**ID2019_141**

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

## Update of the previous health economic evaluation

26-05-2022

Statens legemiddelverk

# PREFACE

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

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

NoMA assesses the submitted evidence for all important clinical outcomes, resource use as well as the assumptions made in the analysis presented by the MA-holder and the presented results. NoMA does not perform its own health economic analyses. If required, NoMA may request additional information and perform additional calculations of the costs and cost effectiveness using the submitted model.
NoMA evaluates the relative efficacy and incremental costs in relation to a relevant comparator. NoMA does not assess the benefit risk balance already assessed under the marketing-authorization procedure. Information about this is provided by EMA.

Single Technology Assessment of pharmaceuticals is intended to support sound decision making on potential introductions of new technologies, and 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 (http://www.legemiddelverket.no/)

# 1 BACKGROUND

This single technology assessment (STA) represents an update of the STA of tisagenlecleucel (Kymriah) for the treatment of second or later line relapsed/refractory diffuse large B cell lymphoma (DLBCL), ID2017_116, 11th June 2019 . In the original submission, the median follow-up time for the pivotal phase II trial (JULIET) was 19.3 months (range: 0.4 to 28.9) from infusion (Data cut-off (DCO) date 21-May-2018). The short follow-up time was an important source of uncertainty in the cost-utility model. Decision Forum (Beslutningsforum) decided not to introduce tisagenlecleucel in September 2019, due to uncertainty surrounding the long-term outcomes and the high cost of treatment in relation to its documented effect.

In this updated STA, NoMA has assessed tisagenlecleucel based on an updated DCO (February 2020), providing an additional 21 months of follow-up for JULIET, according to the request specifications from Ordering Forum (Bestillerforum, request number ID2019_141):

*En oppdatering av den opprinnelige analysen med tilhørende modell med nye effektdata og oppdaterte kostnader gjennomføres ved Statens legemiddelverk for tisagenlecleucel (Kymriah) til behandling av diffust storcellet B-cellelymfom.*

# 2 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 risks of tisagenlecleucel in r/r DLBCL have been documented through the marketing authorization (MA). 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 : *ID2019_141: En oppdatering av den opprinnelige analysen med tilhørende modell med nye effektdata og oppdaterte kostnader gjennomføres ved Statens legemiddelverk for tisagenlecleucel (Kymriah) til behandling av diffust storcellet B-cellelymfom.* The request from Ordering Forum can be found at www.nyemetoder.no. NoMA´s assessment is primarily, 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 administered 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 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. Tisagenlecleucel is given as a single intravenous infusion. Before receiving tisagenlecleucel, patients are treated with lymphodepleting chemotherapy (fludarabine in combination with cyclophosphamide) to decrease the number of competing T cells.

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

**Patient population**
In Norway, approximately 20 r/r DLBCL 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. 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 (2). With current frontline standard of care (R-CHOP, rituximab with cyclophosphamide, doxorubicin, vincristine, and prednisolone), the overall cure rate of adult patients with DLBCL is around 50 – 60%. Patients who relapse will be offered new treatment regimens with chemotherapy followed by high dose chemotherapy and autologous stem cell transplant (HDC-ASCT) in eligible patients after obtaining a new response to second-line therapy. For patients with DLBCL 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 of tisagenlecleucel was demonstrated in one pivotal single-arm phase II study (JULIET) in adult patients with r/r DLBCL. The primary endpoint was the best overall response rate (ORR) determined centrally by an independent review committee (IRC). The ORR was defined as the proportion of patients with complete response (CR) and partial response (PR) based on the Lugano Classification criteria (3) interpreted by Novartis's own Image guideline. The primary efficacy analysis was conducted in the modified intention-to-treat (mITT) population including all patients infused with tisagenlecleucel who

had had the opportunity to be followed for 3 months. Analyses of the enrolled (ITT) population were also conducted and reported. Secondary endpoints included progression free survival (PFS) and overall survival (OS). The JULIET study is ongoing.

