. NoMA acknowledges that a proportion of patients may have a long-term prognosis, but considers the "turning point" to not be identifiable based on the current follow-up in JULIET. NoMA considers the JULIET data to be too immature to robustly estimate a cure fraction, which is a key driver of predicted survival in a mixture cure model, due to the absence of a sustained survival plateau or "turning point" based on the short follow-up in JULIET, and other studies of standard therapy demonstrating excess mortality for at least 5 years after diagnosis. NoMA believes that the cure model likely provides an overly optimistic estimate of the survival benefit with tisagenlecleucel due to the overestimation of the cure fraction and timing of the cure. The use of the spline model, on the other hand, addresses the limitaion of the mixture cure model while reflecting a curative potential of tisagenlecleucel. NoMA considers the spline model to be most plausible and therefore selects it for the base case.

The following results from the latest DCO of 11-Dec-2018 of JULIET is redacted until the data is published:

Figure 18 Updated KM curves with cut off date in December 2018

Submitted health economic analyses - projection of progression-free survival (PFS)

The PFS data for tisagenlecleucel were taken directly from JULIET. Among mixture cure models, the log logistic function provided the best mathematical and visual fit in the ITT population and resulted in the cure fraction of 28%. In the mITT population, the gamma function (with a cure fraction of 34.3%) provided a slightly better mathematical fit than log logistic (cure fraction of 34.7%), but the visual fit was almost identical between those MCM functions. Among standard and spline parametric functions the spline model with two knots provided the best mathematical and visual fit in the ITT population. In the mITT population the spline model with one knot provided the best mathematical fit but the spline model with two knots (2nd best AIC score) provided a better visual fit.

Since PFS data were not available in the CORAL extension studies, PFS was derived from published OS curves built on an assumption that the cumulative hazard function for PFS is proportional to the cumulative hazard function of OS based on a study by Lee et al in NHL (24). In the NHL study, differences in 3-year PFS/event-free survival (EFS) were highly correlated with differences in 5-year OS (correlation coefficient, r, of 0.90 [95% confidence interval (CI) 0.73–0.96]). The PFS:OS ratio was estimated based on the average of R-ICE and R-DHAP arms in the CORAL randomised trial (Figure 19) (Gisselbrecht et al 2010) (10). The ratio was first estimated as the natural log of OS probability divided by the natural log of PFS probability at yearly intervals until the end of the observed period. The overall cumulative hazard ratio between OS and PFS was then calculated as the average of cumulative hazard ratios at all yearly intervals. The resulting ratio is 0.65.
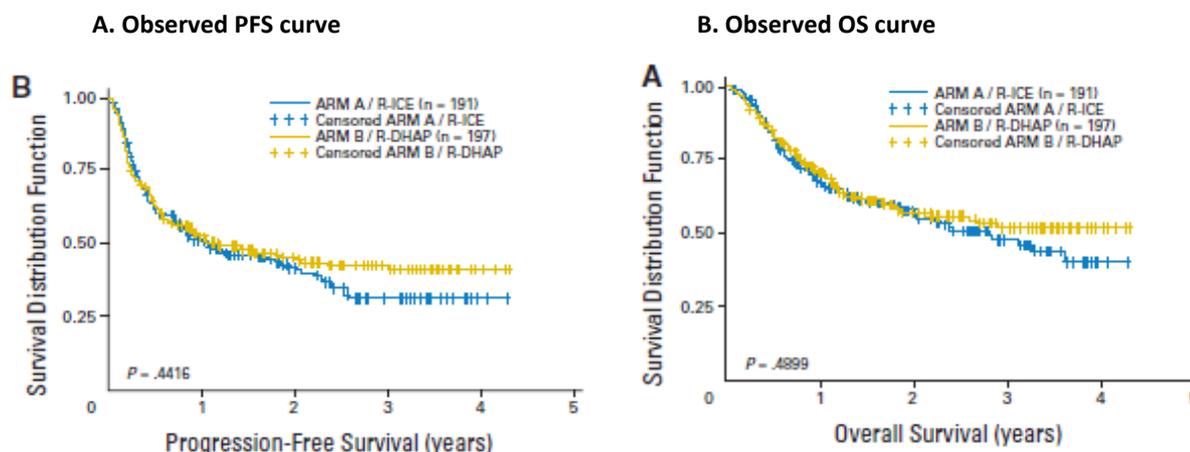
Figure 19 Observed PFS and OS curves from CORAL randomised trial (Gisselbrecht 2010) (10)

NoMA's assessment of PFS

For the tisagenlecleucel arm NoMA selected the spline model with two knots for both the ITT and mITT populations because of the best visual fit and good mathematical fit. Mixture cure models were not considered due to the reasons outlined in the OS evaluation. For consistency and comparability, the same functions were chosen for the ITT and mITT populations.

Due to the lack of PFS data for salvage chemotherapy, the PFS curves were derived from the available OS curves using a PFS:OS ratio based on the data of the original CORAL randomised study. NoMA does not usually accept survival data based on a ratio from the literature, unless the relationship is well documented, and the trial data do not provide the required evidence. Novartis claims that this assumption is justifiable due to a correlation between PFS and OS as observed in previously untreated NHL patients (24). A more relevant reference has not been provided. PFS based on the PFS:OS ratio does not seem to be plausible as a high proportion of progressed patients are predicted to be alive after 20 years (Figure 13, salvage therapy), and patients are at a continuous risk of progression after having been progression free for many years throughout the model. NoMA therefore preferred to use a PFS:OS ratio as derived from extrapolation of the JULIET KM data (i.e. using the spline model with 2 knots) (Figure 17).

NoMA considers the lack of direct evidence on PFS to result in considerable uncertainty with regards to the magnitude of the correlation and the changes in magnitude over time. It is noted, however, that the PFS:OS ratio is used to estimate the PFS curve as opposed to the OS curve which is the key driver of the model.

Conclusions on efficacy parameters

The key limitations of the submitted documentation are:

- Lack of head-to-head comparator trial data and lack of a common comparator for the indirect comparison
- Short follow-up time in JULIET and uncertainty about the long-term effect of tisagenlecleucel
- Failure to adjust for important prognostic factors and effect modifiers between the patient populations in JULIET and the CORAL extension studies in the MAIC.
- Lack of direct evidence on PFS for salvage chemotherapy. PFS was based on the PFS:OS ratio from the literature.
- Lack of patient level data for the comparator arm. Aggregated survival curves were reconstructed from the literature and hence the estimation of the number of events vs. censoring is prone to error. In order to align the starting time of the survival analysis to JULIET's enrolment or infusion, patients who died within the first months in the CORAL extension studies were manually removed by Novartis (i.e. "lead time"- adjusted analysis). The characteristics of these patients are unknown and it is unclear how their exclusion affected the pooled characteristics.

Consequently, the relative effect of tisagenlecleucel vs. comparator cannot be reliably established. NoMA therefore considers this analysis to be highly uncertain. NoMA's preferred assumptions for the base case analysis are as following:

- Use of parametric functions individually fitted to unadjusted KM data. Due to limited availability of patient characteristics in the CORAL extension studies, an adjusted comparison would not be expected to change the results considerably (see Appendix 2 for a full discussion).
- Use of a spline model with two knots for PFS and OS for tisagenlecleucel in the ITT and mITT populations as opposed to a mixture cure model or KM data plus a standardised mortality ratio.

- Use of the Gompertz function for OS extrapolation for the comparator arm and PFS based on the PFS:OS ratio as derived from extrapolation of the JULIET KM data.
- The mortality rate from the salvage therapy arm was applied to tisagenlecleucel (OS) at the point of convergence between the extrapolated OS and PFS curves.
- Use of parametric functions as opposed to the observed data during the study period. Parametric functions smooth the KM curves and lessen the impact of the tail with high censoring rate.

Table 8 Comparison of key assumptions in Novartis's base case and NoMA's base case for tisagenlecleucel

	Novartis's base case	NoMA's base case
OS survival function	Log logistic mixture cure model	- Spline model with 2 knots constrained by the PFS curve - Mortality rate as modelled for the comparator arm from point of convergence
Cure assumption	Both progression-free and progressed patients are "cured" at year 2 post-treatment	Patients that remain progression-free are considered "cured"
Long-term mortality	Equal to the general population	Long-term survivors experience excess mortality as observed in DLBCL studies with longer follow-up
Convergence of OS and PFS curves	No convergence during time horizon	Convergence before month 50 post-treatment

In Novartis's updated base case analysis of 01-Apr-2019 the efficacy for tisagenlecleucel and comparator are based on a parametric function, using spline models with two knots. Beyond 37 months, SMR for long-term DLBCL survivors from Maurer et al (2014) is used (26).

3.4.3   Safety

Submitted clinical studies

The safety profile of tisagenlecleucel is not only affected by the infusion alone, but also by the cytotoxic chemotherapy combinations used as bridging therapy and lymphodepleting regimens patients received prior to infusion, and the medications needed to treat various adverse events (AEs) post-infusion such as antibiotics, gammaglobulines, antipyretics and anti-IL-6 based therapy (e.g. tocilizumab). The rates of AEs described below are mainly based on the DCO of the JULIET study (study C2201) of 08-Dec-2017 (median follow-up: 13.9 months), which is consistent with the EMA label. An overview of the most frequently reported AEs regardless of relationship is presented in Table 9.

The safety profile of tisagenlecleucel was observed to be more severe during an initial acute toxicity phase that encompasses the first 8 weeks post-infusion, most likely due to the rapid T cell expansion and cytotoxic effect of tisagenlecleucel on CD19-positive B-cells. The frequencies of both AEs and serious adverse events (SAEs) were higher during this initial phase and decreased thereafter. The most frequently reported AEs after the initial acute phase, from 8 weeks to 1 year post-infusion, were infections (37.5%), neurological events (5.2%) and febrile neutropenia (2.1%).

Table 9: Adverse events (AE) any time post-tisagenlecleucel infusion in Study C2201 (DCO: 08-Dec-2017), regardless of study drug relationship, by preferred term and maximum grade in more than 10% of patients from All grades (Safety analysis set)

Preferred term	All patients N=111		
	All grades n (%)	Grade 3 n (%)	Grade 4 n (%)
Number patients with at least one AE	111 (100)	31 (27.9)	68 (61.3)
Cytokine release syndrome (CRS)	64 (57.7)	15 (13.5)	9 (8.1)
Anaemia	53 (47.7)	41 (36.9)	2 (1.8)
Pyrexia	39 (35.1)	6 (5.4)	0
Neutrophil count decreased	38 (34.2)	9 (8.1)	28 (25.2)
Platelet count decreased	37 (33.3)	6 (5.4)	25 (22.5)
White blood cell count decreased	37 (33.3)	15 (13.5)	19 (17.1)
Diarrhoea	35 (31.5)	1 (0.9)	0
Nausea	32 (28.8)	1 (0.9)	0
Hypotension	29 (26.1)	7 (6.3)	3 (2.7)
Fatigue	28 (25.2)	7 (6.3)	0
Headache	25 (22.5)	1 (0.9)	0
Hypokalaemia	25 (22.5)	9 (8.1)	0
Neutropenia	22 (19.8)	7 (6.3)	15 (13.5)
Cough	19 (17.1)	0	0
Dyspnoea	19 (17.1)	5 (4.5)	0
Hypomagnesaemia	19 (17.1)	0	0
Hypophosphataemia	19 (17.1)	15 (13.5)	0
Constipation	18 (16.2)	1 (0.9)	0
Febrile neutropenia	18 (16.2)	14 (12.6)	3 (2.7)
Oedema peripheral	17 (15.3)	0	0
Chills	14 (12.6)	0	0
Thrombocytopenia	14 (12.6)	3 (2.7)	10 (9.0)
Decreased appetite	13 (11.7)	4 (3.6)	0
Dizziness	13 (11.7)	0	0
Upper respiratory tract infection	13 (11.7)	2 (1.8)	0
Anxiety	12 (10.8)	1 (0.9)	0

Preferred term	All patients N=111		
	All grades n (%)	Grade 3 n (%)	Grade 4 n (%)
Blood creatinine increased	12 (10.8)	4 (3.6)	0
Tachycardia	12 (10.8)	3 (2.7)	0
Weight decreased	12 (10.8)	3 (2.7)	0
AE = adverse events. A patient with multiple occurrences of an AE is counted only once in the AE category at the maximum toxicity grade. Preferred terms are presented in descending frequency of All patients/All grades column.			

Three patients (2.7%) died within 30 days post-infusion. All deaths were attributed to lymphoma progression. An additional 50 deaths (45%) occurred more than 30 days post-tisagenlecleucel infusion, 42 of which were due to lymphoma progression, two due to multiple organ dysfunction syndrome, and six due to cerebral haemorrhage, chronic kidney disease, duodenal ulcer haemorrhage, neuroendocrine carcinoma, pulmonary haemorrhage and sepsis, respectively. None of the events were suspected to be related to treatment with tisagenlecleucel.

The most frequently reported, serious and life-threatening AE related to tisagenlecleucel is CRS, which was observed in 57.4% (All grades; Grade 3: 14.8%; Grade 4: 7.8%) of the infused patients at the DCO of 21-May-2018 (median follow-up: 19.3 months). CRS was graded using the Penn scale in the JULIET study. This AE is a direct effect of tisagenlecleucel cell expansion, activation and tumour cell killing. CRS occurred within 1 to 9 days in adult patients with DLBCL with a median time to onset of 3 days (except for one patient who reported CRS on Day 51; mean: 4.1 days), and lasted for a median of 7 days (mean: 8.2 days; range: 2 to 30 days). All CRS events occurred exclusively within the first 8 weeks post-infusion. CRS was reversible in most cases and was managed with supportive care and anti-cytokine therapy as needed. Treatment with tocilizumab was required for 27.3% of the patients, and 18.2% needed subsequent treatment with corticosteroids (Table 10). Furthermore, 40.9% of the patients who experienced CRS required intensive care unit (ICU) level care at a median of 5 days (mean: 5.1 days; range: 2 to 12 days) post-infusion, and stayed at the ICU for a median of 5.5 days (mean: 8.5 days; range: 2 to 34 days).

Table 10 Anti-cytokine therapy given during CRS in the JULIET study (Safety analysis set; DCO: 21-May-2018)

	All infused patients (n= 115)
Systemic anti-cytokine therapy given - n (%)	19 (28.8)
Tocilizumab	18 (27.3)
1 dose	8 (12.1)
2 doses	10 (15.2)
≥3 doses	0
Siltuximab	0
Corticosteroids	12 (18.2)
Other	0
All percentages presented below are based on the number of patients with CRS. Only the first CRS episode is summarized for each patient	

The data indicates that CRS may occur regardless of response status. However, the proportion of patients with CRS and associated side effects was greater among patients with high baseline tumour burden compared to those with low tumour burden. Peak serum cytokine levels correlated with CRS severity.

Neurological AEs represent a concern with tisagenlecleucel treatment and were observed in 24.3% (Grade 3: 9.0%; Grade 4: 4.5%) of the infused patients (FAS; n=111). The majority of the neurologic events occurred first 30 days post-infusion, but within the first 8 weeks after treatment. Most common symptoms of these "early" neurological events were agitation, encephalopathy, seizures, tremor, confusional state, delirium, irritability and somnolence. Other manifestations included seizures, aphasia and speech disorder. The median time to onset of neurological events was 7 days and the median time to resolution was 12 days. Neurological events can occur concurrent with CRS, following resolution of CRS or in the absence of CRS. The majority of the neurological events experienced by adult patients with DLBCL resolved completely, but 5% of the patients were not recovered at the time of DCO. Treatment with tocilizumab did not reverse the symptoms, indicating that these neurological AEs were not part of CRS. However, prior history of other CNS diagnoses was considered a risk factor.

B-cell aplasia is a direct effect of tisagenlecleucel and treated patients may therefore experience hypo- or agammaglobulinemia as long as tisagenlecleucel persists in the patients. Since tisagenlecleucel is a cellular immunotherapy that is derived from a mixed population of $CD4^+$ and $CD8^+$ T cells at various stages of differentiation, the CAR-T cells of this medicinal product are expected to follow the normal fate of T cells with different phenotypes. Notably, memory T cells can live for up to six months (27), whereas naive T cells can live up to nine years in healthy humans (28). Available data from the JULIET study demonstrated that the tisagenlecleucel transgene can persist for up to 22 months (nearly 2 years) in the peripheral blood of responding patients with DLBCL. Furthermore, tisagenlecleucel showed a half-life (geometric mean) of approximately 56.6 days in responding DLBCL patients. The observed persistence is expected to increase as the data available matures. In view of that, tisagenlecleucel may potentially be detectable in treated patients for an extended period of time. Hence, depletion of normal B-cells and development of agammaglobulinemi within this timespan constitute a high risk of the treatment.

As expected, successful treatment with tisagenlecleucel resulted in acquired hypogammaglobulinemia due to the loss of normal B cells. Hypogammaglobulinaemia was seen in 7.8% (Grade 3: 2.6%) of the infused patients, and 13.9% had a reported event of low levels of immunoglobulins at the DCO of 21-May-2018 (median follow-up: 19.3 months). Since occurrence of hypo- or agammaglobulinemia might render patients more susceptible to infections, patients who develop hypogammaglobulinemi need to be maintained on supplemental treatment with intravenous gamma globulins (IVIG). Immunoglobuline replacement therapy was given to 33% (38/115) of the infused patients with r/r DLBCL post-tisagenlecleucel infusion. The duration of IVIG treatment had a median and mean of 2 and 5.7 months, respectively, at the time of DCO.

The risk of infections is significantly elevated in patients with DLBCL due to disease- and chemotherapy-induced neutropenia and prior infectious exposures. In addition, development of secondary hypogammaglobulinemia as a result of B-cell aplasia in response to tisagenlecleucel therapy may render the patients more susceptible to infections. Infections were seen in 54.1% of the adult DLBCL patients who received tisagenlecleucel, and 34.2% got infections within the first 8 weeks post-infusion.

Prolonged hematopoietic cytopenia-related AEs that were not resolved during the first 28 days after treatment were seen in 44.1% (Grade 3: 16.2%; Grade 4: 16.2%) of the adult DLBCL patients (n=111). Some of the events were observed several months after the infusion. The aetiology of the cytopenias could be the CAR T-cell therapy itself, the underlying DLBCL, and the anti-DLBCL and lymphodepleting therapies that the patients received prior to infusion. Management of hematopoietic cytopenias was blood product support, growth factors and/or antibiotics as indicated.

Submitted health economic analyses

AE costs and disutilities are considered in the health economic model.

AE costs are described and assessed in section 4.1.3. In summary, AE costs were calculated based on rates of AEs and unit costs per AE. The AE rates inputs were obtained from the JULIET trial data for tisagenlecleucel, and Corazzelli 2009 (29) for salvage chemotherapy. Only grade 3 or 4 with ≥ 5% rate in any of the arms were considered. Both CRS and B-cell aplasia could be associated with substantial resource use, and were included specifically to the tisagenlecleucel arm.

Treatment and AEs disutilities are described and assessed in section 3.4.5. Treatment disutilities for tisagenlecleucel (for the duration of hospitalisation after the infusion), salvage chemotherapy and subsequent SCT were considered. Additional treatment disutilities associated with CRS were added separately.

NoMA´s assessment

Tisagenlecleucel is associated with considerable known risks to the patients, most notably within the first 8 weeks after infusion, although the safety profile is considered manageable and acceptable with regards to the poor prognosis of the patients intended for the treatment. Important adverse events associated with the treatment are CRS, neurotoxicity, and secondary hypogammaglobulinemia due to B-cell aplasia which might render patients more susceptible to infections. Both CRS and B-cell aplasia could be associated with substantial resource use, and are included in the health economic analyses, see section 4.1.3.

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

3.4.4   Health related quality of life (HRQoL)

Submitted documentation

The JULIET study

As part of the secondary objectives in the JULIET study, patient-reported outcomes (PROs) were captured in Short-Form 36 (SF-36).

Utility values were derived by mapping SF-36 data to utility values using the UK EQ-5D tariff. According to Novartis, there is no existing mapping algorithm from SF-36 to EQ-5D utility values developed among lymphoma patients, with reference to the Health Economics Research Centre (HERC) database of mapping studies (WHO, 2014). Instead, a mapping algorithm that was developed by Rowen et al. (30) based on a UK hospital database collected from general population in UK, Health Outcomes Data Repository (HODaR) (31), was used. HODaR was collected from a prospective survey of inpatients and outpatients at Cardiff and Vale NHS Hospitals Trust. The survey included all subjects aged 18 years or older and excluded individuals who were known to have died or with a primary diagnosis on admission of a psychological illness or learning disability.

Published HRQoL studies

Novartis conducted a targeted literature review to identify publications that reported QoL measures for the target population, and two sources were considered relevant and used in the cost-effectiveness model:
- NICE in the UK assessed the pharmaceutical pixantrone monotherapy for treating multiply relapsed or refractory aggressive NHL in 2014 (32). In this NICE Pixantrone STA a systematic literature review was conducted to identify utility data for patients with aggressive NHL (DLBCL is a subgroup of NHL) or in a similar disease area.

- Guadagnolo et al. 2006 developed a decision-analytical model to evaluate follow-up strategies for patients with Hodgkin's disease (33). In this analysis utility and disutility inputs for patients with Hodgkin's disease were consolidated from prior published studies.