Efficacy results provided in the original submission (1):
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 remained confidential at the time of the original submission. Among the 167 patients enrolled in JULIET (ITT population), 115 patients (69%) received infusion with tisagenlecleucel (mITT population). The median time from screening and enrolment to CAR-T administration was 119 days (range: 49 to 396) and 54 days (range: 30 to 357 days), respectively (DCO March 2017). 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 primary endpoint (ORR) was analyzed in patients whose Kymriah was manufactured at the Novartis US facility (147/167 patients). Among the 147 patients in the ITT population, the best ORR was 37%, with a CR rate of 28%. In the mITT (infused) population (n=99), the best ORR and CR were 54.5% and 41%, respectively. The PFS and OS analyses included patients from both the US and EU manufacturing sites. In the ITT population (n=167), the median PFS was 4.6 months (95% CI: 3.7, 5.2), and the median OS was 8.2 months (95% CI: 5.8, 11.7). The rates of PFS at 6 and 12 months were 35% and 31%, respectively, whereas the corresponding rates for OS was 57% and 40%. In the mITT population (n=115) the median PFS was 2.9 months (95% CI: 2.3, 4.2) and the median OS was 11.1 months (95% CI: 6.6, upper range not yet estimable).

Efficacy results provided in the updated submission:
The updated submission used a DCO date of February 2020 (unless otherwise specified), with a median follow-up time of 40.3 months. At the time of the original submission, the study was closed for enrolment and therefore the patient numbers and baseline characteristics remained unchanged. Best ORR and CR rates were also unchanged (DCO date July 2019). In patients achieving CR either as best objective response (BOR) or at month 3, long-term survival (> 24 months) was just below 80%. In the ITT population (n=167), the median PFS was 4.8 months (95% CI: 3.7, 5.3, DCO date July 2019). Compared to the original submission, there were an additional 9 deaths. The median OS remained unchanged at 8.2 months (95% CI: 5.8, 11.7). In the mITT population (n=115) the median PFS and OS remained unchanged at 2.9 months (95% CI: 2.3, 5.2) and 11.1 months (95% CI: 6.6, 23.9), respectively.

Comparator data
As the JULIET trial was designed as a single-arm study, the relative efficacy of tisagenlecleucel compared to standard of care was addressed through indirect treatment comparisons to external data.

In the original submission, Novartis conducted two separate matching-adjusted indirect comparisons (MAICs) using published aggregate data from 1) the CORAL extension studies (4, 5) and 2) SCHOLAR-1 (6). The CORAL study was a phase III, multicenter, randomized trial that compared two different second-line salvage regimens, followed by ASCT, in patients with r/r 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 (i.e. the CORAL extension studies). NoMA concluded that the CORAL extension studies would be an acceptable source for a historical control. However, due to several limitations of the MAIC such as missing data, different starting points for OS and inability to adjust for all important prognostic factors and effect modifiers, the magnitude of the clinical benefit of tisagenlecleucel could not be reliably established.

In the present updated submission, Novartis has accessed patient-level data from the two CORAL extension studies and was able to align the starting point of the OS analysis between JULIET and the CORAL follow-up. Following the selection of patients based on important inclusion and exclusion criteria, both unadjusted (Method A) and adjusted (Method B) indirect treatment comparisons (ITC) were conducted. Both methods attempted to adjust for differences in the number of prior treatment lines, but Method B also adjusted for some differences in confounders via propensity score (PS) methodology. In line with prior CAR-T assessments, both the ITT population (enrolled patients) and the modified ITT (mITT) population (infused patients) were considered relevant for decision making. Furthermore, in clinical practice patients who are transplant ineligible due to failing salvage chemotherapy in the 2$^{nd}$ line, might receive a non-cross resistant salvage therapy at third (or later) line, with a view to proceed to ASCT. Therefore, patients undergoing ASCT were retained in the comparator arm.

NOMA welcomes the updated analyses. Nevertheless, the access to patient-level data and the PS-adjusted analysis did not fully resolve the imbalance in reported patient characteristics between JULIET and the comparator study. Furthermore, whereas the CORAL follow-up population had more favorable disease characteristics, indicators of patient “fitness” (ECOG 0-1, no major organ dysfunction, no major co-morbidities, no CNS involvement, as required in JULIET) were not reported in the CORAL follow-up cohorts and could thus not be adjusted for in the indirect comparisons. Therefore, NoMA could not assess the direction of bias in the ITC. Another identified source of uncertainty in the ITC was the large sensitivity of the relative treatment effect to the removal of patients with missing data in method B as compared to method A, where all patients were retained in the dataset. Lastly, the comparator OS curves produced by method B were more pessimistic that those reported in the real-world setting.

Overall, the access to patient-level data in CORAL follow-up did not decrease the uncertainty of the ITC results, highlighting the issue of comparisons between single-arm studies. As both method A and method B were associated with methodological limitations, in which the magnitude and direction of bias is difficult to assess, NoMA chose to use both estimates in the cost-effectiveness model.

**Clinical Safety**

Safety results provided in the original submission:

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

Another important adverse event is secondary hypogammaglobulinemia due to B-cell aplasia. Patients with reduced immunoglobulins produced by normal B cells are at risk for infections and may need monthly supplemental treatment with intravenous infusions of immunoglobulins (IVIG). The duration of B cell aplasia is unknown, but it may persist as long as tisagenlecleucel is present.

Grade 3 and 4 adverse reactions were reported in 88% of patients. The most common Grade 3 and 4 non-haematological adverse reactions were infections (34%) and cytokine release syndrome (23%). Grade 3 and 4 adverse reactions were more often observed within the initial 8 weeks post-infusion (82%) compared to after 8 weeks post-infusion (48%).

Safety results provided in the updated submission:
Compared to the original submission, there were no significant changes in safety findings with the updated data.

**Cost effectiveness**
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), as well as both the unadjusted (Method A) and adjusted (Method B) ITC's relevant for decision making. NoMA has also calculated the ICER for a deterministic model-averaged scenario, where equal weights were assigned to each of the 4 scenarios. In all scenarios, NoMA has selected spline models with 1 knot to extrapolate OS for tisagenlecleucel and chemotherapy until month 84, after which general population mortality is assumed.

The incremental cost-effectiveness ratios for NoMA's scenarios (based on list price for tisagenlecleucel and salvage chemotherapy excl. VAT) are:

- 3,008,980 NOK per QALY gained (ITT population, method A)
- 1,517,590 NOK per QALY gained (mITT population, method A)
- 946,060 NOK per QALY gained (ITT population, method B)
- 1,085,400 NOK per QALY gained (mITT population, method B)
- 1,396,600 NOK per QALY gained (deterministic model-averaged scenario)

**Budget impact**
NoMA estimated the budget impact of the total healthcare costs for the specialist health services to be around 51 million NOK (ITT analysis) and 74 million NOK (mITT analysis) in the fifth year after introduction, provided that all eligible adult patients with r/r DLBCL are treated with tisagenlecleucel.

# 3 SAMMENDRAG

**Metode**
Hurtig metodevurdering av legemiddelet Kymriah (tisagenlecleucel) til behandling av voksne pasienter med residivert eller refraktært diffust storcellet B-cellelymfom (DLBCL) etter to eller flere systemiske behandlinger. Vurderingen er i henhold til godkjent preparatomtale og bestilling ID2019_141: *En oppdatering av den opprinnelige analysen med tilhørende modell med nye effektdata og oppdaterte kostnader gjennomføres ved Statens legemiddelverk for tisagenlecleucel (Kymriah) til behandling av diffust storcellet B-cellelymfom*. Legemiddelverket har vurdert prioriteringskriteriene knyttet til alvorlighet, nytte og ressursbruk. Vurderingen tar primært utgangspunkt i dokumentasjon innsendt av Novartis.

**Bakgrunn**
Tisagenlecleucel 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 tisagenlecleucel gis til pasienten, vil de modifiserte T-cellene gjenkjenne og drepe kreftcellene, og dermed bidra til å fjerne kreftcellene.

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.

Tisagenlecleucel 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 tisagenlecleucel vanligvis ta 3-4 uker. Mange pasienter vil trenge kjemoterapi for å stabilisere kreftsykdommen mens de venter på infusjon med tisagenlecleucel. 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 (2). 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 til siste behandlingslinje 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.

**Klinisk effekt**

Klinisk effekt for tisagenlecleucel er vist i en åpen, enarmet, fase II studie (JULIET) hos voksne pasienter med residivert eller refraktært (r/r) DLBCL. Primært endepunkt var beste totale responsrate (ORR), som inkluderte komplett respons (CR) og partiell respons (PR). Totaloverlevelse (OS) og progresjonsfri overlevelse (PFS) var sekundære endepunkter. JULIET pågår fortsatt.