Submitted health economic analyses

Health state utilities

In the base case analysis Novartis used utility weights based on data from the JULIET study. In JULIET SF-36-data were collected at screening, month 3, 6, 12, and month 18 for 105, 65, 36, 24, and 9 patients, respectively (DCO 08-Dec-2017). Notably, the majority of the patients who reported PROs after receiving infusion obtained a BOR of either CR or PR. Based on individual patients' health states at the time of SF-36 evaluation, observed SF-36 values were classified into the following categories corresponding to the health states in the model:

- SF-36 measures for relapsed state before treatment: any SF-36 assessments before the treatment start date, where patients were in r/r state from prior treatments.
- SF-36 measures for PFS: any SF-36 assessments when patients are in the PFS state, i.e. on or after the treatment start date and before the date of the first documented progression or death due to any cause. PFS definition is consistent with the PFS definition used in the JULIET study protocol.
- SF-36 measures for Post-PFS: any SF-36 assessment on or after either the PFS event or the censoring date.

Novartis used utility input data from the NICE Pixantrone STA in scenario analyses. Two sets of utility inputs were considered as relevant and referenced by Novartis: i) the utility value recommended by the NICE committee and ii) the utility value initially used in the original manufacturer submission.

Disutility of AEs

Inputs for treatment disutility in the treatment phase (chemotherapy induction) were obtained from Guadagnolo et al. 2006 (33). A decrement of 0.15 for patients undergoing conventional dose salvage chemotherapy is reported and assumed to capture the utility decrements for all short-term AEs associated with the tisagenlecleucel or salvage chemotherapy, with the exception of the CRS. The treatment disutilities were applied for the duration of induction chemotherapy for the comparator arm and for the duration of the hospitalisation starting from the pre-treatment lymphodepleting regimen for tisagenlecleucel.

For the tisagenlecleucel arm, additional treatment disutilities were considered for grade 3 or 4 CRS and for ICU stays not due to CRS. For both events, the patients were assumed to have a utility of 0 (a disutility of 0.83) for the duration of the CRS-related or non CRS-related ICU stay. The CRS rate and the duration of ICU stay were derived from the JULIET trial data.

The model assumed that patients could receive ASCT or alloSCT subsequent to tisagenlecleucel or salvage chemotherapy. Patients receiving subsequent SCT were assumed to have additional disutility, derived from Guadagnolo et al. 2006 (33). Because Guadagnolo et al. did not report any estimate of duration associated with the reported disutility estimates, Novartis assumed the disutility associated with SCT to last for 365 days.

Table 11 QALY-weights used in the model

Input	Utility/Disutility input	Duration	% of patients	Source
Health states utility (base-case - JULIET)				
PFS	0.83	NA	NA	JULIET trial
PD/RL	0.71			
Health states utility (sensitivity - NICE recommendation for Pixantrone submission)				NICE Pixantrone STA
PFS	0.76	NA	NA	
PD/RL	0.68			
Health states utility (sensitivity - Pixantrone manufacturer submission)				
PFS	0.81	NA	NA	
PD/RL	0.60			
Treatment disutility				
Tisagenlecleucel	-0.15	26 days	NA	Guadagnolo et al. 2006 (disutility), assumption (duration)
Salvage chemotherapy	-0.15	72 days		
Other disutility				
ICU stay due to CRS				Assumption: utility=0 during ICU admission (disutility), JULIET (duration and % of patients)
Tisagenlecleucel	-0.83	9.21 days	21.6%	
ICU stay not due to CRS				
Tisagenlecleucel	-0.83	0.86 days	NA	
Subsequent SCT disutility				Guadagnolo et al. 2006
Tisagenlecleucel - ASCT	-0.30	365 days	0.80%	JULIET and UPenn trials
Tisagenlecleucel - Allo SCT	-0.30	365 days	4.80%	JULIET and UPenn trials
Salvage chemotherapy - ASCT	-0.30	365 days	29.85%	SCHOLAR-1 study
Salvage chemotherapy - Allo SCT	-0.30	365 days	10.48%	Van Den Neste et al. 2016 and Van Den Neste et al. 2017
Abbreviations: PFS, progression-free survival; PD/RL, progressive/relapsed disease; ICU, intensive care unit; CRS, cytokine release syndrome; auto SCT, autologous stem cell transplantation; allo SCT, allogeneic stem cell transplantation; NA, not applicable; STA, single technology appraisal				

Age adjusted utilities

Novartis has adjusted the utilities with age by using a multiplicative method as described in NoMA guidelines (34).

NoMA´s assessment

Health state utilities

Novartis used JULIET-based utility inputs in the base case analysis. Patient-level SF-36 has been mapped to EQ-5D data by using a published mapping algorithm. Mapping of utilities is considered an appropriate approach to derive EQ-5D utilities in the absence of EQ-5D trial data, but will increase the uncertainty of the QALY-weights.

UK population-based tariffs were used to calculate health state utilities for PFS and PD. The use of EQ-5D with UK tariffs is recommended in the NoMA guidelines (34). The use of patient-level HRQoL data collected from the population of interest within the same study as input-data for efficacy and safety is generally considered to be a strength.

However, the collection of PROs in the JULIET study raises some issues. PROs may be biased in an uncontrolled, open label trial design. Furthermore, utility scores were only available for 105 patients initially at screening and for a decreasing number of patients over time. In addition, the majority of the patients who reported PROs after receiving infusion were responders. This implies that the number of patients reporting HRQoL-scores for the PD state is low. Hence, the estimated impact tisagenlecleucel had on the quality of life in patients who received the treatment is highly uncertain. The JULIET study has a relatively short median follow-up time. During the follow-up, improvements over time in HRQoL were observed post tisagenlecleucel infusion among the responders.

The QALY-weight of the PFS health state (i.e 0.83) based on JULIET data is relatively high. For comparison, the QALY-weight representing the general population at the same age in Sweden is 0.80 (35, 36). The HRQoL of long term survivors of CAR-T cell therapy in patients with r/r DLBCL is unknown. The JULIET data indicate a relatively high HRQoL. NoMA is concerned whether these values are too optimistic for the long term HRQoL. In a study by Smith et al (2013) persistently low or worsening HRQoL measured with SF-36 were reported by 42% of long term survivors of Non-Hodgkin lymphoma (37).

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

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

Despite the shortcomings of the reported utility data from the JULIET trial, NoMA accepts these utility values due to lack of better data. Utility input from NICE Pixantrone STA is tested in a scenario analysis (Section 4.2.4).

Disutility of AEs

Novartis assumed a disutility of -0.30 for a duration of one year for patients receiving ASCT and alloSCT and a 72-day disutility duration for patients receiving chemotherapy. Under this assumption, the resulting HRQoL for progression-free patients who receive ASCT or alloSCT will be 0.53 in the model for a duration of one year. NoMA has not received any evidence that supports this assumption, and considers the approach taken by Novartis to result in an overly conservative estimate of HRQoL for patients that received ASCT and alloSCT. NoMA prefers an approach that is consistent with the assumed disutility for chemotherapy where the disutility is applied during the treatment phase and assumed to capture all treatment-related disutility. Although some patients may experience longer-term AEs after SCT, including graft versus host disease following alloSCT, NoMA assumes this is captured in the disutility estimate. The American Cancer Society describes that conditioning treatment and the recovery process for stem cell transplants takes about 4 – 8 weeks (38).

NoMA has therefore adjusted the duration of disutility for ASCT and alloSCT equal to the estimate for chemotherapy, hence 72 days.

Novartis used the same assumption as NoMA in their updated base case of 01-Apr-2019, i.e. a disutility of -0.30 for 72 days for patients receiving SCT.

4 HEALTH ECONOMIC ANALYSES

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

4.1 MODEL, METHOD AND ASSUMPTIONS

4.1.1 Model description

Novartis used a three-state partitioned survival (PartSA) model to assess the cost-effectiveness of tisagenlecleucel compared to salvage chemotherapy. A simplified representation of the model structure is shown in Figure 20. The three states include PFS, progressive/relapsed disease (PD/RL), and death. At any time point, the proportion of patients under the PFS curve is in the PFS health state. The proportion of patients over the OS curve is in the state of death. The remaining patients are in the PD/RL health state. Survival curves in the PartSA approach are typically based on independent analyses of OS and PFS endpoints, and a correlation structure between OS and PFS is therefore not explicitly modelled. In this STA a correlation between OS and PFS has been assumed in the comparator arm, as discussed in chapter 3.4.2.
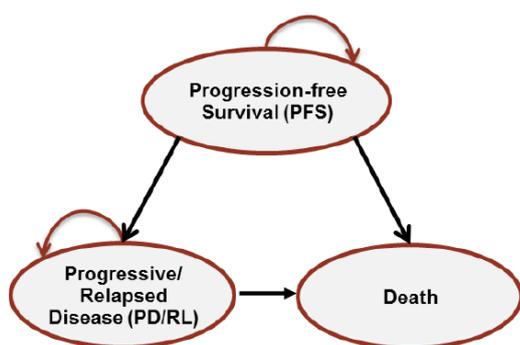
Figure 20 Model structure (source: submission by Novartis)

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

NoMA´s assessment

The implementation of the model in Excel was unnecessarily complex and lacked transparency. Changing important parameters and assumptions was not straightforward and the model was very slow to evaluate. This limited NoMA's options to assess the model validity.

The PartSA model structure is a common approach in oncology to estimate the effect of treatment based on data from clinical trials. The model takes into account the effect of treatment on survival, disease-related symptoms and treatment-related side effects. PartSA models are described in detail in the literature (39). Strengths include the direct relationship between reported study endpoints and survival functions used in the PartSA model to estimate the proportions of patients in the alternative health states in the model. This makes development and communication of the model relatively easy. An important limitation of PartSA models is that the survival functions are typically modelled independently, which can be problematic since events are often structurally dependent and prognostic (such as progression and survival). This may imply that extrapolation of trends beyond the study period is not always appropriate, especially when study data is immature (e.g., median OS or PFS is not reached). Since transition probabilities (e.g. survival for progressive patients) are not explicitly modelled in PartSA models, the possibility of evaluating the plausibility of the extrapolation is limited. Alternative approaches such as state-transition models may include explicit transitions, but it may be challenging to find sufficient data to estimate all relevant transition probabilities.

4.1.2 Analysis perspectives

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

NoMA´s assessment

The healthcare perspective and the discount rate are in accordance with the Norwegian guidelines (34). The monthly cycle length is sufficient for reflecting short-term changes in costs and health states. The lifetime horizon is appropriate for capturing a curative potential of tisagenlecleucel.

4.1.3 Resource use and costs

Submitted documentation

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

Leukapheresis

Costs of leukapheresis (NOK 44 502) are sourced from Rigshospitalet in Denmark. The unit costs are summarised in Table 12.

Table 12: Unit costs for leukapheresis from Rigshospitalet in NOK (source: submission by Novartis)

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

Lymphodepleting chemotherapy

Patients treated with tisagenlecleucel receive lymphodepleting chemotherapy before infusion. Drug costs for lymphodepleting regimens were calculated as a function of unit drug costs, dosing, and proportion of patients receiving each regimen: Regimen 1 (73%), including fludarabine and cyclophosphamide, and Regimen 2 (19.8%), including bendamustine. The distribution of patients to each regimen is obtained from the JULIET trial (see section 3.2). Vial sharing was not considered when estimating the drug costs in the base case.

Treatment costs

Treatment costs consisted of drug/procedure acquisition costs, outpatient administration costs, and hospitalisation and ICU costs. Vial sharing was not considered when estimating the drug cost in the base-case. Table 13 shows a summary of treatment costs for intervention and comparator. The table includes only direct treatment costs of drug price and hospitalisation, and does not include potential downstream follow-up and end-of life costs.

Table 13: Summary of treatment costs for intervention and comparator strategy (source: submission by Novartis)

Treatment strategy	Total treatment cost (NOK)
Tisagenlecleucel	3 365 425
Salvage chemotherapy	321 962

Tisagenlecleucel

Novartis used a unit price of tisagenlecleucel in the model of NOK 3 082 800. Novartis assumed that all patients are hospitalised when they receive the infusion of the CAR-T cells. On average, tisagenlecleucel patients were hospitalised at the general ward for 27.9 days and were hospitalised at the ICU for 0.9 days

for reasons other than CRS, based on the JULIET trial. The resulting total hospitalisation costs is NOK 251 033 and total ICU cost is NOK 31 591.

Table 14 Unit costs for treatment procedures (source: submission by Novartis)

Cost input	Cost in NOK	Source
Daily hospitalisation costs	9 000	By assumption. SAMDATA 2015 and NHS National schedule of reference costs 2015-2016
Daily ICU costs	35 000	By assumption. SAMDATA 2015 and NHS National schedule of reference costs 2015-2016

Salvage chemotherapy

Salvage chemotherapy was modelled as a mixed comparator, consisting of Gem-Ox, IVE, ESHAP and DHAP combined with rituximab, based on input from NHS guidelines as the standard of care. In the Novartis base case, the four regimens are assumed to be distributed equally.

For all regimens, the dosing schedules are obtained from London Cancer Guidelines. The number of cycles and average cycle duration were sourced from Corazzelli 2009 (29) for (R)-Gem-Ox, Zinzani 1994 (40) for (R)-IVE, NICE NHL Guidelines and Martin 2008 (41) for (R)-ESHAP, and London Cancer Guidelines (42) for (R)-DHAP. In the model, Novartis assumed an average of 4 treatment cycles.

The treatment costs of salvage chemotherapy is estimated using weighted average costs of the different regimens, informed from NHS clinical guidelines. Drug unit costs were based on LIS price estimated from Farmastat statistics (2016) and Felleskatalogen.

For each chemotherapy regimen, it is assumed that 60.8% of patients received the regimen in combination with rituximab, based on Danese (2016) (43).

Novartis assumed total or partial inpatient setting for some of the regimens. An administration cost was calculated by multiplying the DRG cost of 917A by 2, resulting in NOK 4 295 per day and was added to regimens in outpatient setting. The average daily hospitalisation cost was assumed to be NOK 17 933 with reference to SAMDATA, with an average hospitalisation of 12.5 days based on Wang (2017) (44).

Table 15 Salvage chemotherapy unit prices and dosage (source: submission by Novartis)

Chemotherapy	Mg/day	Mg/unit	Cost (NOK)/unit	Administrations per cylce
Gemcitabine	1000 mg/m²	1000 mg	1430	1 (day 2)
Oxaliplatin	100 mg/m²	50 mg	1803	1 (day 2)
Rituximab	375 mg/m²	200 mg	4220	1 (day1)
Ifosfamide	3000 mg/m²	2000 mg	724	3 (days 1-3)
Etoposide	200 mg/m²	100 mg	145	3 (days 1-3)
	40 mg/m²			4 (days 1-4)
Epirubicin	50 mg/m²	50 mg	680	1 (day 1)
Methylprednisolone acetate	500 mg/m²	1000 mg	1302	5 (days 1-5)
Cytarabine	2000 mg/m²	2000 mg	384	1 (day 1)
Cisplatin	25 mg/m²	50 mg	198	4 (days 1-4)
	100 mg/m²	100 mg	338	1 (day 1)
Dexamethasone	40 mg/m²	100 mg	472	4 (days 1-4)

Novartis estimated the total treatment cost per patient for salvage chemotherapy at NOK 321 962, which includes the total drug/procedure cost of NOK 69 773, total hospitalisation cost of NOK 224 207 and total administration cost of NOK 27 982.

Subsequent SCT

Novartis assumed that patients can receive subsequent alloSCT or ASCT after initial treatment in the model. The cost and disutility of subsequent SCT were added separately for the proportion of patients who received subsequent SCT for each treatment arm. The subsequent SCT rate for tisagenlecleucel and salvage chemotherapy is presented in Table 16.

Table 16 Subsequent SCT rates used in the model from JULIET and CORAL extension studies

Treatment	Subsequent alloSCT rate (%)	Subsequent ASCT rate (%)	Source
Tisagenlecleucel	5.22%	0.87%	JULIET trial data
Salvage chemotherapy	7.55%	21.22%	Van Den Neste 2016, Van Den Neste 2017

In an input of 02-May-2019, Novartis stated that the clinicians they have consulted estimate that about 3-5 out of 15 r/r DLBCL patients will receive alloSCT each year in Norway, and less than 5% will receive ASCT. Novartis consider the proportion of 29% receiving subsequent SCT in the unadjusted CORAL extension

population to be representative for Norway, but that the distribution of alloSCT and ASCT should be about 25% and 5%, respectively.

The cost of SCT (both allogenic and autologous) was based on information from clinical experts and various DRG costs (DRG price list for 2018). Specifically, SCT costs was considered in three parts: pre-treatment and stem cell harvesting, the cost of the procedure, and the cost of long-term follow-up (Table 17 and Table 18). Novartis assumed stem cell harvesting cost to be included in the initial SCT procedure.

The cost associated with the alloSCT procedure was based on DRG 413, DRG 414 (chemo conditioning) and DRG481B (procedure), with a total weight of 25.31, resulting in a cost of NOK 1 099 337. In the first year after treatment, follow-up was assumed to involve 8 out-patient visits, including test and imaging (DRG 917O + 2500). In the second year follow-up costs involved 6 visits. The total follow-up cost was estimated to NOK 60 223. The follow-up cost input was weighted by the proportion of patients who remained alive at different time periods (i.e. 6 months, 12 months, and 24 months) after the SCT procedure.

For ASCT, the cost associated with the initial procedure was based on DRG413, 414 and 481A, resulting in a total cost of 379 344 NOK. Follow-up costs in the first and second year was assumed to be equal to the follow-up costs after alloSCT.

Table 17 Cost of allogenic stem cell transplantation (alloSCT) including pre-treatment (source: submission by Novartis)

Treatment	Cost in NOK	DRG weight	Source
AlloSCT			
Cost associated with initial SCT procedure	1 099 337	1.359 + 23.955	DRG 413 and 414 (chemo conditioning) and DRG 481B (procedure)
Follow-up cost after SCT procedure (first year)	34 413	0.0530	8 out-patient clinic visits incl blood test and imaging. DRG 917O + 2500
Follow-up cost after SCT procedure (second year)	25 810	0.0530	6 out-patient clinic visits incl blood test and imaging. DRG 917O + 2500

Table 18 Cost of autologous stem cell transplantation (ASCT) including pre-treatment (source: submission by Novartis)

Treatment	Cost in NOK	DRG weight	Source
ASCT			
Cost associated with initial SCT procedure	379 344	1.359 + 7.376	DRG 413 and 414 (chemo conditioning) and DRG 481A (procedure)
Follow-up cost after SCT procedure (first year)	34 413	0.0530	8 out-patient clinic visits incl blood test and imaging. DRG 917O + 2500
Follow-up cost after SCT procedure (second year)	25 810	0.0530	6 out-patient clinic visits incl blood test and imaging. DRG 917O + 2500

Medical follow-up costs pre and post progression

Follow-up costs consisted of the costs of the outpatient visits and laboratory tests and procedures (e.g. full blood count, electrocardiogram, and bone marrow biopsy). The costs were assumed to vary by treatment, health state, and the time horizon.

For patients that remained in the progression-free state, the frequency of medical follow-up was derived from the NICE guideline of NHL for the comparator arm, and from the JULIET protocol for the tisagenlecleucel arm. The monthly pre-progression costs are displayed in Table 19.

Table 19: Monthly pre-progression follow-up costs for the first 5 years (source: submission by Novartis)

Treatment	Cost PFS (year 1) in NOK	Cost PFS (year 2) in NOK	Cost PFS (year 3-51) in NOK	Cost PFS (post 5 years) in NOK
Tisagenlecleucel	4292	693	555	198
Salvage chemotherapy	954	954	477	477

Unit costs per provider visit and per test/procedure were collected from Norwegian fee schedules and the NHS Reference costs 2015–2016 (Table 20).

Table 20: Unit costs for follow-up procedures (source: submission by Novartis)

Description	Cost in NOK	Code	Year of cost	Source
Consultant visit	2 301.68	9170	2018	DRG price list 2018 (6 tests)
Haematology panel	60	707a	2018	Lovdata poliklinikk-takster
Coagulation panel	270	707c	2018	Lovdata poliklinikk-takster (10 tests)
Chemistry panel	100	707a	2018	Lovdata poliklinikk-takster
Cerebrospinal fluid (CSF)	2 378	917A	2018	DRG price list 2018
Serum test	304.37		2015	NICE Guideline: Non-Hodgkin's lymphoma
Bone marrow biopsy and/or aspirate	5 351.79	SA33Z	2016	NHS Reference Costs 2015-2016 (6 tests)
Comprehensive metabolic panel	60	707a	2018	Lovdata poliklinikk-takster (6 tests)
Serum lactate dehydrogenase (LDH)	60	707a	2018	Lovdata poliklinikk-takster (1 test)
Uric acid	10	707a	2018	Lovdata poliklinikk-takster
PET/CT scan	1 575	CT3	2018	Lovdata poliklinikk-takster (4 tests)
Liver function tests	40	707a	2018	Lovdata poliklinikk-takster (3 tests)
Renal/kidney function tests	30	707a	2018	Lovdata poliklinikk-takster

Monthly post-progression cost was applied following disease progression until death, with the exception of the last month before death. The monthly post-progression cost was obtained from Muszbek 2016 (45), and was estimated to be NOK 38 375. The costs are summarised in Table 21.