Effektresultater i opprinnelig innsending (1):

Ved datakutt 21-05-2018 var median oppfølgingstid 19,3 måneder (fra 0,4 til 28,9 måneder) etter infusjon. Data fra et senere datakutt (11-12-2018) ble også vurdert, men var konfidensielle. Av 167 pasienter som ble innrullert i JULIET («intension-to treat» (ITT) populasjon), fikk 115 (69 %) infusjon med tisagenlecleucel (modifisert ITT populasjon). Median tid fra innrullering til CAR-T infusjon var 54 dager (fra 30 til 357 dager) og median tid fra screening til infusjon var 119 dager (fra 49 til 396 dager) (datakutt mars 2017). Årsaker til frafall før infusjon var død (n=16), legens beslutning (n=16), at tisagenlecleucel ikke kunne produseres (n=13), bivirkninger (n=4), pasientens beslutning (n=2) og protokollavvik (n=1).

Det primære endepunktet (ORR) ble analysert for de pasientene som fikk tisagenlecleucel produsert på den amerikanske produksjonsenheten (147/167 pasienter). Blant de 147 innrullerte pasientene, var beste ORR 37 %, med en CR rate på 28 %. I mITT (infuserte) populasjonen (n=99) var beste ORR 54,5 % og 41 % av pasientene oppnådde CR. PFS og OS analysene inkluderte pasienter fra både den amerikanske og den europeiske produksjonsenheten. I ITT populasjonen (n=167) var median PFS 4,6 måneder (95 % KI: 3,7, 5,2) og median OS var 8,2 måneder (95 % KI 5,8, 11,7). PFS ratene ved 6 og 12 måneder var 35 % respektive 31 %, og de korresponderende ratene for OS var 57 % og 40 %. I mITT populasjonen (n=115) var median PFS 2,9 måneder (95% KI: 2,3, 4,2) og median OS var 11,1 måneder (95% KI: 6,6, øvre grense ikke nådd).

Effektresultater i oppdatert innsending:

I den oppdaterte innsendingen er det brukt et datakutt fra februar 2020 (med mindre noe annet er spesifisert), med en median oppfølgingstid på 40,3 måneder. Ved den opprinnelige innsendingen var JULIET studien stengt for videre innrullering, og derfor er det ingen endringer i pasientantall eller grunnlinjekarakteristika. Responsratene (beste ORR og CR) er også uendret (datakutt juli 2019). For pasienter som oppnådde CR, enten som beste ORR eller ved 3 måneder, er andelen langtids overlevere (>24 måneder) rett under 80 %. I ITT populasjonen er median PFS 4.8 måneder (95 % CI: 3,7, 5,3, datakutt, juli 2019). Sammenliknet med den opprinnelige innsendelsen har det tilkommet ytterligere 9 dødsfall. Median OS forblir uforandret på 8,2 måneder (95 % CI: 5,8, 11,7). I mITT populasjonen (n=115) er median PFS og OS uforandret på 2,9 (95 % CI: 2,3, 5,2) måneder respektive 11,1 (95 % CI: 6,6, 23,9) måneder.

Komparatordata:

JULIET studien var en ukontrollert studie, og den relative effekten av tisagenlecleucel sammenliknet med standard behandling er derfor basert på en indirekte sammenligninger med eksterne data.

I den opprinnelige innsendingen, gjennomførte Novartis indirekte sammenligninger (matching-adjusted indirect comparisons, MAIC) med to ulike historiske kontroller, 1) CORAL forlengelsesstudiene (4, 5) og 2)

SCHOLAR-1 (6). CORAL var en randomisert, fase III studie som sammenlignet to kjemoterapiregimer, etterfulgt av ASCT, i andrelinjebehandling av pasienter med r/r DLBCL. Pasienter i CORAL som fikk tilbakefall etter ASCT (n=75) eller som sviktet på kjemoterapi og ikke gikk videre til ASCT (n=203), er fulgt opp i de to CORAL forlengelsesstudiene. Legemiddelverket vurderte at CORAL forlengelsesstudiene kunne aksepteres som kilde for historisk kontroll. Det var imidlertid flere begrensninger ved de innsendte analysene, inkludert manglende data, ulike starttidspunkt for OS og manglende justering for viktige forskjeller mellom armene. Legemiddelverket konkluderte derfor at det ikke var mulig å komme fram til et pålitelig estimat for den kliniske effekten av tisagenlecleucel.