Table 21 Resource use post progression from Muszbek 2016 (source: submission by Novartis)

Description	Units	Price/Cost, £	Source
Costs associated with progressive/relapsed health state			
Professional and social services	Per 4 weeks	1993.89	38
Health care professional costs	Per 4 weeks	990.74	38, 47
Treatment follow-up costs	Per 4 weeks	18.44	47
Subsequent treatment costs	One off/on progression	1723.68	34, 35
Hospital costs	Annual	1982.03	38, 47
Progression costs	One off on progression	798.20	35, 38

AE = adverse event; CCP = current clinical practice.
*Based on a weighted average of distribution of AEs and cost per each AE. Cost does not reflect variations in incidence.

Adverse event costs

AE costs were calculated for tisagenlecleucel, SCT and salvage chemotherapy and were based on rates of AEs and their unit costs. The rates were obtained from the JULIET trial data for tisagenlecleucel and Corazzelli 2009 (29) for salvage chemotherapy. Only grade 3 or 4 with ≥ 5% rate in any of the arms were considered.

CRS is an AE that is specific to treatment with tisagenlecleucel, and could be associated with substantial resource use. CRS event costs were calculated as the sum of the ICU admission cost and tocilizumab ("antidote") treatment and administration costs. Length of ICU stay and the dosing of tocilizumab related to CRS were obtained from the JULIET trial data. Total CRS cost per event is estimated to be NOK 309 774.

B-cell aplasia resulting in secondary hypogammaglobulinemia is a long-term AE specific to treatment with tisagenlecleucel. Only patients who experience hypogammaglobinemia are assumed to receive supplementary IVIG treatment. Novartis considered that 14% of patients who receive tisagenlecleucel infusion will experience hypogammaglobinemia, based on SmPC. Furthermore, Novartis assumed a median treatment duration of 11.4 months. Monthly IVIG treatment cost was calculated as the cost of IVIG (assuming a body weight of 78.5 kg, with dosing 400mg/kg, 1 dose) and an administration cost per infusion of NOK 2 386. The accumulated IVIG treatment cost was NOK 25 104.

Terminal care costs

Novartis assumed that patients who die incur a one-time cost of NOK 30 034, based on adult patients with cancer diagnosis reported in Georghiou et al. 2014 (46).

NoMA´s assessment

Hospitalisation costs

Hospitalisation costs are used to calculate treatment costs for both tisagenlecleucel, salvage chemotherapy, and respective AEs. Novartis assumed a mean hospitalisation cost of NOK 9 000 per bed day for tisagenlecleucel and of NOK 17 933 for salvage chemotherapy, based on SAMDATA 2015 and the NHS reference costs 2015-2016. Novartis's argument for assuming double unit cost per bed day for salvage chemotherapy compared to tisagenlecleucel is weakly substantiated. For ICU, Novartis assumed the cost to be NOK 35 000 per bed day.

The NoMA guidelines mention SAMDATA as a source of data on cost per hospital admission if DRG or other more reliable sources are not considered sufficient (34). The SAMDATA average of resource use per day at hospitals includes a range of procedures with different complexity. The data from SAMDATA shows that Oslo University Hospital (OUS) has a higher average resource use per day than other hospitals in Norway. This may reflect that OUS performs more complex procedures than other hospitals in Norway as many highly specialised services are centralised at OUS. CAR-T cell treatment of r/r DLBCL patients is assumed to be performed at OUS.

A recent study by Lindemark et al (2017) assessed the cost effectiveness of the Norwegian ICU compared with the general ward (47). In this study they calculated a mean cost of general ward and ICU stay in Norway. The mean cost used in this study was NOK 8 000 (4 000-12 000) per bed day at general ward and NOK 50 000 (30 000-70 000) per bed day at ICU (48). The data are sourced from personal interviews with four hospital trusts in Norway.

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

> *"1) The assumption that treating the critically ill in a ward setting would probably attract resources to the most advanced functions. Hospitals deal with levels of care below high level ICU (multi-organ support) differently, therefore we chose a mean from the higher range of reported data, and*

> *2) The fact that in 2001, the ratio of the cost per ICU day to hospital bed day was estimated to be six (this is the latest study of the cost of an ICU bed-day in Norway available). The ratio here would be 50 000/8 000 = 6.25."*

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

NoMA uses the cost of NOK 8 000 per bed day at general ward from Lindemark et al in both treatment arms. This is consistent with the STA of tisagenlecleucel for the treatment of paediatric and young adult patients with r/r B-cell ALL (3).

Novartis submitted additional information regarding the cost of hospital stay for comparator arm on 1-Apr-2019. Novartis assumed that 17.5 per cent of patients in comparator arm needs treatment at ICU. This was based on input from Danish clinicians in the Danish decision on tisagenlecleucel for treatment of pediatric ALL. This would increase the costs of hospital cost for comparator arm to 12 433 NOK. Clinicians NoMA has contacted has assumed that about 5% of patients need to be treated at ICU. This increase the average cost to about 9500 NOK per bed day.

Lindemark et al assumed that the ICU cost is highest in the first 24 hours and then falls substantially, with reference to Kahn et al (49) and Dasta et al (50). Normalised to the average cost of an ICU bed day, Lindemark modelled ICU daily costs such that ICU days 1 and 2 were 3- and 1.5-times more costly, respectively, than ICU day 3 onwards. The average ICU length of stay in Lindemark was 5 days. NoMA acknowledges that patients experiencing grade 3 and 4 CRS are hospitalised in ICU for a longer time period than the average length of stay in the Lindemark study. This may suggest a lower average cost of ICU stay per day for handling CAR-T related CRS. On the other hand, ICU treatment for this patient population is assumed to be critical and complex.

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

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

Using the Lindemark et al approach gives an average of NOK 39 631 NOK per bed day for 3.58 days in ICU for reason unrelated to CRS, and NOK 30 195 per bed day for 8.5 days in ICU due to CRS. The mean duration of ICU stay, related and unrelated to CRS, is sourced from the JULIET trial.

Novartis used the same costs per bed day (general ward and ICU) as NoMA in their updated base case of 01-Apr-2019.

Tisagenlecleucel treatment costs

Hospitalisation length of stay

In the JULIET study the mean hospital length of stay for tisagenlecleucel treatment was 27.8 days from start of lymphodepleting therapy, including hospitalisation due to lymphodepleting therapy, tisagenlecleucel infusion, and monitoring after infusion.

Norwegian clinical experts have estimated that Norwegian patients will be hospitalised for approximately 3-5 days when they receive lymphodepleting therapy. In the base case, NoMA assumes hospitalisation for 4 days due to lymphodepleting therapy. In a scenario analysis, NoMA uses 3 days at hospital plus 2 days at a patient hotel. The unit costs of the patient hotel is NOK 565 per night (51).

For tisagenlecleucel infusion and monitoring after infusion, Norwegian clinical experts estimate that the duration of hospitalisation for a standard (median) patient would be around 11 days in Norwegian clinical practice. A recent abstract of real-world results on another CAR-T product, axi-cel, shows a median duration of hospital stay of 14 days (13). The distribution of these data is likely to be skewed to the right, hence it is reasonable to expect the mean to be greater than the median. In the axi-cel STA NoMA used a mean duration of hospitalisation of 17.6 days from the time of infusion as observed in the ZUMA-1 clinical study (median 15 days) . Based on input from the clinicians, NoMA does not assume that the length of hospitalisation will differ much between the two CAR-T treatments in Norwegian clinical practice. NoMA therefore uses the same mean duration of hospitalisation (17.6 days) from the time of infusion as in the axi-cel STA, since this estimate is in line with real-world data and closer to the Norwegian clinicians estimate.

Summarised, the total hospitalisation length of stay for tisagenlecleucel treatment (lymphodepleting therapy, infusion, monitoring) in NoMA's basecase is 21.6 days (4 days + 17.6 days).

According to the SmPC (52), patients should stay close to a qualified treatment centre up to 28 days (4 weeks) post-infusion. According to the clinicians, patients who live near OUS may stay at home after 11 days. Patients who do not live near OUS will stay at the patient hotel. In a scenario analysis, NoMA has calculated that patients stay in the hospital for 11 days post-infusion, and then they stay either in the patient hotel or at home for up to 28 days, i.e for 14 days in total. (see section 4.2.4).

In the updated base case analysis of 01-Apr-2019, Novartis used an estimate of 11 days in hospital (NOK 8 000 per bed day) and 16.9 days in a patient hotel (NOK 565 per bed day).

Leukapheresis

Novartis used cost estimates of leukapheresis from Rigshospitalet in Denmark. NoMA has received data on the costs of leukapheresis from the Section of cell laboratory at the OUS (53). These costs represent the average unit costs from the clinical trials of CAR-T cell therapy at OUS. The costs ascribed to leukapheresis and preparation of CAR-T cells from both OUS and Rigshospitalet are summarised in Table 22 (comparison made by NoMA).

Table 22: Unit costs for leukapheresis and preparation of CAR-T cells per patient at OUS and Rigshospitalet

	OUS (NOK)	Rigshospitalet (NOK)
1. Production and shipment of frozen cells:		
Material and reagents	23 566	16 124 (Apheresis, incl. Analysis)
Working hours for leukapheresis and freezing teams (4 hrs doctor, 18 hrs bio technician)	11 332	8 384 (Cell Freezing)
Facilities (Cleanroom, liquid nitrogen storage, QC-lab)	38 889	
Batch documentation, QC and release	11 111	
Shipment, including documentation (3 hrs bio technician)	1 308	6 450 (Shipment)
Total price per production (per patient)	86 206	30 958
2. Receiving and intermediate storage of cells and documentation:		
Storage in liquid nitrogen	2 222	
Work in relation to receiving, intermediate storage and documentation (3 hrs bio technician)	1 308	
Total price for receiving, intermediate storage and documentation per patient	3 530	13 544 (Receiving, containing, transport and defrosting)
3. Thawing of cells bedside:		
Preparation of dry shipper, transfer of cells and documentation (1 hr doctor, 3 hrs bio technician)	2 179	
Working hours for thawing, documentation and transportation (1 hr doctor, 3 hrs bio technician)	2 179	
Total price for thawing bedside (per patient)	4 358	
Hourly wage doctor: NOK 871 (54)		
Hourly wage nurse/bio technician: NOK 436 (54)		
Total price:	94 094	44 502

Novartis submitted additional information regarding the leukapheresis costs on 1-Apr-2019. In an updated estimate from Novartis the leukapheresis costs is NOK 23 063. Detailed description of the leukapheresis costs, and NoMA's assessment can be found in Appendix 4.

The discrepancies between the Novartis' estimate and the cost estimates received from the cell lab at the OUS mainly concerns *1) Production and shipment of frozen cells.* The OUS produce the cells at a clean room at the cell laboratory. According to Josefsen, the freezing of the cells does not need to be done in a clean room. However, as a clean room facility is established at the OUS it is efficient to use the clean room (it would be waste of resources to establish another lab for freezing the cells). However, if the freezing production was purchased in a competitive market place, the price of the product would not reflect the costs of maintaining a clean room, but rather the costs of maintaining a QC-lab. NoMA has therefore omitted the fixed costs of the clean room in the cost effectiveness analysis to reflect only the efficient use of the production at the OUS, in line with other competitive market places for this product.

The input for cost of leukapheresis in NoMA's base case is 55 205 NOK.

Bridging chemotherapy

Among the 115 patients who received tisagenlecleucel infusion in the JULIET study (DCO: 21-May-2018), 102 patients (88.7%) had received antineoplastic therapy after enrolment and prior to tisagenlecleucel infusion. Hence, 102 of 167 patients (61.1%) in the ITT population received bridging therapy.

In the model, the bridging therapy is assumed similar to salvage chemotherapy. Novartis included drug costs and administration costs for one cycle of salvage therapy, but did not include hospitalisation costs . The median number of bridging regimens each patient received in the JULIET study was 1 (range 1-5) and the mean number was 1.7 regimen per patient. In total, 83% of the patients who received bridging chemotherapy prior to tisagenlecleucel infusion did not receive more than two treatment regimens (see section 3.2).

NoMA uses the mean number of regimens received prior to infusion (1.7) and includes hospitalisation costs. The total costs of bridging chemotherapy increase from NOK 16 078 in Novartis's original base case to NOK 43 306 in NoMA's base case.

Novartis included hospital costs in their updated base case of 01-Apr-2019, but maintained their original assumption of 1 cycle bridging chemotherapy. Novartis argued that it is not realistic that patients can get 1.7 cycles of bridging therapy in addition to lymphodepleting therapy if the manufacture and release of tisagenlecleucel takes less than 4 weeks in a real-life setting. Novartis also suggested that bridging chemotherapy should not be included in STA's for CAR-T therapies as this is a protocol driven cost and may vary in clinical trials. In NoMA's opinion the cost of bridging therapy should be included since the effect is already included. Most of the patients received bridging chemotherapy before infusion with tisagenlecleucel in JULIET, and it is not possible to disentangle the survival benefit of tisagenlecleucel from the effect of bridging chemotherapy.

Lymphodepleting chemotherapy

Among the 111 patients who received tisagenlecleucel infusion in the JULIET study (DCO: 08-Dec-2017), 92.8% received lymphodepleting chemotherapy after enrolment and prior to tisagenlecleucel infusion (see section 3.2). NoMA has accepted the cost input for lymphodepleeting therapy.

Tisagenlecleucel

The price of tisagenlecleucel in the submitted model was NOK 3 082 800. This price did not reflect the pharmacy markup, as Novartis assumed that tisagenlecleucel can be delivered directly to hospitals. According to NoMA's guidelines the maximum pharmacy selling price (PSP), including the pharmacy markup and excluding VAT, should be used in the analysis.

NoMA regulates the maximum pharmacy markup. The aim of the pharmacy markup is to cover the pharmacy expenses in handling prescribed expeditions. The pharmacy markup consist of a fixed amount of 29 NOK for each package in addition to 2% of the PSP (markup as of 01-Jan-2019). This regulation ensures that the pharmacy is remunerated for both actions of handling the prescriptions, and for the cost of storage and risk of drug disposal. The package price is closely connected to the costs of capital for the pharmacy with expensive packages leading to higher capital costs and risks compared to cheaper packages.

NoMA writes in the report Evaluation of pharmacy markup from 2016 the following (our translation)(55):

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

According to Novartis, they will provide replacement of the product or issue credit for unusable products. Tisagenlecleucel is shipped directly to the cell lab, the costs of the storage is minimal. However, the pharmacy have other costs associated with tisagenlecleucel, for instance, preparing the staff and working hours for documentation.

The simple structure of the pharmacy markup let the pharmacies to cross subsidize their expenses, as some packages may add an income to the pharmacy less than the cost of expedition, while other packages may add income higher than the cost of expedition. In NoMA's opinion the pharmacy markup is a good proxy estimate of the mean cost for the pharmacy. The pharmacy markup is regulated to cover the total expenses to comply with all prescriptions as regulated by law and regulations. Hence, it will be an important part of the budget consequences for the hospital, and the pharmacy. However, due to the specific circumstances regarding tisagenlecleucel, we consider the markup as a transfer cost. According to national guidelines of economic analysis transfer costs should not be included in the analysis of cost effectiveness. However, the costs may be an important part of the budget analysis (56). NoMA will therefore not add the pharmacy markup into the tisagenlecleucel price as a part of the cost effectiveness analysis in this specific case. We include pharmacy markup in a sensitivity analysis. The pharmacy markup will be included in the budget analysis.

In the ITT population, 115 patients (68.9%) were infused with tisagenlecleucel in the JULIET study, and the tisagenlecleucel costs are included only for infused patients in the ITT model. The remaining 52 non-infused patients received treatment with salvage chemotherapy.

Comparator treatment costs

Novartis modelled salvage chemotherapy as a mixed comparator, consisting of (R)-Gem-Ox, (R)-IVE, (R)-ESHAP and (R)-DHAP sourced from NHS guidelines. According to Norwegian clinicians, the type of salvage chemotherapy varies with the patients' characteristics and aim of treatment. For r/r DLBCL patients relevant to this STA, the most common treatments would be R-GDP, R-EPOCH, R-DHAP, R-Gem-OX and in rare cases R-ICE. This is summarised in Table 23.

Table 23 Salvage chemotherapy used as comparator to CAR-T cell treatments in Norway

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

In terms of drug cost per treatment, there is only little variation between the listed alternatives of salvage chemotherapy combinations.

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

Novartis assumed that 60.8% of the patients receive the regimen in combination with rituximab in their original base case, based on Danese 2016 (US population) (43). According to Norwegian clinicians, it is common in Norwegian clinical practice to add rituximab to all of the chemotherapy combinations listed in Table 23. Rituximab is more costly per treatment compared to the other medicinal products of the regimens. The Norwegian Procurement Agency launched a tender for rituximab that came into effect on 1-Feb-2019. The tender price is lower than the official list price but is confidential by legislation and cannot be revealed in this report. The rituximab price impact on the ICER calculation is, however, small. In NoMA's scenarios we have used the official rituximab list price. Otherwise our ICER calculations would have to be redacted from the public and Novartis.

Novartis assumed that two of these four regimens require inpatient treatment with an average hospitalisation length of stay of 12.5 days based on Wang et al. (57). The Wang observational study only included one of the chemotherapy regimens mentioned by the Norwegian clinicians.

NoMA therefore uses the inputs from the Norwegian clinicians in our base case. This includes rituximab to all patients, and hospitalisation length of stay in line with the estimates provided in Table 23. The estimated mean number of days in hospital for all cycles of the different regimens is 11.7 days, and in addition 3 days on average for treating febrile neutropenia. This is somewhat higher than Novartis' estimate of 12.5 days.

Subsequent SCT

Novartis estimated the cost of subsequent SCT (both allogenic and autologous) based on information from an expert clinician and various DRG costs (DRG price list for 2018). The code DRG 917O used by Novartis to calculate follow-up costs after SCT procedure is for myeloproliferative conditions. Instead, NoMA uses the corresponding code for lymphoma, DRG 917A. In addition, NoMA uses the updated DRG weighting and unit price from 2019 (58).

Table 24 Unit costs used by NoMA. Update of DRG cost estimates

Procedure	DRG used	Unit cost 2019 (NOK)
alloSCT	DRG 481B	841 951
ASCT	DRG 481A	248 946
Chemotherapy conditioning	DRG 413 and 414	59 836
Follow-up visits	917A	1 875
Blood tests and imaging	-	2 500

The use of updated DRG cost estimates results in a total cost of NOK 370 039 for ASCT and NOK 963 044 for alloSCT. Novartis used the same SCT costs as NoMA in their updated base case of 01-Apr-2019.

In the tisagenlecleucel arm, NoMA uses the same rates of alloSCT and ASCT as Novartis in the analyses, based on the rates in the JULIET trial.In the comparator arm, NoMA assumes subsequent transplant rates of 38% and 45% in the "lead time"-adjusted ITT and mITT CORAL populations, respectively (see section 2.1.2). NoMA has calculated the proportion of patients receiving alloSCT and ASCT in the CORAL extension studies, see Table 25. Of the patients who received SCT, about 26% had alloSCT and 74% had ASCT. NoMA uses this distribution to calculate the costs of subsequent SCT in the base case.

Table 25 Proportion of patients receiving SCT in CORAL extension studies

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

In an input of 02-May-2019, Novartis stated that the clinicians they have consulted estimate that about 3-5 out of 15 r/r DLBCL patients will receive alloSCT each year in Norway, and that less than 5% will receive

ASCT. Novartis consider the proportion of 29% receiving subsequent SCT in the unadjusted CORAL extension population to be representative for Norway, but that the distribution of alloSCT and ASCT should be about 25% and 5%, respectively. In a scenario analysis, NoMA has shown the impact on the ICER of adjusting the proportion of alloSCT and ASCT in line with Novartis's assumption.

Follow-up costs

Unit costs per provider visit and per test/procedure were collected from Norwegian tariffs and the NHS Reference costs 2015–2016 (NHS, 2017). As described above, NoMA uses DRG 917A (poliklinisk konsultasjon vedr lymfom, leukemi, myelomatose og visse andre benmargssykdommer) instead of DRG 917O (poliklinisk konsultasjon vedr myeloproliferative tilstander eller udifferensierte svulster) for outpatient consultations.

The follow-up costs post progression is based on input from Muszbek 2016 (45). This article refers to the pixantrone submission to NICE. The estimated resource use of professional and social services in the pixantrone submission contains a calculation error. The calculation is showed in Table 26.

Table 26: Resource use and costs associated with professional and social services used in the manufacturer's model (Pixantrone report table 37)

Resource	Resource use (days)[a]			Unit costs of resource (£)	Duration	Source
	PFS on 3rd (or 4th) line treatment	PFS, discontinued 3rd (or 4th) line treatment	PD			
Residential care	2.99	0.75	–	71.00	28 days	Unit costs of health and social care[69]
Day care	1.12	0.28	1.87	36.00	28 days	
Home care	4.67	1.17	9.33	28.89	28 days	National Audit Office, End of Life Care.[70]
Hospice	0.65	0.16	12.13	136.57	Annual	
Total per cycle costs (£)[b]	**119.10**	**29.78**	**498.47**		–	

[a] Estimated from expert clinical opinion.
[b] Calculated as a weighted average of unit costs per week (i.e., unit cost/duration*7 days); weighted by resource use.
Abbreviations used in table: PD, progressive disease; PFS, progression-free survival.

In this calculation the resource use input for progressive disease hospice services are 12.13 days annually. However, the calculation *Total per cycle costs* in Table 26 is based on an estimate of 12.13 days every 28 days, instead of every 365 days. Thereby the total cycle costs (weekly cycle) in Table 26 is about 4 times higher than what the reported input suggest. The total costs per cycle should be £116 instead of £498.

The monthly costs (4 weeks) will then be £464 instead of £1993.45 (as used in the Novartis analyses). Applying the correct estimate of monthly cost of social services will result in comparable input used in NICE's STA of axicabtagene ciloleucel for treating DLBCL and primary mediastinal B-cell lymphoma (PMBCL) after 2 or more systemic therapies [ID1115], where costs of social services is estimated to be £607 (prices in 2016).

When this is applied to the calculation of monthly follow-up costs used in the original model by Novartis, the total monthly cost is reduced from NOK 38 375 to NOK 19 844. Novartis used the same monthly follow-up cost as NoMA (NOK 19 844) in their updated base case of 01-Apr-2019.

Adverse event costs

CRS

CRS is an AE that is specific to treatment with tisagenlecleucel, and could be associated with substantial resource use. Novartis calculated the CRS cost by summarising the costs of ICU and drug costs for treating CRS.

During hospitalisation, some patients (23.5%) were admitted to the ICU for a mean of 8.5 days related to CRS. Novartis added the costs of ICU on top of the general ward costs and thereby double counted the costs of hospitalisation for patients admitted to ICU in the analyses. NoMA adjusts for this by adding only the incremental costs of ICU admittance in the analysis.

According to Novartis, the physicians are now more experienced in treating CRS. Fever monitoring and earlier use of tocilizumab have resulted in lower rates of ICU admissions. This may imply that the costs of CRS are somewhat lower in clinical practice, than was observed in the JULIET study. However, a recent abstract of real-world results on another CAR-T product, axi-cel, shows that more patients were admitted to ICU in US clinical practice (32%) (13) than in the axi-cel ZUMA-1 clinical trial (13%).

B-cell aplasia

According to the Hospital Procurement trust Panzyga is the preferred pharmaceutical for supplementary IVIG treatment for treating B-cell aplasia since September 2017 (59). This is also confirmed by Norwegian clinical experts.

The recommended dose for Panzyga is 0.2 – 0.4 g per kg every 3-4 weeks. The average weight for patients in the JULIET trial was 78.51 kg. NoMA has assumed an average dose of 0.3 g per kg every 3-4 weeks. This corresponds to 27 g every monthly cycle. This dose requires the following packages:

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

Norwegian clinical experts expect that patients will switch treatment from Panzyga to subcutaneous treatment (the medicinal products Hizentra or Gammanorm). These treatments do not require administration costs, however, as the price of these treatments is higher we assume that the monthly costs of Panzyga will be similar to that of Hizentra or Gammanorm. For simplicity we have used a unit

price and administration costs of Panzyga for the entire period of IVIG treatment. The total monthly costs used in NoMA's base case is NOK 18 448. Novartis used the same monthly IVIG-cost as NoMA (NOK 18 448) in their updated base case of 01-Apr-2019.

Novartis assumed that 14% of patients infused with tisagenlecleucel will receive supplementary IVIG for an average treatment duration of 11.4 months. Upon request NoMA received patient level data on IVIG treatment duration from Novartis. In total, 38 of 115 infused patients (33%) received IVIG treatment at some point after infusion with tisagenlecleucel, and 5 patients were still on IVIG treatment at the end of follow-up. NoMA used this data to construct a KM curve for time until IVIG treatment discontinuation. NoMA added 1 day to the last observed day of IVIG administration to account for patients that only received 1 infusion - since the first day of IVIG administration in these patients was equal to the last day of administration, these patients would otherwise have been excluded in the analysis (since their treatment duration would have been equal to 0).

NoMA estimated a restricted mean survival time of 188 days (6.2 months) on IVIG treatment (60). Clinical experts stated that IVIG treatment is also common for patients on salvage chemotherapy. Hypogammaglobulinaemia was seen in 7.8% (Grade 3: 2.6%) of the patients that were infused with tisagenlecleucel, and 13.9% had a reported event of low levels of immunoglobulins at the DCO of 21-May-2018 (median follow-up: 19.3 months). The difference between the proportion of patient with hypogammaglobulinaemia (7.8%) and the total IVIG use in 33% of patients could be explained by previous lines of treatment, which can also be expected to be present in the comparator arm. NoMA therefore multiplied a treatment duration of 6.2 months with the monthly treatment cost of NOK 18 448 and the proportion of infused patients with treatment related hypogammaglobulinaemia (7.8%). This resulted in a total cost of NOK 8 921, which NoMA used as a one-time cost in its base-case analysis. This is a conservative estimate, since 5 patients were still on IVIG treatment at the end of follow-up. Furthermore, the estimate does not account for the patients at risk who may initiate IVIG treatment beyond the observed follow-up period. The actual costs for IVIG treatment may therefore be higher than estimated.

Terminal care costs

Novartis included terminal care costs of NOK 30 043, based on the overall cost of terminal care reported in Georghiou et al. 2014 for adult cancer patients in the last three months of life (46). In NoMA's opinion, cost estimates based on treated DLBCL patients are more relevant to this STA than cost estimates based on a general patient population with various cancer diagnosis. Hence, NoMA uses the terminal care costs based on treated DLBCL patients of NOK 57 820 obtained from Wang et al. 2017 (57). Novartis used the same terminal care cost as NoMA (NOK 57 820) in their updated base case of 01-Apr-2019.

4.2 RESULTS

NoMA has estimated the incremental cost-effectiveness ratio (ICER) for tisagenlecleucel compared to salvage chemotherapy. Multiple important limitations and uncertainties in the analyses were identified and remain. NoMA therefore considers the cost-effectiveness estimate to be highly uncertain.

In section 3.1 NoMA discussed the relevance of the population characteristics for this analysis. We concluded that it is relevant to present analyses of both the ITT and mITT populations for the decision makers. In the ITT population, the efficacy of tisagenlecleucel is measured from the time of enrolment to account for the delay in manufacturing and the pre-treatment regimens patients received while waiting for the infusion. In the mITT population, the effect of tisagenlecleucel 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.

NoMA's calculations of cost effectiveness are mainly based on the documentation and model submitted by Novartis. Table 27 summarises the changes NoMA has made to Novartis's original base case analysis:

Table 27 Changes to Novartis's base case made by NoMA

Parameter	Novartis's original base case	NoMA's base case	Novartis's updated base case (01-Apr-2019)
Basic initial change from the original submission			
Starting time of the survival analysis	Survival measured from relapse to match OS starting time from the CORAL extension studies	"Lead time"-adjustment: - Survival measured from enrolment (ITT) or from infusion (mITT) in JULIET - The initial events after relapse were removed from the CORAL extension studies	Survival measured from enrolment (ITT) in JULIET. Sensitivity analysis with survival measured from infusion (mITT)
Changes applied to the model where survival is measured from enrolment or infusion:			
Tisagenlecleucel: OS survival function	Log logistic mixture cure model	- Spline model with 2 knots constrained by the PFS curve - Mortality rate as modelled for the comparator arm from point of convergence	- Spline model with 2 knots - SMR-adjusted mortality beyond 37 months from Maurer (26)
Comparator: OS survival function	Log logistic mixture cure model	Gompertz function	Spline model with 2 knots
Tisagenlecleucel: PFS survival function	Log logistic mixture cure model	Spline model with 2 knots	- Spline model with 2 knots

			- PFS flats up until it reaches OS after 60 months
Comparator: PFS survival function	Based on the PFS:OS ratio from CORAL randomised trial (10)	Based on the OS:PFS ratio as modelled for tisagenlecleucel	Based on the PFS:OS ratio from CORAL randomised trial (10)
Cure assumption	Both progression-free and progressed patients are "cured" at year 2 post-treatment	Patients that remain progression-free are considered "cured"	Same as NoMA
Convergence of OS and PFS curves	No convergence during time horizon	Convergence before month 50 post-treatment	Convergence at month 60 post-treatment
Health related quality of life			
Disutility post SCT	1 year of disutility Source: Assumption	Disutility for the duration of the procedure + recovery (72 days) Source: American Cancer Society (38)	Same as NoMA
Resource use			
Leukapheresis costs	NOK 44 502 Source: Rigshospitalet in Denmark	NOK 55 205 Source: Oslo University Hospital	NOK 44 502 Source: Rigshospitalet in Denmark
Hospitalisation cost per bed day	NOK 9 000 (tisagenlecleucel) NOK 17 933 (comparator) Source: SAMDATA 2015, NHS reference costs 2015-2016	NOK 8 000 (tisagenlecleucel) NOK 9500 (comparator) Source: Lindemark (47), clinical experts and assumptions	NOK 8 000 (tisagenlecleucel) NOK 12 433 (comparator)
ICU cost per bed day	NOK 35 000 Source: SAMDATA 2015, NHS reference costs 2015-2016	Day 1: NOK 70 000 Day 2: NOK 35 000 Day 3 onwards: NOK 23 333 Source: Lindemark (47), assumptions	Same as NoMA
Comparator: Hospitalisation length of stay	12.5 days + outpatient administration costs Source: Clinical expert opinion, NHS cancer guidelines	14.7 days, no outpatient administration costs Source: Clinical expert opinion	11.7 days, no outpatient administration costs* Source: Clinical expert opinion
Tisagenlecleucel: Hospitalisation length of stay	26.46 days Source: JULIET	21.6 days (4 days lymphodepleting therapy + 17.6 days infusion and monitoring) Source: Clinical expert opinion, Yescarta STA	14 days (+ 16.89 days in patient hotel) Source: Clinical expert opinion

Comparator: Drug costs	60.5% of patients receive rituximab	100% of patients receive rituximab	Same as NoMA
Bridging chemotherapy	NOK 26 068 Drug costs and outpatient administration costs of 1 cycle	NOK 74 062 Drug costs and hospitalisation costs of 1.7 cycles Source: JULIET	NOK 47 053 Drug costs and hospitalisation costs of 1 cycle
SCT costs	AlloSCT: NOK 1 159 560 ASCT: NOK 439 567	AlloSCT: NOK 963 044 ASCT: NOK 370 039 DRG code and unit price updated	Same as NoMA
Comparator: Subsequent SCT rate (alloSCT/ASCT)	29% (7.5%/21.5%) Source: CORAL extension studies	ITT population: 38% (10%/28%) mITT population: 45% (11.7%/33.3%) Source: "lead time"-adjusted CORAL data, assumption	29% (7.5%/21.5%) Source: CORAL extension studies
Post progression follow-up costs (monthly)	NOK 38 375 Source: Muszbek (45)	NOK 19 844 Source: Muszbek (45) (recalculated)	Same as NoMA
Terminal care costs	NOK 30 034 Source: Georghiou (46)	NOK 57 820 Source: Wang (44)	Same as NoMA
AEs – B cell aplasia: IVIG treatment unit costs (monthly)	NOK 13 343 (Octagam)	NOK 18 448 (Panzyga)	Same as NoMA
AEs – B cell aplasia: IVIG treatment total costs	NOK 25 104 Treatment duration of 11.4 months for 14% of the patients. Source: Assumption	NOK 8 921 Estimated restricted mean survival time of 188 days (6.2 months) on IVIG treatment for 7.8% of patients subtracting IVIG use in comparator arm. Source: JULIET	NOK 37 572 * Estimated restricted mean survival time of 188 days (6.2 months) on IVIG treatment for 33% of patients. Source: JULIET

*In line with NoMA's draft base case of 21-Jan-2019

Red coulor: ICER increase from Novartis's original base case
Green colour: ICER decrease from Novartis's original base case
Yellow colour: relatively small changes in ICER

The results of Novartis's updated base case of 01-Apr-2019 and NoMA's base case are presented in the next paragraphs.

4.2.1 Effectiveness

The total life years gained (LYG) and quality adjusted life years gained (QALYs) of tisagenlecleucel and salvage chemotherapy are summarised in the table below for both the ITT and mITT populations. Novartis' base case is the ITT scenario in the updated base case of 01-Apr-2019. All results are reported per patient and discounted at a discount rate of 4%.

| | Novartis's updated base case (01-Apr-2019) | | | | NoMA's base case | | | |
| | ITT – base case | | mITT | | ITT | | mITT | |
	Tisagen lecleucel	Salvage Chemo	Tisagen lecleucel	Salvage Chemo	Tisagen lecleucel	Salvage Chemo	Tisagen lecleucel	Salvage Chemo
Total LYG	5.11	3.04	6.06	3.04	4.44	3.11	5.29	3.91
Total QALYs	4.08	2.18	4.84	2.18	3.62	2.41	4.31	3.07
Incremental LYG	2.07		3.02		1.33		1.38	
Incremental QALYs	1.90		2.66		1.21		1.25	

The main difference between NoMA's base case and Novartis's updated base case is the comparison of JULIET vs. CORAL extension studies. NoMA's base case is built on a "lead time"-adjusted analysis where the CORAL patients who died early, and hence would not be eligible for JULIET, are removed. This adjustment increased the subsequent SCT rate and survival in the comparator arm.

4.2.2 Costs

The total costs of the different cost components of tisagenlecleucel and salvage chemotherapy treatment are summarised in the table below for both ITT and mITT populations for Novartis's updated base case of 01-Apr-2019 and NoMA's base case.

| In NOK | Novartis's updated base case (01-Apr-2019) | | | |
| | ITT (base case) | | mITT | |
Type of cost	tisagenlecleucel	salvage chemo	tisagenlecleucel	salvage chemo
Total costs	**2 698 024**	**861 606**	**3 686 869**	**861 606**
Pre-treatment	62 668	-	47 534	-
Treatment	2 290 827	240 077	3 218 123	240 077
- *Drug/procedure*	*2 153 723*	*94 611*	*3 084 800*	*94 611*
- *Administration*	*-*	*-*	*-*	*-*
- *Hospitalisation*	*137 104*	*145 466*	*133 323*	*145 466*
AEs	73 599	5 981	104 174	5 981
Follow-up before progression	38 837	8 843	39 881	8 843
Subsequent SCT	42 583	151 281	61 838	151 281
Follow-up post progression	142 350	403 675	170 310	403 675
Terminal care	47 160	51 748	45 010	51 748

In NOK	NoMA's base case			
	ITT		mITT	
Type of cost	tisagenlecleucel	salvage chemo	tisagenlecleucel	salvage chemo
Total costs	**2 690 845**	**550 859**	**3 654 161**	**597 515**
Pre-treatment	106 628	-	58 237	-
Treatment	2 339 437	234 199	3 291 371	234 199
- *Drug/procedure*	2 152346	94 611	3 082 800	94 611
- *Administration*	-	-	-	-
- *Hospitalisation*	187 092	139 588	208 571	139 588
AEs	51943	5 981	75 504	5 981
Follow-up before progression	38 239	18 169	39 110	22 559
Subsequent SCT	36 816	199 204	53 464	235 899
Follow-up post progression	69 116	41 709	89 736	49 606
Terminal care	48 665	51 596	46 739	49 814

The total costs of tisagenlecleucel and salvage chemotherapy are summarised in the table below for both the ITT and mITT populations. Novartis chose the mITT population as the base case.

In NOK	ITT			mITT		
	Total costs		Incremental costs	Total costs		Incremental costs
	tisagenlecleucel	salvage chemo	difference	tisagenlecleucel	salvage chemo	difference
Novartis's updated base case (01-Apr-2019)	2 698 024	861 606	1 836 418	3 686 869	861 606	2 825 264
NoMA's base case	2 690 845	550 859	2 139 986	3 654 161	597 515	3 056 646

The most important cost differences between the ITT and the mITT populations are driven by the cost of tisagenlecleucel. In the ITT population, 30% of patients did not receive the infusion and hence the cost is excluded.

The main differences between Novartis's base case and NoMA's base case are the follow-up post progression costs. In Novartis's base case some of the patients receiving salvage chemotherapy stayed progressed and alive for a long time (up to 27 years). In NoMA's base case the PFS for salvage therapy is derived from the OS:PFS ratio from JULIET resulting in a shorter post progression period.

4.2.3 Incremental cost effectiveness ratios (ICER)

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

Incremental Cost Effectiveness Ratios (ICERs) - cost per LYG			
		ITT	mITT
Novartis's updated base case (01-Apr-2019)	Cost/LYG	887 238	935 679
NoMA's base case	Cost/LYG	1 609 064	2 217 683

Incremental Cost Effectiveness Ratios (ICERs) - cost per QALY gained			
		ITT	mITT
Novartis's updated base case (01-Apr-2019)	Cost/QALY	966 583	1 061 711
NoMA's base case	Cost/QALY	1 774 534	2 412 732

4.2.4 Sensitivity and scenario analyses

Novartis has performed one way sensitivity analysis and a probabalistic sensitivity analysis. The key drivers that affect the ICER in Novartis's sensitivity analysis are the price of tisagenlecleucel, extrapolation of survival, discount rate and health state utility.

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

	Parameter	NoMA's base case	Scenario analyses	ICER in scenario analyses (NOK)
	NoMA's scenarios (ITT population)	**See 4.2.2 for all changes**	-	**1 774 534**
1	CORAL population	Adjusted for "lead time" bias	Unadjusted for "lead time" bias (survival starting at recent relapse) Subsequent SCT rate reduced to 29%	1 393 483
2	Utilities - Health states	PFS: 0.83 PD: 0.71 Source: JULIET	PFS: 0.76 PD: 0.68 Source: NICE Pixantrone STA	1 918 056
3	Tisagenlecleucel: Hospitalisation length of stay	21.6 days (4 days lymphodepleting therapy + 17.6 days infusion and monitoring) Source: Clinical expert opinion, Yescarta STA	14 days (lymphodepleting therapy, infusion, and monitoring). + 14 days in patient hotel (NOK 565 per bed day) Source: Clinical expert opinion, SmPC, Regulations of patient travel.	1 744 332
4	Tisagenlecleucel pharmacy markup	Not included Price of tisagenlecleucel: NOK 3 082 800	Included Price of tisagenlecleucel: NOK 3 167 606	1 822 960
5	Comparator: Subsequent SCT rate (alloSCT/ASCT)	ITT population: 38% (10% alloSCT and 28% ASCT) Source: "lead time"-adjusted CORAL data, assumption	ITT population: 30% (25% alloSCT and 5% ASCT) Source: Clinical expert opinion (Novartis)	1 756 459

Description of the scenario analyses

1) Starting time of the survival analysis: enrolment in JULIET and last relapse in CORAL extension studies as opposed to the "lead time"-adjusted analysis. Gompertz functions were chosen for extrapolation.

2) Health related quality of life: Both methods of estimating health state utilities have shortcomings. The JULIET trial have higher HRQoL scores compared to the general population. Using the utility estimates from JULIET trial will increase the benefit of remission and thereby decrease the ICER. Using the utility estimates from the NICE pixantrone STA will decrease the benefit of remission and thereby increase the ICER.

3) Hospitalisation length of stay – tisagenlecleucel treatment: According to an appointed clinician, the patients should stay at the hospital for 14 days from the start of lymphodepleting therapy. After this they may stay at home or in a patient hotel. The SmPC states that all patients should be near the qualified treatment centre for up to 4 weeks (28 days). The reimbursement tariff for staying at a hotel is NOK 565 (51). NoMA uses this as a proxy for the cost of a hotel stay. With fewer days at the hospital, resources are reduced.

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

NoMA has estimated an incremental cost-effectiveness ratio for tisagenlecleucel compared to chemotherapy. Multiple important limitations and uncertainties in the analysis were identified and remained, and NoMA therefore considers the cost-effectiveness estimates to be highly uncertain.

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

– 1.8 million NOK per QALY gained in the ITT population (enrolled patients)
– 2.4 million NOK per QALY gained in the mITT population (infused patients)

A scenario analysis where the survival analysis started from enrolment (ITT) in JULIET and from last relapse in the comparator arm resulted in an ICER of 1.4 million NOK per QALY gained.

5   BUDGET IMPACT ANALYSIS

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

A)   The technology is recommended for use in clinical practice by the regional health authorities for the eligible patient population as described in this STA

B)   The technology is not recommended for use in clinical practice.

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

5.1   ESTIMATION OF THE NUMBER OF PATIENTS POTENTIALLY ELIGIBLE FOR TREATMENT

Clinical experts recruited by the regional health authorities have estimated that around 40 patients with relapsed/refractory DLBCL will be eligible for treatment with Kymriah (tisagenlecleucel) each year in Norway.

The number of patients expected to be treated in the first 5 years if Kymriah is recommended for use in clinical practice is presented in Table 28. The number of patients expected to be treated if Kymriah is not recommended is presented in Table 29.

Table 28 The number of patients expected to be treated with Kymriah (tisagenlecleucel) in the next 5 years – scenario where Kyrmiah (tisagenleucel) is recommended

	År 1	År 2	År 3	År 4	År 5
Kymriah (tisagenlecleucel)	20	20	20	20	20
Salvage chemotherapy	0	0	0	0	0
Total	20	20	20	20	20

Table 29 The number of patients expected to be treated with Kymriah (tisagenlecleucel) in the next 5 years – scenario where Kyrmiah (tisagenleucel) is not recommended

	År 1	År 2	År 3	År 4	År 5
Kymriah (tisagenlecleucel)	0	0	0	0	0
Salvage chemotherapy	20	20	20	20	20
Total	20	20	20	20	20

5.2 COST ESTIMATES

NoMA has calculated the budget impact for two scenarios:

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

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

Drug costs in NOK per patient per year after treatment initiation according to scenario 1 are presented in Table 30 (ITT population) and Table 31 (mITT population).

Table 30 Drug costs per patient per year after treatment initiation. List price, including VAT and undiscounted, ITT population.

	Year 1	Year 2	Year 3	Year 4	Year 5
Kymriah (tisagenlecleucel)	2 690 432	0	0	0	0
Salvage chemotherapy	118 264	0	0	0	0

Table 31 Drug costs per patient per year after treatment initiation. List price, including VAT and undiscounted, mITT population

	Year 1	Year 2	Year 3	Year 4	Year 5
Kymriah (tisagenlecleucel)	3 853 500	0	0	0	0
Salvage chemotherapy	118 264	0	0	0	0

Healthcare costs in NOK per patient per year after treatment initiation according to scenario 2 are presented in Table 32 (ITT population) and Table 33 (mITT population).

Table 32 Healthcare costs per patient per year after treatment initiation. List price, including VAT and undiscounted, ITT population.

	Year 1	Year 2	Year 3	Year 4	Year 5
Kymriah (tisagenlecleucel)	3 159 798	27 929	16 542	10 432	6 469
Salvage chemotherapy	519 559	19 286	12 032	6 223	3 663

Table 33 Healthcare costs per patient per year after treatment initiation. List price, including VAT and undiscounted, mITT population.

	Year 1	Year 2	Year 3	Year 4	Year 5
Kymriah (tisagenlecleucel)	4 348 201	31 809	19 282	11 121	5 653
Salvage chemotherapy	560 320	20 460	14 509	6 964	3 551

5.3 BUDGET IMPACT

The estimated budget impact in NOK as a result of drug costs only (scenario 1) for the eligible patient population is presented in Table 34 (ITT population) and Table 35 (mITT population).

Table 34 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
Kymriah (tisagenlecleucel) recommended for use	53 808 648	53 808 648	53 808 648	53 808 648	53 808 648
Kymriah (tisagenlecleucel) not recommended for use	2 365 274	2 365 274	2 365 274	2 365 274	2 365 274
Budget impact of recommendation	51 443 375	51 443 375	51 443 375	51 443 375	51 443 375

Table 35 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
Kymriah (tisagenlecleucel) recommended for use	77 070 000	77 070 000	77 070 000	77 070 000	77 070 000
Kymriah (tisagenlecleucel) not recommended for use	2 365 274	2 365 274	2 365 274	2 365 274	2 365 274
Budget impact of recommendation	74 704 727	74 704 727	74 704 727	74 704 727	74 704 727

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 36 (ITT population) and Table 37 (mITT population).

Table 36 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
Kymriah (tisagenlecleucel) recommended for use	63 195 955	63 754 530	64 085 364	64 293 998	64 423 382
Kymriah (tisagenlecleucel) not recommended for use	10 391 189	10 776 906	11 017 545	11 142 001	11 215 255
Budget impact of recommendation	52 804 766	52 977 624	53 067 819	53 151 997	53 208 127

Table 37 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
Kymriah (tisagenlecleucel) recommended for use	86 964 015	87 600 191	87 985 828	88 208 240	88 321 296
Kymriah (tisagenlecleucel) not recommended for use	11 206 410	11 615 603	11 905 776	12 045 050	12 116 070
Budget impact of recommendation	75 757 605	75 984 588	76 080 053	76 163 190	76 205 225

The budget impact of a positive recommendation for Kymriah for the eligible patient population as described in this STA is estimated to be around 53-76 million NOK including VAT in the fifth year after introduction. The calculations are uncertain and based on simplifications.

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

6 SUMMARY AND DISCUSSION

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

NoMA's assessment of the benefit criterion:

The clinical efficacy and safety of tisagenlecleucel was demonstrated in one pivotal phase II study (JULIET) in adult patients with r/r DLBCL.

The best overall response rate was 54% among the patients who received a tisagenlecleucel infusion at least 3 months prior to the DCO of 21-May-2018 in the JULIET trial. The rate of PFS and OS at 12 months were 31% and 40%, respectively, in the ITT population. The median OS was 10.6 months (95% CI: 8.3 to 16.1). Data from the latest DCO of 11-Dec-2018 were also assessed but remain confidential.

The JULIET trial was designed as a single arm study, and Novartis has conducted a MAIC with salvage chemotherapy as comparator to document the relative efficacy. However, as the MAIC approach failed to address important differences between the arms, there is little difference between unadjusted and MAIC-adjusted comparisons. The key issue with the comparison vs. CORAL extension studies is the pronounced "lead time" bias favouring JULIET which would not be present if JULIET was a randomised controlled trial. Consequently, the magnitude of the benefit of tisagenlecleucel is unclear as it is largely impacted by the early deaths in the CORAL extension studies. NoMA's base case is built on a "lead time"-adjusted analysis which aligns the starting time of the survival analysis in both arms to the JULIET trial, and where the CORAL patients who would not be eligible for JULIET are removed.

NoMA considers it plausible that patients that remain progression-free may have a long-term prognosis. NoMA considers the JULIET data however to be too immature to robustly estimate a cure fraction, which is a key driver of predicted survival in a mixture cure model, due to the absence of a sustained survival plateau or "turning point" based on the short follow-up in JULIET, and other studies demonstrating excess mortality for at least 5 years after diagnosis. The spline model used in NoMA's base case, on the other hand, addresses the limitation of the mixture cure model while reflecting a curative potential of tisagenlecleucel. OS for tisagenlecleucel flattens out at the point of convergence between the OS and PFS curves, which means that patients that remain progression-free are considered "cured" and have a long-term prognosis. Otherwise progressed patients would remain alive over the model time horizon, which is an assumption that is not supported by any evidence nor clinical plausibility in the absence of curative treatment options after progression.

NoMA's assessment of the resource criterion:

The analyses considered the following cost components: leukapheresis, bridging and lymphodepleting chemotherapy costs for the tisagenlecleucel arm, drug acquisition, and procedure costs for

tisagenlecleucel 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 tisagenlecleucel is NOK 3 082 800 excluding VAT and pharmacy markup. The mean total healthcare cost was approximately 2.7 million NOK per patient for tisagenleucel and 0.6 million NOK per patient for salvage chemotherapy in NoMA's base case analysis (ITT population), resulting in a mean incremental healthcare cost of 2.1 million NOK per patient. The costs for treatment and AEs are higher for tisagenlecleucel compared to salvage chemotherapy, and the cost for subsequent SCT are lower. The main cost component is the price of tisagenlecleucel.

NoMA's assessment of the severity criterion:

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

NoMA's assessment of budget impact:

NoMA estimated the budget impact for the specialist health services to be around 53 – 76 million NOK including VAT in the fifth year after introduction, if all eliglible adult patients with r/r DLBCL are treated with tisagenlecleucel.

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

The clinical studies of tisagenlecleucel are considered to have considerable shortcomings to inform the STA. The JULIET trial has a single arm study design, is small (115 infused patients), and with a follow-up time just above 2 years.

The study lacks a contol arm, and it is therefore not possible to compare outcomes from this trial with outcomes from the comparator trials without a high degree of uncertainty. Scenario analyses shows that duration of hospitalisation, utilities, pharmacy markup and subsequent SCTs may impact the ICER to some degree. However, the most important parameter seems to be the adjustment of the starting time for the survival analysis, i.e the "lead time"-adjustment.

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

Norwegian Medicines Agency, 11-06-2019

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APPENDIX 1 SEVERITY AND SHORTFALL

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

The calculation of absolute shortfall is done in stages:

1) The mean age at start of treatment for the relevant Norwegian patient group which is being considered for the new treatment is defined. We refer to the age as A. The average age of patients enrolled in the JULIET trial was 58 years. According to Norwegian clinicians the median age in clinical practice will be about 60 years. This is consistent with a recent abstract of real-world results on another CAR-T product, axi-cel, where the median age was 60 years (13). NoMA will therefore use 60 years as A.
2) The number of remaining QALYs (undiscounted) for an average person from the general population with the age A is estimated. We refer to this as $QALYs_A$. We use mortality data for the Norwegian population from Statistics Norway (61) in calculating expected remaining lifetime at different ages. This is combined with age-specific quality of life data to calculate quality adjusted remaining lifetime for different ages. Pending reliable Norwegian figures, we use Swedish age-specific quality of life data, with value sets based on UK general population available for EQ-5D, based on Sun et al (36) and Burstrøm et al (35). See Table 38 below.
3) The prognosis for the relevant Norwegian patient group is calculated. The prognosis is the average number of remaining QALYs (undiscounted) for the patient group with the current standard treatment. We refer to this as P_A. We calculate the prognosis from the number of QALYs the patients can expect with the comparator treatment in the health economic analysis.
4) The absolute shortfall (AS) is the difference between the estimated number of remaining QALYs for the general population at the same age (point 2) and the expected number of remaining QALYs for the patient group with the comparator treatment (point 3).
5) Absolute shortfall (AS) = $QALYs_A - P_A$

Table 38 Calculation of severity

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

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

Expected remaining QALYs in the general population

Table 39 shows the expected remaining QALYs and health state utility values (HSUV) respectively, by age for the general population. Expected remaining QALYs are based on mortality data for the Norwegian population from Statistics Norway (61) and the age-specific HSUV in the right hand column.

Pending reliable Norwegian figures, the HSUV from two Swedish studies have been used (35, 36). In the studies, Swedish age-specific quality of life data is combined with British population-based EQ-5D value-setting tariffs (62).

HSUV for the age group 21-73 years are taken from Sun et al (36), which is the most recent of the two Swedish studies and has the greatest number of respondents. In this publication, HSUV for other age groups are not presented. For the age group 0-20 years, we have assumed that HSUV are somewhat higher than for the age group 20-33 years. We have set it at 0.89.

In order to obtain fairly even age ranges, we have established an age group 74-88 years based on data from Burstrøm et al (35). For this group, we have calculated a simplified weighted average which gives a HSUV of 0.76 (rounded). The calculation is based on the following: For the age group 74-79 years we assume a HSUV at 0.79 based on Burstrøm et al. For the age group 80-88 years we use a HSUV of 0.74 from Burstrøm et al.

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

Table 39 Expected remaining QALYs and HSUV in the general population

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

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

APPENDIX 2 MATCHING-ADJUSTED INDIRECT COMPARISON (MAIC) OF TISAGENLECLEUCEL VS. SALVAGE THERAPY (CORAL EXTENSION STUDIES)

Due to the single arm trial design of JULIET (C2201), Novartis presented an indirect treatment comparison to a historical control using MAIC. MAIC use individual patient data from trials of one treatment to match baseline summary statistics reported from trials of another treatment. After matching, by using an approach similar to propensity score weighting, treatment outcomes are compared across balanced trial populations.

Patient-level data from JULIET and published aggregate data from CORAL extension studies (7, 8) were used for MAIC.

JULIET is an ongoing pivotal single arm, open-label, multi-center, phase II study to determine the safety and efficacy of tisagenlecleucel in adults with r/r DLBCL. Adults with relapsed or refractory disease after ≥2 lines of chemotherapy, including rituximab and anthracycline, and either having failed ASCT, or were ineligible for or did not consent to ASCT, were enrolled. All JULIET patients, regardless of number of prior lines of therapy, were included in the analyses to provide sufficient sample sizes for baseline adjustment in comparisons to the CORAL extension studies. As of May 21, 2018, a total of 167 patients were enrolled (i.e., enrolled population) and 115 patients were infused with tisagenlecleucel (i.e. infused population).

CORAL (10) is a phase III, multicenter, randomised trial that compared the efficacy of three cycles of R-ICE or R-DHAP as second-line therapy, followed by ASCT with or without rituximab maintenance, in patients with relapsed DLBCL. Among 477 patients randomised to R-ICE or R-DHAP, 255 patients who achieved CR, PR, or SD after the third cycle of salvage treatment received consolidation with BEAM followed by ASCT. CORAL extension study 1 (7) includes 75 patients in the CORAL observational follow-up phase who relapsed after ASCT. CORAL extension study 2 (8) includes 203 patients in the CORAL observational follow-up phase who failed to proceed to ASCT. Patients in the CORAL extension study were required to fail only two lines of prior therapy.

Baseline characteristics were measured at screening in the JULIET trial. In the CORAL extension studies, baseline characteristics were measured at second relapse for patients who relapsed after ASCT and at CORAL failure for patients who failed to proceed to ASCT. Variables included in the matching adjustment were gender, IPI risk classification (<3 vs. ≥3), ASCT as the most recent therapy and relapsed after ASCT (yes vs. no) and refractory to last line of treatment (yes vs. no). These variables were similarly distributed across the studies (Table 40). Age, ECOG performance status and disease stage were not individually matched as they are already included as components in the IPI risk classification. Adjusting for number of lines of prior therapy was not feasible since all patients in the CORAL extension studies received exactly two lines of prior therapy. Similarly, primary diagnosis (DLBCL vs. non-DLBCL) was not matched for because all patients in CORAL extension studies were considered to have DLBCL as the primary diagnosis.

Table 40 Matching Patient Characteristics between JULIET (Both Cohorts) and Pooled CORAL Extension Studies

	Before Matching			After Matching		
	JULIET FAS Both Cohorts	**JULIET Enrolled Both Cohorts[1]**	**CORAL Extension Studies**	**JULIET FAS Both Cohorts**	**JULIET Enrolled Both Cohorts [1]**	**CORAL Extension Studies**
	N=115	**N=166**	**N=278**	**N=115**	**N=166**	**N=278**
Male	61.7%	63.3%	62.9%	63.0%	62.9%	62.9%
Low IPI risk classification (< 3)	58.3%	55.4%	59.3%	59.3%	59.3%	59.3%
ASCT as the most recent therapy and relapsed after ASCT	26.1%	23.5%	27.0%	27.0%	27.0%	27.0%
Refractory to last line of treatment	53.9%	58.4%	52.9%	52.9%	52.9%	52.9%

[1] one patient with missing IPI risk classification data was excluded

In the infused population, all 115 patients were reweighted to match the average patient characteristics for CORAL extension studies. An effective sample size was calculated to detect situations in which extreme weights may lead to low statistical power for the comparison. The effective sample size after matching was 115, indicating that there was no evidence of extreme weights. In the enrolled set, the effective sample size after matching was 163 (down from 166), also indicating that there was no evidence of extreme weights. Consequently, all patients from JULIET were retained for MAIC.

In the CORAL extension studies, OS was defined as the time from relapse post-ASCT to death from any cause for patients who had ASCT as the most recent therapy and, for patients who failed to proceed to ASCT, as time from failure of CORAL induction therapy to death from any cause. To align with the definition of OS in the CORAL extension studies, a different OS definition was used in JULIET when comparing with CORAL extension studies. Specifically, OS in JULIET was then defined as time from a) relapse after the most recent therapy, b) the last dose of the most recent therapy, or c) the most recent ASCT, whichever occurred the latest before enrolment, to death from any cause. The results of MAIC are presented in

Table 42, and Figure 21- Figure 22.

The proportional hazards assumption was not met indicating that the HR between two treatments may vary over time. Consequently, the OS HRs should be viewed with caution.

Table 41 Comparison of Outcomes of JULIET Infused and Pooled CORAL Extension Studies

	Before Matching				After Matching			
	JULIET Infused[1] [A]	CORAL Extension Studies[2] [B]	Response Difference (95% CI) [A] - [B]	P-value[3]	JULIET Infused[1] [A]	CORAL Extension Studies[2] [B]	Response Difference (95% CI) [A] - [B]	P-value[4]
Response Rates[5]	**N=99**	**N=278**			**N=99**	**N=278**		
CR[6]	40.4%	28.4%	12.0% (0.9%, 23.1%)	<0.05*	41.0%	28.4%	12.6% (1.8%, 23.4%)	<0.05*
ORR (CR + PR)	53.5%	40.3%	13.2% (1.8%, 24.7%)	<0.05*	53.6%	40.3%	13.3% (2.2%, 24.4%)	<0.05*
OS[7]	**N=115**	**N=266**			**N=115**	**N=266**		
Median, 95% CI (month)	16.3 (11.5, NE)	5.8 (4.7, 7.2)			16.3 (11.6, NE)	5.8 (4.7, 7.2)		
Log-rank test				<0.01*				<0.01*
HR, 95% CI ([A] vs. [B])	0.42 (0.32, 0.57)			<0.01*	0.42 (0.32, 0.55)			<0.01*

Abbreviations: ASCT: Autologous Stem Cell Transplantation; CI: Confidence Interval; CR: Complete Response; HR: Hazard Ratio; KM: Kaplan-Meier; NA: Not Applicable; NE: Not Evaluable; NR: Not Reached; ORR: Overall Response Rate; OS: Overall Survival; PR: Partial Response.

Notes:

[1] For response rates, JULIET patients with tisagenlecleucel infused (EAS, Main Cohort) who had at least 3 month follow-up prior to data cutoff date (May 21, 2018) were included. For OS, JULIET patients infused (FAS, Main Cohort and Cohort A) were included.

[2] For response rates, CORAL patients who relapsed after ASCT (N=75) or failed to proceed to ASCT (N=203) were included. Among 222 CORAL patients who failed to proceed to ASCT, 203 patients enrolled in the extension study were included; 13 patients died and 6 patients withdrew by patient request before enrolment to the extension study. OS data were reported for 266 CORAL patients in two study publications including 73 (out of 75) patients who relapsed after ASCT and 193 (out of 203) patients who failed to proceed to ASCT.

[3] Before matching, CR rate and ORR were compared using the Chi-squared test. For OS, the log-rank test was used to compare two KM curves, while the Cox proportional hazards model was developed for HR estimation.

[4] After matching, the weighted Chi-squared test was used for CR rate and ORR comparison. For OS, the weighted log-rank test was used to compare KM curves, while the weighted Cox model was developed for HR estimation.

*Table 42 Comparison of Efficacy Outcomes of JULIET Enrolled and Pooled CORAL Extension Studies*

	Before Matching				After Matching			
	JULIET Enrolled[1] [A]	CORAL Extension Studies[2] [B]	Response Difference (95% CI) [A] - [B]	P-value[3]	JULIET Enrolled[1] [A]	CORAL Extension Studies[2] [B]	Response Difference (95% CI) [A] - [B]	P-value[4]
Response Rates[5]	N=146	N=278			N=146	N=278		
CR[6]	27.4%	28.4%	-1.0% (-10.0%, 8.0%)	0.82	28.9%	28.4%	0.5% (-8.4%, 9.5%)	0.91
ORR (CR + PR)	36.3%	40.3%	-4.0% (-13.7%, 5.7%)	0.42	38.3%	40.3%	-2.0% (-11.6%, 7.5%)	0.68
OS[7]	N=166	N=266			N=166	N=266		
Median, 95% CI (month)	10.6 (8.3, 16.1)	5.8 (4.7, 7.2)			10.9 (8.5, 16.3)	5.8 (4.7, 7.2)		
Log-rank test				<0.01*				<0.01*
HR, 95% CI ([A] vs. [B])	0.54 (0.42, 0.69)			<0.01*	0.53 (0.42, 0.68)			<0.01*

[1] For response rates, JULIET patients enrolled in the Main Cohort were included. For OS, JULIET patients enrolled were included. For both comparisons, one patient with missing IPI risk classification data was excluded.

[2] For response rates, CORAL patients who relapsed after ASCT (N=75) or failed to proceed to ASCT (N=203) were included. Among 222 CORAL patients who failed to proceed to ASCT, 203 patients enrolled in the extension study were included; 13 patients died and 6 patients withdrew by patient request before enrolment to the extension study. OS data were reported for 266 CORAL patients in two study publications including 73 (out of 75) patients who relapsed after ASCT and 193 (out of 203) patients who failed to proceed to ASCT.

[3] Before matching, CR rate and ORR were compared using the Chi-squared test. For OS, the log-rank test was used to compare two KM curves, while the Cox proportional hazards model was developed for HR estimation.

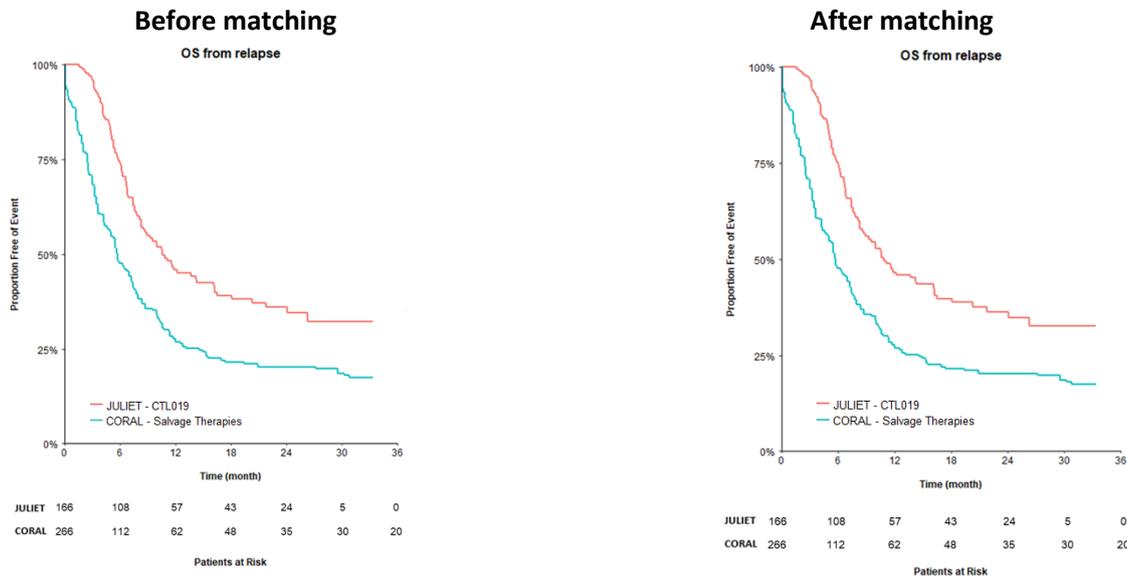**Before matching**   **After matching**
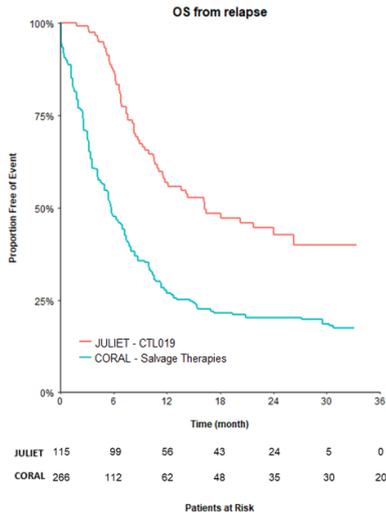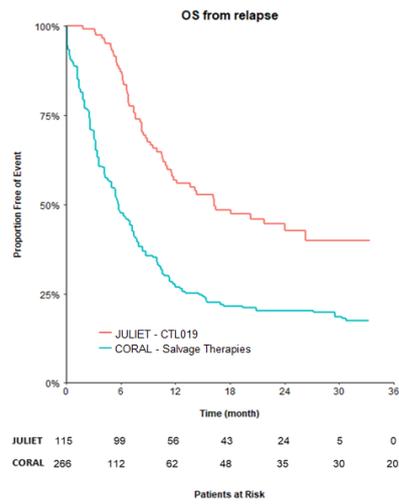
Notes:
[1] Data cutoff date for JULIET: May 21, 2018; the trial is still ongoing.
[2] All data for CORAL were used in generating the KM curves; the KM curves displayed were truncated at the maximum of JULIET follow-up.

Figure 21 Kaplan-Meier Curves of OS Comparing JULIET Infused (FAS, Both Cohorts) and Pooled CORAL Extension Studies. OS measured form most recent relapse.

Before matching

After matching

[1] Data cutoff date for JULIET: May 21, 2018; the trial is still ongoing.
[2] All data for CORAL were used in generating the KM curves; the KM curves displayed were truncated at the maximum of JULIET follow-up.

Figure 22 Kaplan-Meier Curves of OS Comparing JULIET (Enrolled, Both Cohorts) and Pooled CORAL Extension Studies. OS measured form most recent relapse.

The key limitations described by Novartis was an imbalance in previous lines of therapy between JULIET and CORAL. In the JULIET study, 51.4% of patients in the FAS received at least three lines of prior treatment, while the patients presented in the CORAL extension studies were required to be candidates for third-line chemotherapy by design. As patients who received more prior therapies are expected to have worse efficacy outcomes with chemotherapies compared to patients who received fewer prior therapies, this difference in populations would be expected to bias the comparison of outcomes against the JULIET population. Also, IPI data were only available for 115 (out of 203) patients who failed to proceed to ASCT and 67 (out of 75) patients who relapsed after ASCT in the CORAL extension studies, which may result in residual confounding due to inadequate adjustment for baseline IPI. Lastly, the ORR results for CORAL extension studies need to be interpreted with caution as 26/203 and 56/203 were CR and CR/PR already before starting the 3rd line treatment. As with any comparison of non-randomised treatment groups, this comparison was subject to potential bias due to unobserved or unmeasurable confounding.

NOMA's assessment of JULIET vs CORAL extension studies comparison

Studies included in the MAIC were identified through a Systematic Literature Review (SLR) conducted by Novartis according to the best practices for systematic searching, including those published by the Cochrane Collaboration. The SLR was comprehensive and transparent. The search criteria, sources, inclusion and exclusion criteria were clearly stated.

NoMA considers CORAL extension studies as being an acceptable source of a historical control in the Norwegian setting. The OS after second relapse is very similar to the survival of DLBCL patients with two or more relapses or progressions from the Oslo University Hospital Lymphoma Register which capture 35-40% of all DLBCL cases in Norway (Figure 7, Section 3.1).

Similar to JULIET, the original CORAL study selected for better patients (patients were considered eligible for ASCT at the time of relapse/refractoriness to 1st line treatment). In terms of patient characteristics in the CORAL extension studies, NoMA recognizes that patients in JULIET were more heavily pre-treated which could bias the results against JULIET. In the JULIET study, 51.4% of patients in the infused population received at least three lines of prior treatment, while the patients presented in the CORAL extension studies were required to be candidates for third-line chemotherapy by design. However, the subgroup analysis in JULIET demonstrates that there is no difference in efficacy of tisagenlecleucel in terms of ORR in patients who received two or less prior lines of anti-neoplastic therapy (ORR of 53% [95%CI: 38.3-67.5]) or more than two (ORR of 50.0% [95%CI: 34.6-65.4]). There is, therefore, no evidence suggesting that the OS for tisagenlecleucel would be improved if only candidates for third-line chemotherapy were included.

Matching was conducted on four variables only; gender, IPI risk classification (<3 vs. ≥3), ASCT as the most recent therapy (yes vs no) and refractory to last line of treatment (yes vs. no). Table 40 shows that JULIET and CORAL extension studies were almost identical in terms of these variables prior to matching, therefore the effective sample size was not affected by MAIC. The number of matching variables was generally small. Matching by baseline prognostic factors is at the core of MAIC. The reliability of the current comparison appears to be severely compromised due to unavailability of matching variables. It is also unclear how the IPI risk classification (<3 vs. ≥3) was conducted for pooled CORAL extension studies, given that the proportion of patients with ≥3 was not published for CORAL extension study 2. It is also noticed that IPI score was not collected in 43% of patients in CORAL extension study 2 which is a significant limitation given the small number of matching variables. Lastly, matching was not conducted for the difference in histological subgroups. Specifically, 100% of patients in the pooled CORAL extension studies had DLBCL as the primary diagnosis. In JULIET, 79% of patients had DLBCL, 19% TFL, and 2% other. The ORR in patients with DLBCL arising from TFL was 83.3% (95% CI: 58.6 to 96.4) at the DCO of 08-Dec-2017, whereas the ORR for the remaining patients (n=74) was 44.6% (95% CI: 33.0, 56.6). The probability for being remission-free 3 months after infusion was similar in responding patients with DLBCL and those with DLBCL arising from TFL (81.4% vs 76.9%). The median OS in the DLBCL subgroup was 10.1 months (95% CI: 5.6 to 17.9), while the median OS for patients with DLBCL arising from TFL was not yet reached. Furthermore, results from the supportive study A2101J also demonstrate a better ORR to treatment with tisagenlecleucel compared to patients with primary DLBCL.

It was of concern that all patients in the CORAL extension studies who relapsed were included in the comparison, irrespectively of whether they had poor prognosis or not. It is clear from Figure 21 and Figure 22 that patients who died on day 1 after relapse were included in CORAL, hence the sharp unusual drop at time 0. Instead, in JULIET, only patients with life expectancy of above 3 months were eligible. In addition, patients evidently had to be alive to be enrolled in JULIET (artificial 100% survival until month 1.88), whereas many patients died quite quickly after relapse in the CORAL extension. This results in a clear bias

favouring JULIET. Furthermore, patients had to be evidently alive to receive infusion in JULIET (100% survival until month 3.96) indicating a clear selection of the fittest patients who survived many months from relapse to infusion. Novartis was, therefore, asked to present the following analyses:

➢ Additional Analysis 1: where the enrolled set from enrolment from JULIET is compared to CORAL where deaths occurring within the first 1.88 months (i.e. mean time from screening to enrolment in JULIET) from relapse are not accounted for. In this analysis the intension was to compare CORAL to the enrolled set in JULIET which had to wait some months from screening to enrolment. Here, the deaths occurring in the first months in CORAL should be removed from the risk set and the adjusted risk set at 1.88 months should be the new denominator at time 0 in the survival analysis. The results are presented in Figure 23 (left figure).

➢ Additional Analysis 2: as above but where the infused set from infusion from JULIET is compared to CORAL where deaths occurring within the first 3.96 months (i.e. mean time from screening to infusion in JULIET) from relapse are not accounted for. In this analysis the intension was to compare CORAL to the infused set in JULIET which had to wait some months from screening to infusion. Here, the deaths occurring in the first months in CORAL are removed from the risk set and the adjusted risk set at 3.96 months is the new starting risk at time 0 in the survival analysis. The results are presented in Figure 23(right figure).
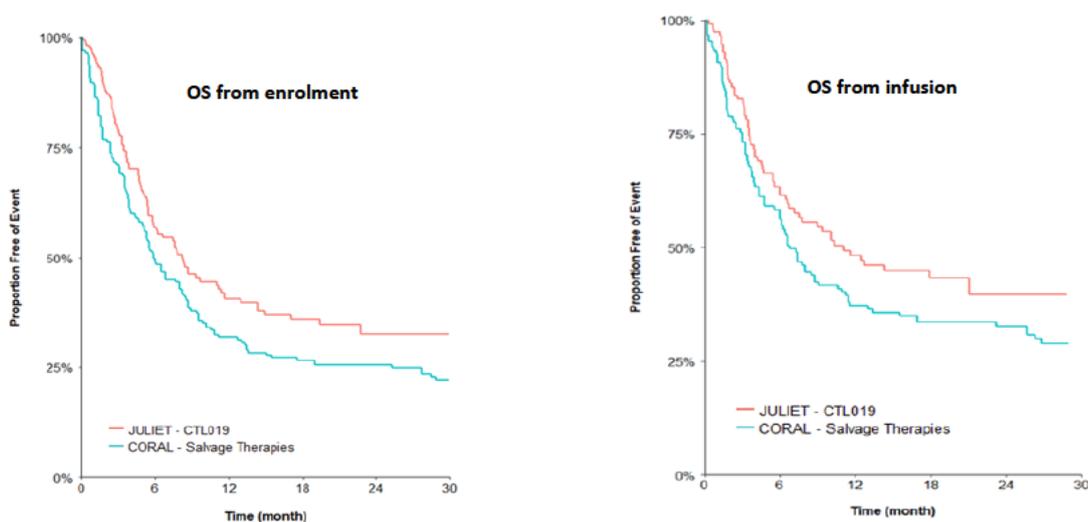

Figure 23 Additional Analyses: OS from enrolment (the enrolled set, left) and OS from infusion (the infused set, right). «Lead time»-adjusted comparisons of JULIET vs. CORAL.

Novartis has outlined the following limitations of those additional analyses:

- In the absence of patient-level data for CORAL extension studies, pseudo-patient level OS data were used. The numbers of patients who were censored at each time point could not be estimated accurately as no censoring information was reported.
- Only naïve indirect comparison could be conducted in these additional analyses, as there was no data on patient characteristics reported for the subset of CORAL patients after excluding those

who died or censored within the first few months; the cross-study heterogeneity in patient characteristics may bias the results. There were approximately 50% of patients received prior SCT in JULIET, while there were 27% of patients received prior SCT in CORAL extensions. All patients in the CORAL extension studies received two lines of previous therapies, while more than 50% patients in the JULIET received at least 3 lines of previous therapies.

- The sample size for CORAL extension studies decreased due to exclusion of patients. As an estimate, 22.6% and 43.6% of patients from the CORAL extensions were removed for analysis 1 and 2, respectively. The removal of 43.6% of patients from CORAL extension studies resulted in a sample size of 134 as compared to 115 from JULIET (infused patients).
- In CORAL extension study 2, among patients who failed 2nd-line salvage regimens, 28% (56/203) of patients reported CR/PR prior to initiation of 3rd line treatment.

NoMA recognizes the limitations but would like to point out that the company's base case comparison with CORAL extension studies via MAIC does not address the above limitations. Specifically, the MAIC comparison was also based on reconstructed aggregate published data as opposed to patient-level data from CORAL extension studies. In the pooled CORAL extension studies only two patients were censored in the first 4 months, indicating that exclusion of patients who died within the first 1.88 or 3.96 months has not affected the reconstruction of KM graphs to a high extend. The MAIC comparison is considered more a naïve comparison than a matched comparison due to the small number of matching variables. The results do not differ considerably before matching and after matching. Consequently, choosing an unadjusted comparison over an adjusted comparison is not expected to change the results considerably. Furthermore, the consequences of differences in previous lines of therapy and the level of prior SCT between CORAL extension studies and JULIET are unclear as the response rate in JULIET does not seem to be affected by the presence of prior HSCT therapy (ORR of 50% for no, 54% for yes), or the number of prior antineoplastic therapies (53% for 2 lines, 50% for >2 lines). Lastly, 20.6% of mITT patients in JULIET reported CR/PR from the prior bridging therapy. The proportion is only slightly lower than prior to the initiation of salvage therapy in the CORAL extension studies (28%) and hence it is unlikely that the prior response would bias the results of the current comparison considerably.

In summary, there are many methodological issues underlying the provided MAIC comparison. NoMA recognizes that certain patient characteristics such as fewer lines of previous therapies in CORAL extension studies might have biased the results in favour of CORAL, but at the same time hystopathological subtype profile likely favours the JULIET study. The challenge of the comparison is that patient characteristics were not reported in the same way and there was a high proportion of missing data. Therefore, matching for important prognostic factors and effect modifiers could not be conducted. As the result, the comparison vs. CORAL is considered more as a naïve comparison rather than an adjusted comparison. The key issue with the comparison vs. CORAL is the clear lead time bias favouring JULIET, which the MAIC does not appropriately adjust for. Consequently, the magnitude of the tisagenlecleucel benefit is unclear as it is largely impacted by the early deaths in the CORAL extension studies. In addition, the starting time for the OS analysis in the MAIC analysis was restricted to that reported in the CORAL publications (i.e. from relapse to last treatment). The additional analyses requested by NoMA attempt to address the issue of the lead time bias by removing those patients who

died early in the CORAL extension studies and adjusting patients at risk accordingly. The starting time for OS analysis becomes the time from enrolment or the time from infusion. NoMA considers the "lead time"-adjusted analyses the most relevant analysis for decision making.

APPENDIX 3 MATCHING-ADJUSTED INDIRECT COMPARISON (MAIC) OF TISAGENLECLEUCEL VS. SALVAGE THERAPY (SCHOLAR-1)

Patient-level data from JULIET and published aggregate data from SCHOLAR-1 (9) were used for MAIC.

JULIET is an ongoing pivotal single arm, open-label, multi-center, phase II study to determine the safety and efficacy of tisagenlecleucel in adults with r/r DLBCL. Adults with relapsed or refractory disease after ≥2 lines of chemotherapy, including rituximab and anthracycline, and either having failed ASCT, or were ineligible for or did not consent to ASCT, were enrolled. All JULIET patients, regardless of number of prior lines of therapy, were included in the analyses to provide sufficient sample sizes for baseline adjustment in comparisons to the SCHOLAR-1 study. As of May 21, 2018, a total of 167 patients were enrolled (i.e., enrolled population) and 115 patients were infused with tisagenlecleucel (i.e., infused population).

SCHOLAR-1 is the largest patient-level pooled retrospective meta-analysis that characterised response rates and survival of salvage chemotherapy among patients with refractory DLBCL. The specific chemotherapy regimens used among these patients were not reported. Patient-level data were collected in the SCHOLAR-1 study from 636 patients from 4 sources: 1) observational cohorts from MD Anderson Cancer Center (MDACC), 2) the Molecular Epidemiology Resource of the University of Iowa/Mayo Clinic Lymphoma Specialized Program of Research Excellence (IA/MC), and from the follow-up analyses of 2 large phase III randomised controlled trials: 3) Canadian Cancer Trials Group study LY.12, and 4) the Lymphoma Academic Research Organization (LYSARC) Collaborative Trial in Relapsed Aggressive Lymphoma (CORAL) study.

The patient populations are generally comparable in the JULIET and SCHOLAR-1 trials based on the inclusion/exclusion criteria. However, the SCHOLAR-1 study only included patients who met one of the following criteria defining the refractory status in the context of this analysis: 1) progressive disease as best response to any line of chemotherapy, 2) stable disease as best response to ≥4 cycles of first-line therapy or 2 cycles of later-line therapy, or 3) relapse ≤12 months (365 days) post ASCT. In contrast, the JULIET trial included not only DLBCL patients who met SCHOLAR-1 criteria, but also patients who relapsed after multiple previous therapies, and patients who relapsed >12 months post ASCT. Consequently, patients in the JULIET trial who were PD or SD as best response to chemotherapy or relapsed ≤12 months post-ASCT following SCHOLAR-1 refractory criteria were included in the comparison of JULIET vs. SCHOLAR-1. Among 115 JULIET infused patients, 91 patients met the SCHOLAR-1 inclusion criteria and were included in the MAIC of OS. In the enrolled set, 135/167 were included. The comparison of OS was conducted against 603 patients with OS data available in SCHOLAR-1.

In terms of patient characteristics, both studies included a similar proportion of male patients (e.g., 61.3% in JULIET [mITT] and 64.0% in SCHOLAR-1) and the median age was similar (e.g., 56 years for JULIET [mITT] and 55 years for SCHOLAR-1). In addition, based on an exploration of the infused population in the JULIET trial, patients in the JULIET trial had a similar proportion of primary refractory patients to SCHOLAR-1 (30.6% and 28.0% respectively) and a similar proportion of patients categorised into the low risk group

per IPI classification (<2) (27.9% in JULIET mITT vs. 30.5% in SCHOLAR-1). However, JULIET had a lower proportion of patients who were refractory to ≥2nd line (38.7% vs. 50.0%). In addition, SCHOLAR-1 included patients with ECOG 0-4, whereas JULIET included only patients with ECOG 0-1.

Variables included in the matching adjustment were gender, primary diagnosis (DLBCL vs. non-DLBCL), International Prognostic Index (IPI) risk classification (<2 vs. ≥2) and refractory category (primary refractory, refractory to ≥second-line therapy, relapsed ≤12 months post-ASCT). Age, Eastern Cooperative Oncology Group (ECOG) performance status, and disease stage were not matched individually, as they are already included as components in the IPI risk classification. The total number of lines of prior chemotherapy and ASCT received was not included in the matching due to limited availability of these measures in SCHOLAR-1 (approximately 22% of patients had missing data, and the reasons for missingness were unspecified).

Patient characteristics prior and after matching are presented in Table 43. After matching, all matched-on baseline characteristics were exactly balanced between the study populations. The effective sample size after matching was 76 in the infused set (down from 115) and 104 in the enrolled set (down from 135), indicating that there was no evidence of extreme weights.

Table 43 Matching Patient Characteristics between JULIET (Both Cohorts) and SCHOLAR-1 (for OS comparison)

	Before Matching			After Matching		
	JULIET FAS, Both Cohort	JULIET Enrolled, Both Cohorts[1]	SCHOLAR-1	JULIET FAS, Both Cohort	JULIET Enrolled, Both Cohorts[4]	SCHOLAR-1
	N=91	N=135	N=636	N=91	N=135	N=636
Male	60.4%	63.0%	64.0%	64.0%	64.0%	64.0%
DLBCL	82.4%	80.0%	93.5%	93.5%	93.5%	93.5%
Low IPI risk classification (< 2)	24.2%	18.5%	30.5%	30.5%	30.5%	30.5%
Primary refractory	37.4%	38.5%	28.0%	28.0%	28.0%	28.0%
Refractory to ≥2 lines	48.4%	48.1%	50.0%	50.0%	50.0%	50.0%

The comparisons of OS between JULIET (mITT who met the SCHOLAR-1 inclusion criteria) and SCHOLAR-1 before and after matching are shown in

Table 44 and Figure 24. Before matching, tisagenlecleucel was associated with a 36% lower hazard of death than salvage chemotherapies (log-rank p-value<0.01; HR [95% CI] = 0.64 [0.47, 0.85]). The proportional hazards assumption for OS was acceptable (P-value>0.05). After matching, the hazard of death remained significantly lower with tisagenlecleucel vs. salvage chemotherapies (weighted log-rank p-value<0.05; HR [95% CI] = 0.66 [0.48, 0.90]). In the JULIET trial OS was defined as the time from first tisagenlecleucel infusion to death due to any reason (definition per-trial protocol). In the SCHOLAR-1 study OS was defined as the time from the initiation of salvage chemotherapy for refractory disease to death due to any cause.

Table 44 Comparison of Efficacy Outcomes of JULIET Infused and SCHOLAR-1.

	Before Matching				After Matching			
	JULIET Infused[1]	SCHOLAR-1[2]	Response Difference (95% CI)	P-value[3]	JULIET Infused[1]	SCHOLAR-1[2]	Response Difference (95% CI)	P-value[4]
	[A]	[B]	[A] - [B]		[A]	[B]	[A] - [B]	
Response Rates[5]	**N=77**	**N=523**			**N=77**	**N=523**		
CR[6]	39.0%	7.0%	32.0% (20.8%, 43.1%)	<0.01*	38.9%	7.0%	31.9% (21.1%, 42.7%)	<0.01*
ORR (CR + PR)	49.4%	26.0%	23.4% (11.5%, 35.2%)	<0.01*	49.0%	26.0%	23.0% (11.5%, 34.5%)	<0.01*
OS[7]	**N=91**	**N=603**			**N=91**	**N=603**		
Median, 95% CI (month)	11.1 (6.0, NE)	6.3 (5.9, 7.0)			11.7 (6.6, NE)	6.3 (5.9, 7.0)		
Log-rank test				<0.01*				<0.05*
HR, 95% CI ([A] vs. [B])	0.64 (0.47, 0.85)			<0.01*	0.66 (0.48, 0.90)			<0.05*

* Denotes p-value < 0.05

Abbreviations: ASCT: Autologous Stem Cell Transplantation; EAS: Efficacy Analysis Set; CI: Confidence Interval; CR: Complete Response; FAS: Full Analysis Set; HR: Hazard Ratio; KM: Kaplan-Meier; NE: Not Evaluable; ORR: Overall Response Rate; OS: Overall Survival; PR: Partial Response.

Notes: [1] For response rates, JULIET patients in the Main Cohort (treated with tisagenlecleucel from US manufacturing facility) who met the SCHOLAR-1 refractory criteria and had evaluated responses were included. For OS, JULIET patients infused (FAS, Main Cohort and Cohort A) who met the SCHOLAR-1 refractory criteria were included. [2] For response rates, SCHOLAR-1 patients with evaluated responses (N=523) were included. OS data were reported for 603 patients in SCHOLAR-1. [3] Before matching, CR rate and ORR were compared using the Chi-squared test. For OS, the log-rank test was used to compare two KM curves, while the Cox proportional hazards model was developed for HR estimation. The proportional hazards assumption was not met indicating that the HR between two treatments may vary over time.[4] After matching, the weighted Chi-squared test was used for CR rate and ORR comparison. For OS, the weighted log-rank test was used to compare KM curves, while the weighted Cox model was developed for HR estimation. [5] Among 77 JULIET patients, 7 with best overall response unknown were imputed as non-responders. [6] CR was assessed by Lugano Classification criteria in JULIET and by International Working Group 1999 criteria in the SCHOLAR-1 study. [7] In JULIET, OS was defined as time from infusion to death from any cause. For SCHOLAR-1 patients, OS was defined as time from commencement of salvage therapy for refractory disease to death due to any cause.

Before Matching

After Matching
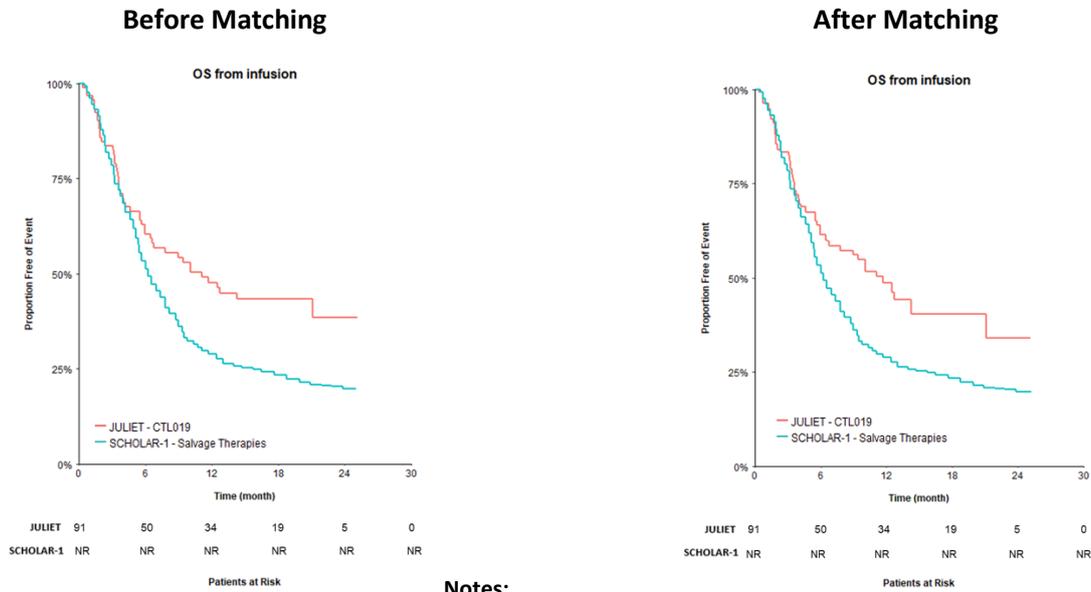
Notes:

[1] Data cutoff date for JULIET: May 21, 2018; the trial is still ongoing.
[2] All data for SCHOLAR-1 were used in generating the KM curves; the KM curves displayed were truncated at the maximum of JULIET follow-up. Number of patients at risk was not reported (NR) in SCHOLAR-1.

Figure 24. Kaplan-Meier Curves of OS Comparing JULIET Infused (FAS, Both Cohorts) and SCHOLAR-1[1,2]. OS from infusion.

In the enrolled population, tisagenlecleucel was associated with a 19% lower hazard of death than salvage chemotherapies before matching, though the difference was not statistically significant (log-rank p-value=0.09; HR [95% CI] = 0.81 [0.64, 1.02]). The proportional hazards assumption for OS was acceptable (P-value>0.05). After matching, a 24% lower hazard of death than salvage chemotherapies was observed and the difference in hazard of death became significant (weighted log-rank p-value=0.06; HR [95% CI] = 0.76 [0.58, 0.99]). The results are presented in Table 45 and Figure 25 below.

Table 45 Comparison of Efficacy Outcomes of JULIET Enrolled and SCHOLAR-1

	Before Matching				After Matching			
	JULIET Enrolled[1] [A]	SCHOLAR-1[2] [B]	Response Difference (95% CI) [A] - [B]	P-value[3]	JULIET Enrolled[1] [A]	SCHOLAR-1[2] [B]	Response Difference (95% CI) [A] - [B]	P-value[4]
Response Rates[5]	**N=118**	**N=523**			**N=118**	**N=523**		
CR[6]	25.4%	7.0%	18.4% (10.2%, 26.6%)	<0.01*	29.3%	7.0%	22.3% (13.9%, 30.7%)	<0.01*
ORR (CR + PR)	32.2%	26.0%	6.2% (-3.1%, 15.5%)	0.19	35.7%	26.0%	9.7% (0.4%, 19.0%)	<0.05*
OS[7]	**N=135**	**N=603**			**N=135**	**N=603**		
Median, 95% CI (month)	7.6 (5.4, 11.2)	6.3 (5.9, 7.0)			8.7 (5.9, 14.9)	6.3 (5.9, 7.0)		
Log-rank test				0.09				0.06
HR, 95% CI ([A] vs. [B])	0.81 (0.64, 1.02)			0.08	0.76 (0.58, 0.99)			<0.05*

* Denotes p-value < 0.05

Abbreviations: ASCT: Autologous Stem Cell Transplantation; EAS: Efficacy Analysis Set; CI: Confidence Interval; CR: Complete Response; FAS: Full Analysis Set; HR: Hazard Ratio; KM: Kaplan-Meier; NA: Not Applicable; NE: Not Evaluable; NR: Not Reached; ORR: Overall Response Rate; OS: Overall Survival; PR: Partial Response.
Notes: [1] For response rates, JULIET patients enrolled in the Main Cohort who met the SCHOLAR-1 refractory criteria were included. For OS, JULIET patients enrolled who met the SCHOLAR-1 refractory criteria were included. [2] For response rates, SCHOLAR-1 patients with evaluated responses (N=523) were included. OS data were reported for 603 patients in SCHOLAR-1. [3] Before matching, CR rate and ORR were compared using the Chi-squared test. For OS, the log-rank test was used to compare two KM curves, while the Cox proportional hazards model was developed for HR estimation. The proportional hazards assumption was not rejected. [4] After matching, the weighted Chi-squared test was used for CR rate and ORR comparison. For OS, the weighted log-rank test was used to compare KM curves, while the weighted Cox model was developed for HR estimation. [5] Among 118 JULIET patients, 7 patients with best overall response unknown and 41 patients without tisagenlecleucel infusion were imputed as non-responders; no unconfirmed responses were used for patients whose follow-up prior to the data cut-off date was less than three months. [6] CR was assessed by Lugano Classification criteria in JULIET and by International Working Group 1999 criteria in the SCHOLAR-1 study. [7] In JULIET, OS was defined as the time from enrolment to death from any cause. For SCHOLAR-1 patients, OS was defined as the time from commencement of salvage therapy for refractory disease to death due to any cause.

Before Matching   **After Matching**
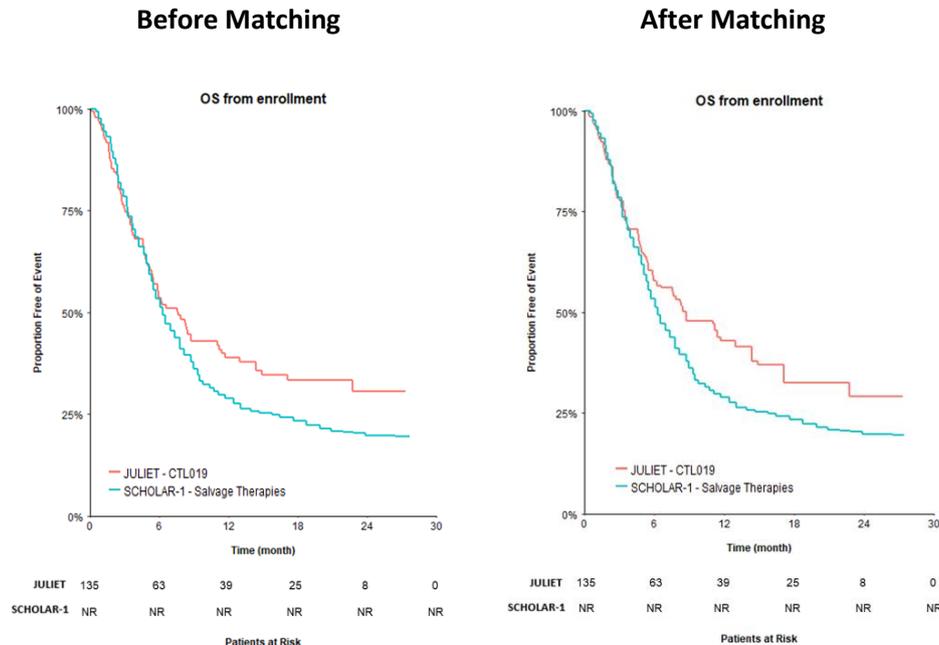
[1] Data cutoff date for JULIET: May 21, 2018; the trial is still ongoing.
[2] All data for SCHOLAR-1 were used in generating the KM curves; the KM curves displayed were truncated at the maximum of JULIET follow-up. Number of patients at risk was not reported (NR) in SCHOLAR-1.

Figure 25 Kaplan-Meier Curves of OS Comparing JULIET Enrolled (Both Cohorts) and SCHOLAR-1.·OS from enrolment.

The comparisons between JULIET and external control groups drawn from SCHOLAR-1 are subject to limitations. It was not possible to adjust for all baseline characteristics of interest. Only observed baseline factors that were consistently reported in both studies were included in the adjustment. Baseline variables such as the number of prior lines of chemotherapy and prior ASCT could not be matched due to limited or incomplete information in the SCHOLAR-1 publication. The timing of data collection for baseline patient characteristics also differed between the two studies: data were collected at screening for JULIET, while SCHOLAR-1 measured characteristics at diagnosis for observational cohorts and at randomisation for randomised trials. Furthermore, information was not provided in the SCHOLAR-1 study on the range of time between baseline assessment and the start of treatment. The comparisons between JULIET and SCHOLAR-1, despite adjustment for multiple important baseline characteristics, may be subject to residual confounding due to unobserved or unmeasurable cross-trial differences in patient characteristics. This is an inherent limitation for any comparison of non-randomised treatment groups. There were differences in the outcome definitions. First, different definitions of response (Lugano Classification for JULIET, 1999 IWG response criteria for SCHOLAR-1) were used in the two studies. However, an exploratory analysis using the JULIET data suggested minimal potential for bias due to this difference. Secondly, efficacy outcomes were only evaluable in some SCHOLAR-1 patients (523/636 with reported

response and 603/636 with reported survival), which might result in selection bias due to survivorship or other reasons.

NOMA's assessment of JULIET vs SCHOLAR-1 comparison

Studies included in the MAIC were identified through a Systematic Literature Review (SLR) conducted by Novartis according to the best practices for systematic searching, including those published by the Cochrane Collaboration. The SLR was comprehensive and transparent. The search criteria, sources, inclusion and exclusion criteria were clearly stated.

Patient inclusion and exclusion criteria were not fully aligned between JULIET and SCHOLAR-1. Only patients who met SCHOLAR-1 inclusion criteria (i.e. PD or SD as best response to chemotherapy or relapsed ≤12 months post-ASCT) were selected from JULIET. Consequently, 24/115 relapsed patients from the infused population, and 32/167 relapsed patients from the enrolled population in JULIET were excluded from MAIC. The generalisability of the results in terms of the wider tisagenlecleucel indication is, therefore, questioned.

Published patient characteristics were generally similar between SCHOLAR-1 and JULIET. However, SCHOLAR-1 included patients with ECOG 0-4, whereas JULIET included only patients with ECOG 0-1. The ECOG status is considered an important prognostic factor which could not be adjusted for in the comparison. Furthermore, the data were collected at screening for JULIET, while SCHOLAR-1 measured characteristics at diagnosis for observational cohorts and at randomisation for randomised trials. Consequently, matching based on the IPI score is problematic as variables such as age, ECOG performance status, and disease stage change over time. Furthermore, in SCHOLAR-1 the registries included all patients who had DLBCL irrespectively of their co-morbidities or life expectancy. In JULIET patients had to have a life expectancy of 3 months, and adequate organ functions and no active CNS involvement. In situations where matching for patient characteristics is limited, it is even more important to select the most appropriate patient population based on the inclusion criteria. Overall, NoMA does not believe that SCHOLAR-1 and JULIET had matching patient populations.

The large amount of missing data in SCHOLAR-1 is a concern, both with respect to the matching of baseline characteristics and with respect to the validity of the comparison in general. For instance, in the LY.12 study, <50% of patients were evaluated for response, and for some subgroups in the pooled population (i.e. disease stage and IPI), data were available for only 239/523 (46%) and 228/523 (44%) patients, respectively. Similarly, OS data were reported in only 81/136 responding patients (60%). Matching was performed on four variables and due to the high proportion of missing information (22%), it did not match for the total number of lines of prior chemotherapy or ASCT received. From the available information on the total number of lines of prior treatment at baseline, it is evident that the JULIET population was more heavily pre-treated (55% in JULIET vs <1% in SCHOLAR-1 had received >2 lines of therapy at baseline). An unanchored MAIC assumes that all effect modifiers and prognostic factors are accounted for. This assumption is very strong, and largely considered impossible to meet. Failure of this assumption leads to an unknown amount of bias in the unanchored estimate.

The key advantage of SCHOLAR-1 as a comparator is the large sample size. NoMA acknowledges that the study may well represent the refractory DLBCL population. However, due to the differences in inclusion criteria, timing of patient characteristics assessment, differences in life expectancy, co-morbidities and due to the high proportion of missing data, it is deemed inappropriate to accept SCHOLAR-1 as the primary source of a historical control for JULIET.

APPENDIX 4 LEUKAPHERESIS COSTS

This appendix consists of two parts. Part 1 is submitted from Novartis 1-Apr-2019 regarding the leukapheresis costs provided by the OUS. Part 2 is NoMA's assessment of Novartis's arguments.

Part 1: Submitted from Novartis

Novartis has assumed a leukapheresis cost of 44 502 NOK which we believe is a conservative and high estimate and should be enough to cover costs for the hospital. The cost estimate provided from Oslo University Hospital must be seen in the context that Novartis is paying the hospital cell lab for doing this work in clinical trials. In the negotiations, the hospital had a clear interest of getting the highest possible fee, and we would argue that the amount does not reflect the real cost for the hospital.

Our estimate based on input from Denmark is very likely an overestimate of the actual leukapheresis costs. In the Amgros submission, the estimate provided from Rigshospitalet was considered to include an unreasonable markup and a leukapheresis cost of 6 395 NOK (4 957 DKK, a 2016 unit cost from Rigshospitalet inflated) was used and on top it was added the 8 384 NOK Cell Freezing cost.

A total cost of 14 779 NOK was used and approved in the Danish submission.

The Danish cost "Apheresis, incl. Analysis"+ "Cell freezing" includes working hours, material and reagents, and overhead/facility costs. We provide further information below to justify this claim. A Norwegian leukapheresis cost of ~23 000 NOK would probably have been a more appropriate estimate; especially when considering international benchmark the cost of 44 502 NOK submitted by Novartis is very high.

Breakdown of cost component in the OUS estimate

Material and reagents costs are overestimated

The citrate added to avoid coagulation is not an expense agent. To avoid hypocalcemia from the citrate, calcium could be administered to avoid cramps, with other Replacement fluids, such as albumin or fresh frozen plasma, this could be estimated to USD 125 to USD 600 per treatment[2].

Disposable sets produced by manufacturers will vary between USD 40 and USD 90 per treatment[4]. Older references will state that an apheresis unit costs roughly 50,000 USD (range 20 000 to 157 000) to purchase[3,4], whereas newer estimates are in the lower end of that range: 19 000 to 32 000 USD[4]. That

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[2] L. Wood, The Global Apheresis Market to 2023: Expected to Grow at a CAGR of 10.89% -- Increasing Global Disease Burden is Driving Growth, (2018). https://www.globenewswire.com/news-release/2018/12/07/1663716/0/en/The-Global-Apheresis-Market-to-2023-Expected-to-Grow-at-a-CAGR-of-10-89-Increasing-Global-Disease-Burden-is-Driving-Growth.html (accessed March 25, 2019).
[3] World Health Organization (WHO), Apheresis units - Hospital medical equipment - general information, (2012). https://www.who.int/medical_devices/innovation/hospt_equip_3.pdf (accessed March 23, 2019).
[4] R. Lyons, Apheresis in the Office Setting, J. Oncol. Pract. 4 (2008) 94–95. doi:10.1200/JOP.0817002.

cost of technology decreases with time is frequently seen. WHO estimated that a machine would last for 8 years[5]. An article explains how 250-300 procedures are completed on their 4 machines per year[6].

The capital expenditure for the equipment could be distributed on 70 patients per year over 8 years and that is less than 100USD per patient (even if a machine is assumed to cost 50 000USD).

((125+600)/2 + (40+90)/2 + ~100)USD * 8.45 NOK/USD = 4 457 NOK

Working hours for leukapheresis and freezing teams are overestimated

A leukapheresis is a fairly standard process. A leukapheresis will usually involve a nurse per two machines and a physician to be on call[6] (hypocalcemia is the main thing to be aware of [5], and primary reason why a physician would be on call) and at a very maximum one could add 30 minutes of physician time.

A leukapheresis will take between 2 and 4 hours[5,6], and within approximately 2 hours after leukapheresis, analyses and freezing will be completed, i.e. this part of the process will not take more than two hours.

It would be conservative to estimate three hours of nurse/bio technician time the leukapheresis and an additional hour for preparation, effectively assume the a nurse/bio technician will stand bedside per patient and monitor the process and do no preparations for next patient, nor any documentation, while the patient is there. Two hours is a fair estimate for analyses and freezing for a bio technician. A 30 minutes of physician time would be a conservative estimate

Bio technician (3+1+2 hours) * 436 + Doctor: 0.5 hour *871 = Total: 3 051.5 NOK

Facilities (Cleanroom, liquid nitrogen storage, QC-lab) & **Storage in liquid nitrogen are overestimated**

OUS estimates 2 222+38 889 = 41 111 NOK

Savestemcells.dk will collect and cryopreserve cells for 20 years for 1 995+22 000 DKK, i.e. 31 000 NOK. This cost includes facilities, shipment, nitrogen and working hours, for 20 years and a need to return a profit to shareholders. Savestemcells.dk will store the cells an additional 5 years for an additional 3 000 DKK. This proves that the cost of facilities and goods are not costly.

Probably a cost of 1 995 DKK (~2 573 NOK) is fair for 'deposits and claims' from the cryobank – and this includes a double counting of the working hours for the freezing teams counted above and shipment. Let's also assume the apheresis material is kept 5 years (= 3 000DKK = 3 870 NOK).

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[5] T. Plesner, Metode ved stamcelletransplantation, (2017). https://www.cancer.dk/hjaelp-viden/kraeftbehandling/behandlingsformer/stamcelletransplantation/metode-ved-stamcelletransplantation/ (accessed March 26, 2019).

[6] Aarhus Universitetshospital, Stamcellehøst - opsamling af blodstamceller, (2016). http://www.auh.dk/siteassets/afdelinger/klinisk-immunologisk-afdeling/klinisk-immunologisk-afdeling_ny/pjecer-og-vejledninger/behandling_kia/stamcellehost-2016.pdf (accessed March 26, 2019).

"Batch documentation, QC and release" and "Shipment, including documentation" are overestimated:

11 111 NOK would cover 25.5 hours of nurse time which is almost a full week of work. We believe this estimate is not realistic. QC is done in the two hours before freezing, and in our view it looks like the cost of 11 111 NOK was chosen as it is the amount needed to bring 38,889 NOK for the facilities to a very round number: 50,000 NOK. The cost of shipping is covered by Novartis, and we cannot figure out how 25.5 working hours are needed for batch documentation.

There also seems to be some double counting: more documentation, 3 hours, after shipment. The cost of shipment is covered by Novartis and Anne-Fischer Nielsen from Rigshospitalet in Denmark, was probably not aware of this when offering the estimate.

We believe the estimates from OUS are invalid. The dry-vapor shipper is picked up on the pallet by our currier, at our expense, and the hospital documents this. The time used in this process should be maximum 2 hours reflecting a cost of 872 NOK.

In the table below we have summarized the estimate from OUS, the estimate from Rigshospitalet in Denmark and our own estimates after doing some additional research. Even though we believe a cost of 23 063 NOK is the most realistic estimate, we will ask NoMA to consider the previous submitted cost of 44 502 NOK in the analysis.

Table 2: Cost of leukapheresis: Estimate from OUS, Rigshospitalet in Denmark and Novartis

	OUS estimate (NOK)	Rigshospitalet estimate (NOK)	Novartis updated estimate (NOK)
1. Production and shipment of frozen cells:			
Procedure/task			
Material and reagents	23 566	16 124 (Apheresis, incl. Analysis) & 8 384 (Cell Freezing)	4 457
Working hours for leukapheresis and freezing teams (4 hrs doctor, 18 hrs bio technician)	11 332		3 052
Facilities (Cleanroom, liquid nitrogen storage, QC-lab)	38 889		2 573 + 3 870
Batch documentation, QC and release	11 111		872
Shipment, including documentation (3 hrs bio technician)	1 308	6 450 (Shipment)	0
Total price per production (per patient)	**86 206**	**30 958**	**14 824**
2. Receiving and intermediate storage of cells and documentation			
Storage in liquid nitrogen	2 222		2 573
Work in relation to receiving, intermediate storage and documentation (3 hrs bio technician)	1 308		1 308
Total price for receiving, intermediate storage and documentation per patient	**3 530**	**13 544 (Receiving, containing, transport and defrosting)**	**3 881**
3. Thawing of cells bedside:			
Preparation of dry shipper, transfer of cells and documentation (1 hr doctor, 3 hrs bio technician)	2 179		2 179
Working hours for thawing, documentation and transportation (1 hr doctor, 3 hrs bio technician)	2 179		2 179
Total price for thawing bedside (per patient)	**4 358**		**4 358**
Hourly wage physician 871,-			
Hourly wage nurse/bio technician 436,-			
Total price:	**94 094**	**44 502**	**23 063**

International benchmarking

Kymriah has recently been under HTA review in several other countries, and below we have collected leukapherisis costs used and approved by other HTA bodies.

Denmark: An apheresis cost of 6 395 NOK (a 2016 unit cost from Rigshospitalet inflated) was used and on top it was added a 8 384 NOK Cell Freezing cost. The total cost used in the Danish submission: **14 779 NOK**

Finland: FiMEA used € 1 732 for Apheresis (Novartis submitted €1 408) and € 500 cryopreservation, p 32 of the ALL assessment: **21 450 NOK**

Sweden: a cost of ~7 000SEK was used and approved in the Yescarta assessment[7]. For the Kymriah assessments, the same cost of 7 460SEK (2019 level) will be used by TLV i.e.: **6 938 NOK**

UK: £1,020 was used an approved by NICE as seen in their appraisal document p 172[8], i.e.: **11 322 NOK**

US, an apheresis procedure is approximately USD 2500 per treatment[4]: **21 125 NOK**

Germany, assuming the leukapheresis is done during a 5 days in-patient admission: **37 086 NOK**

Für die Leukapherese der SZT gibt es folgende Erlöse für folgende Verweildauern:

- A42C – Stammzellentnahme bei Eigenspender ohne Chemotherapie, Alter >15 Jahre, ohne schwerste CC):
  - Erlös: 3.859,10 Euro: (bei einem Bundesbasisfallwert 2018).
  - Mittlere Verweildauer: 5 Tage.
  - Untere und obere Grenzverweildauer: 2 bis 10 Tage.

To summarize, we believe cost estimate used for leukapheresis is not valid. It is coming from a commercial setting and including a significant profit. In our best estimate the cost should be approximately 23 000 NOK, hence we believe the submitted number of 44 502 NOK is conservative and in the higher end. The international benchmark further supports that the cost of 94 000 NOK used by NoMA is not correct.

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[7] Tandvårds- Och Läkemedelsförmånsverket (TLV), Underlag för beslut i landstingen - Yescarta (axicabtagene ciloleucel), Diarienummer: 51/2018. (2018). https://www.tlv.se/download/18.192533fa166f516fb27bb5ab/1542290744988/bes181107_underlag_yescarta.pdf (accessed March 26, 2019).

[8] National Institute for Health and Care Excellence, Single Technology Appraisal Tisagenlecleucel-T for treating relapsed or refractory diffuse large B-cell lymphoma [ID1166], (2019). https://www.nice.org.uk/guidance/ta567/evidence/appraisal-consultation-committee-papers-pdf-6718510621 (accessed March 26, 2019).

Part 2: NoMA's assessment

Description of OUS input

NoMA's assessement of leukapheresis and freezing costs are based on information provided by Dag Josefsen, Head of the Department of Cellular Therapy at Oslo University Hospital (53). By request from NoMA, Dag Josefsen has decomposed the costs, see Table 46 below. The costs estimates in Table 46 does not include overhead costs.

Novartis's estimated costs of *2) Receiving and intermediate storage of cells and documentation* and *3) Thawing of cells bedside* seems to be in line with the estimates provided by the OUS (see Table 2 from Novartis above). The discrepancies between the Novartis's estimate and the cost estimates received from the cell lab at the OUS mainly concerns *1) Production and shipment of frozen cells.*

Table 46 Cost of apheresis at the OUS (excl. overhead costs)

Leukapheresis
1 Physician	4 hours	3.484,00 NOK
2 Bioengineers	9 hours (total)	3.879,00 NOK

QC Leukapheresis
1 Bioengineer	3 hours	1.308,00 NOK

Material	16.200,00 NOK

24.871,00 NOK

Freezing of leukapheresis
2 Bioengineers	5 hours (total)	2.180,00 NOK

Material	5.000,00 NOK

7.180,00 NOK

1 day clean room use

Thawing of cells bedsite
2 Persons	7 hours (1hr doctor+6hr biotechn)	3.487,00 NOK
Taxi costs		600,00 NOK

4.087,00 NOK

Receiving and intermediate storage of cells
2 Bioengineers + QP	4 hours (total)	3.530,00 NOK
Storage in liquid nitrogen		2.000,00 NOK

5.530,00 NOK

Additional costs

Cleanroom use:

Maintenance, Cleaning, Equipment, QS, Storage, Electricity, Clothing, Monitoring: 35.000,00 NOK/day

Product release:

Documentation, release certificate: 10.000,00 NOK

Production and shipping of frozen cells:

The OUS produce the cells at a clinical room at the cell laboratory. The cell laboratory is physically separated from the clinical department. This implies that the responsible physician needs to be present the whole time of the procedure, i.e. 4 hours. The physician is according to the OUS source not able to do any other clinical work when situated in the cell lab.

The cell laboratory use the four eyes principle, which requires two bioengineers for 4.5 hours, including 0.5 hour pre-preparations.

Freezing of cells:

The OUS utilize the clean room facility for the cell freezing as part of the apheresis process of the tisagenlecleucel product. The clean room facility is, however, more expensive to run and maintain than a regular QC lab. The price of the clean room facility includes all the yearly costs of running and maintenance of the clean room, except capital costs. The total yearly costs are divided by the number of times the clean room is used, at OUS about 250 times each year.

Shipment and documentation:

NoMA has not been able to source the exact calculation of the "documentation and shipment" costs estimated by the OUS. This contains the working hours for following the governmental regulations, accreditations (i.e JACIE), follow strict documentation and release procedures, including quality control testing, before shipment.

NoMA's assessment

Novartis has submitted an updated estimate of costs of apheresis. Novartis referenced a web based newspaper to provide estimates for materials and reagents. The costs of disposable sets add up to $90 and replacement fluids add up to maximum $600 (63). Even though the web newspaper has not referenced the source, it seems that they have used an article from the Congressional Office of

Technology Assessment (OTA). The OTA provided Congressional members in the US with objective analysis of scientific and technical issues and closed in 1995. The article *The Safety, and Cost effectiveness of therapeutic apheresis* from July 1983 use the exact similar cost estimates as the web article referenced by Novartis (63, 64). NoMA presume that the OTA-report from 1983 is the source in the web-newspaper. In NoMA's opinion this is an outdated source of information regarding leukapheresis costs associated with CAR-T production. However, NoMA has not been able to source the exact cost estimates of materials and reagents from the OUS. In a publication by R. Lyons the disposables are estimated to cost between $1500 to $3000 (65). The publication is from 2008 and may be somewhat outdated, however, in line with the estimate from OUS.

Furthermore, the procedure and working hours required for the apheresis, as described by Dag Josefsen, is in line with the description in the Lyons publication (65). Novartis used two patient information leaflets as references for patient time spent on leukapheresis operations (66, 67). One of these is from a Danish University hospital (Aarhus Universitetshospital), and their estimate is in line with the estimate from the OUS. The other is from a patient cancer society and is not in line with either the OUS or the Aarhus university hospital.

According to Dag Josefsen the price of stemcell harvest product from the cell lab to the Benmarggiverregisteret (The Norwegian Bone Marrow Donor Registry, NBMDR) is NOK 39 000. Bone marrow harvesting is a somewhat similar procedure as T-cell harvesting for the tisagenlecleucel product. However, the bone marrow product do not use the freezing facilities. The costs of production and shipment in the tisagenlecleucel case is about NOK 44 000, excluding the clean room, the materials and the working hours for the freezing operation. The cost of production and documentation seems to be in line with the price of the bone marrow harvest produced at the cell lab for the NBMDR.

There may be differences between hospitals for the procedure of apheresis and freezing of cells. At the OUS the production is situated in the cell laboratory, and not bedside in the clinic. Hence, this operation requires a physician to be present during the whole production time of the apheresis product.

For the cost of freezing the cells, Novartis used an estimate provided by the website savestemcells.dk. The total price for freezing stem cells is about NOK 31 000. This number is somewhat lower than the OUS estimate and also includes a profit share for the investors. However, the two numbers cannot be directly compared. Savestemcells.dk may not use a clean room facility and they may have more than 250 products each year, which would lower the mean costs. In their estimate, Novartis has only included the price of storing the frozen stem cells for five years, and not included the much higher price of the freezing operation. The price of storage for 5 years is not relevant in this case.

The average costs for using the clean room constitute a substantial part of the OUS cost estimate. The accuracy of the estimate is dependent on the total costs of maintaining the clean room and the number of times it is used on a yearly basis. It is possible that the frequency of use of the clean room will increase with time, and thereby reducing the average costs.

According to Josefsen, the freezing of the cells do not need to be done in a clean room. However, as a clean room facility is established at OUS it is efficient to use the clean room (it would be waste of

resources to establish another lab for freezing the cells). However, if the freezing production was purchased in a competitive market place, the price of the product would not reflect the costs of maintaining a clean room, but rather the costs of maintaining a QC-lab. NoMA has therefore omitted the fixed costs of the clean room in the cost effectiveness analysis to reflect only the efficient use of the production at the OUS, in line with other competitive market places for this product.

NoMA has included the estimate of the overhead costs, that typically consist of general hospital administration, central laundry, medical records, cleaning, porters, power and so on. NoMA assumes this covers the costs of maintaining the QC-lab.

The input for cost of leukapheresis in NoMA's base case is 55 205 NOK.

The costs of the clean room may explain some of the differences between the cost estimates provided by the Danish Rigshospitalet and the OUS, and make it difficult to compare these cost estimates directly, from one country to another.

VEDLEGG 1 KOMMENTARER FRA PRODUSENT

Novartis takker for muligheten til å kommentere Legemiddelverkets rapport i forbindelse med hurtig metodevurdering av Kymriah (tisagenlecleucel) til behandling av voksne pasienter med residivert eller refraktært diffust storcellet B-cellelymfom (DLBCL) etter to eller flere systemiske behandlinger.

Legemiddelverket har utarbeidet en god og svært grundig rapport. Vurderingen har tatt lang tid (dokumentasjon innsendt 2. juli 2018), men dette skyldes i stor grad at vi har fått anledning til å levere oppdatert informasjon i form av nye modeller og nye studieresultater underveis i saksbehandlingen. Dette har forsinket saken, men også styrket beslutningsgrunnlaget. Novartis har hatt god dialog med Legemiddelverket i saken, og det er nå enighet mellom Legemiddelverket, kliniske eksperter og Novartis på mange av antagelsene som benyttes i den legemiddeløkonomiske modellen.

På et viktig område er vi imidlertid sterkt uenig med Legemiddelverket, og vi oppfatter det slik at både medisinske eksperter og andre anerkjente helseøkonomiske miljøer, som NICE[i] i England, støtter vårt syn. Dette gjelder vurderingen av overlevelse mellom Kymriah som vist i JULIET[ii]-studien og komparatorarmen. Novartis mener at CORAL[iii iv] (pasienter i tredjelinje DLBCL) og de innhentede dataene fra OUS' lymfomregister for DLBCL pasienter i tredjelinje vil være en relevant sammenligning til JULIETs ITT populasjon der overlevelse måles fra inkludering i studien.

NICE i England mener at forskjellen i overlevelse mellom Kymriah i JULIET-studien og CORAL som historisk kontroll sannsynligvis er større enn det Novartis velger å anføre i Norge. De har derfor valgt å nedjustere overlevelsen i CORAL slik at Kymriah kommer bedre ut. Til sammenligning velger Legemiddelverket å gjøre det stikk motsatte ved å forbedre overlevelse i sammenligningsarmen. Figuren nedenfor illustrerer hvordan NICE, Novartis og Legemiddelverket har sammenlignet overlevelse fra JULIET og CORAL studiene. Figuren er laget for å illustrere metodikken og er ikke en presis gjengivelse av overlevelse i JULIET, CORAL samt justeringene til NICE og SLV.
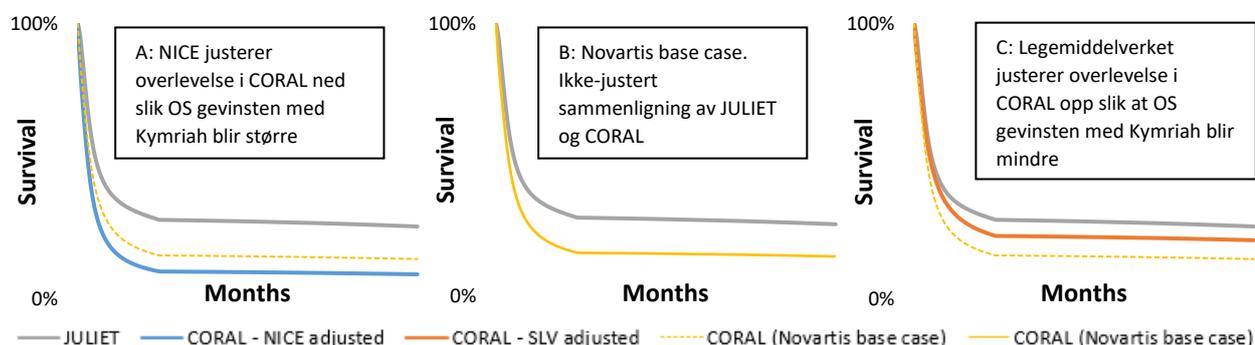
Legemiddelverket hevder videre at pasientpopulasjonen i JULIET er en nøye selektert pasientgruppe med særlig god prognose siden man krevde en forventet overlevelse på 12 uker der behandling med kjemoterapi var tillatt. Eksperter som var med i det kliniske studieprogrammet for Kymriah støtter ikke dette. JULIET-pasientene var tungt forbehandlet, og de ble ikke vurdert som aktuelle for stamcelletransplantasjon. Kymriah var deres eneste gode gjenværende behandlingsalternativ og man

ønsket å inkludere flest mulig pasienter i studien. Cirka 20 % av pasientene i JULIET døde i løpet av de første 3 månedene etter inklusjon. Dette viser med all tydelighet at JULIET studien ikke inkluderte en gruppe pasienter med særlig god prognose, slik Legemiddelverket hevder.

Legemiddelverket argumenterer videre for at JULIET-pasientene vil være «fit for stamcelle-transplantasjon». Etter vår mening er det en lite relevant vurdering siden det var et krav i JULIET at pasientene nettopp *ikke* skulle være aktuelle for en stamcelletransplantasjon (SCT).

Novartis er også uenige i flere andre antagelser Legemiddelverket har gjort i sin legemiddeløkonomiske analyse: Antall sykehusdøgn for Kymriah overestimeres, kostnaden ved bivirkningshåndtering (CRS) forventes å bli lavere i klinisk praksis med økende erfaring, kostnaden ved kjemoterapibehandling i påvente av Kymriah er for høy og livskvalitetstapet ved SCT er betydelig underestimert.

Norge har noen av Europas ledende eksperter innen DLBCL-behandling med CAR-T. Vi synes derfor det er overraskende at Legemiddelverket ikke har validert sine justeringer av forskjell i overlevelse mellom JULIET- og CORAL-studiene med fagmiljøet. De kliniske ekspertene kunne bidratt med å vurdere hva som vil være en plausibel effektforskjell mellom Kymriah og alternativ kjemoterapi.

At Legemiddelverket og NICE vurderer effekten av Kymriah helt ulikt viser at det er en usikkerhet i denne saken. Vi har stor respekt for at det er en vanskelig sak å vurdere, og derfor mener vi at det er viktig å involvere klinikere, samt at man nøye vurderer hva som bør inn i en hovedanalyse og hva som er mer relevant for en «worst case scenario»-analyse.

Legemiddelverkets hovedanalyse basert på ITT-populasjonen der effekten i CORAL er oppjustert i disfavør av Kymriah viser en IKER på 1,8 million kroner per vunnet kvalitetsjusterte leveår (figur C). Novartis mener at denne analysen bærer preg av å være en mer «worst case» analyse og ikke gir et balansert bilde av kostnadseffektiviteten til Kymriah. I en alternativ analyse der effekten i JULIET sammenlignes direkte med CORAL kommer Legemiddelverket til en IKER på 1,4 millioner kroner (OS fra figur B). Novartis mener at en IKER på 1,4 millioner kroner for Kymriah er et konservativt men realistisk estimat der usikkerheten kan ligge både på undersiden og oversiden. I vår hovedanalyse beregnet vi en IKER på underkant av 1 million kroner (OS fra figur B).

Kymriah som en celle- og genterapi er spesiell siden kostnaden belastes på dag 1 (engangsbehandling), mens den potensielle effekten kommer senere. Usikkerhet i forhold til langtidseffekt får derfor stor betydning. Novartis tar all finansiell risiko inntil pasientene faktisk har fått sin Kymriah infusjon. Dersom en pasient av en hvilken som helst årsak ikke får Kymriah etter at cellene er produsert dekkes kostnaden av Novartis. Dette reduserer den økonomiske usikkerheten. Novartis vil følge alle kommersielle pasienter i et register, og vi gjør også en direkte sammenlignende studie innen DLBCL. Novartis kan derfor dele resultater og erfaringer fra kommersiell behandling av norske pasienter med Beslutningsforum/Legemiddelverket dersom Kymriah blir tatt i bruk for DLBCL. Tilgang til «real world evidence» for Norge vil kunne bidra til å redusere usikkerheten rundt den medisinske nytten av Kymriah.

Vi vil oppfordre Beslutningsforum til å vurdere totalkostnaden ved å innføre Kymriah til DLBCL opp mot det totale antall pasienter som forventes å bli behandlet med Kymriah både innenfor kliniske studier og i kommersiell bruk. Novartis har siden 2015 kjørt flere Kymriah-studier ved OUS, og det planlegges en rekke studier for Kymriah og CAR-T i årene som kommer. OUS er et av våre viktigste studiesentre i Europa,

og vi har hatt et særdeles godt samarbeid på studiesiden. Dette samarbeidet ble forøvrig trukket frem over en hel side i stortingsmelding om helsenæringen[v] 5. april 2019.

Novartis har tilbudt Kymriah til en pris som vi mener er kostnadseffektiv tatt i betraktning sykdommens alvorlighet og potensialet for langvarig effekt. Vi håper Beslutningsforum vil fatte en positiv beslutning slik at norske pasienter med DLBCL kan få tilgang til en ny og svært lovende behandlingsmulighet.

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