I den oppdaterte innsendingen har Novartis fått tilgang til individuelle pasientdata fra de to CORAL-forlengelsesstudiene, og har dermed kunnet likestille start punktet for OS analysene mellom JULIET og CORAL. Etter seleksjon av pasienter basert på viktige inklusjons/eksklusjonskriterier har Novartis gjennomført både en ujustert (Metode A) og en justert (Metode B) indirekte sammenlikning. Begge metodene forsøkte justere for forskjeller i antall tidligere behandlingslinjer, men Metode B justerte også for noen forskjeller i konfunderende faktorer ved hjelp av propensity score (PS) metodologi. I likhet med tidligere metodevurderinger av CAR-T produkter, ble både ITT populasjonen (innrullerte pasienter) og mITT populasjonen (infuserte pasienter) ansett som relevante for beslutningsgrunnlaget. Videre kan pasienter som ikke er aktuelle for transplantasjon pga. manglende respons på kjemoterapi i 2. linje, i klinisk praksis behandles med et ikke-kryssresistent kjemoterapi regime i 3. eller senere linje, med målsetning om ASCT. SLV valgte derfor å beholde pasienter som fikk ASCT i komparatorarmen.

Tilgangen til individuelle pasientdata og den PS-justerte analysen, løste imidlertid ikke ubalansen i grunnlinjekarakteristika mellom JULIET og sammenlikningsstudien. Sammenliknet med JULIET populasjonen hadde CORAL oppfølgingspopulasjonen flere fordelaktige sykdomskarakteristika, men indikatorer på pasientens allmenntilstand (ECOG 0-1, ingen betydelig organdysfunksjon, ingen betydelig komorbiditet, ikke noe CNS involvering, slik påkrevd i JULIET studien) var ikke rapportert for CORAL og kunne dermed ikke justeres for i analysene. Derfor kan legemiddelverket ikke vurdere retningen på bias i den indirekte sammenlikningen. En annen kilde til usikkerhet er den store følsomheten det relative effektestimatet viser for eksklusjon av pasienter med manglende data i Metode B sammenliknet med Metode A. I tillegg er overlevelses kurvene for komparator fra Metode B mer pessimistiske enn det som er rapportert basert på real-world data.

Tilgangen til individuelle pasientdata har derfor ikke redusert usikkerheten ved de indirekte sammenlikningene, noe som understreker de grunnleggende problemene med å tolke resultater fra ukontrollerte pivotale kliniske studier. Da begge metodene (A og B) var forbundet med metodologiske begrensninger der størrelse og retningen på bias var vanskelig å bestemme, valgte Legemiddelverket å benytte begge metodene i kostnadseffektivitetsmodellen.

**Sikkerhet**

Sikkerhetsresultater i opprinnelig innsending:

De fleste får bivirkninger etter infusjon av tisagenlecleucel. Etter hvert som de aktiverte CAR-T cellene proliferer i pasienten og dreper kreftceller, vil inflammatoriske cytokiner frigjøres. Dette kan forårsake cytokinfrigjøringssyndrom (CRS) med symptomer som høy feber, lavt blodtrykk og pustevansker. En annen vanlig og alvorlig bivirkning er nevrotoksisitet. De vanligste nevrologiske bivirkningene er encefalopati, 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 tisagenlecleucel er til stede 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 %). Bivirkninger 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 %).

Sikkerhetsresultater i den oppdaterte innsendelsen:

Sammenliknet med den opprinnelige innsendelsen, var det ingen endringer av betydning i sikkerhetsfunnene med de oppdaterte dataene.

**Kostnadseffektivitet**
Legemiddelverket har estimert en inkrementell kostnad-effektbrøk (IKER) for tisagenlecleucel sammenlignet med kjemoterapi. Legemiddelverket mener at både ITT-populasjonen (innrullerte pasienter) og den modifiserte ITT (mITT)-populasjonen (infuserte pasienter), samt den ujusterte (metode A) og justerte (metode B) indirekte sammenligningen er relevante for beslutningen. Legemiddelverket har også beregnet en deterministisk vektet IKER, ved bruk av like sannsynlighetsvekter for de 4 scenariene. I alle scenariene har Legemiddelverket valgt å bruke spline modeller med 1 knute for å ekstrapolere OS for tisagenlecleucel og kjemoterapi frem til måned 84, og deretter har Legemiddelverket antatt at mortaliteten er lik den generelle befolkningen.

IKERe for tisagenlecleucel sammenlignet med kjemoterapi i Legemiddelverket sine scenarier er:

- 3 008 980 NOK per vunnet QALY (ITT populasjon, metode A)
- 1 517 590 NOK per vunnet QALY (mITT populasjon, metode A)
- 946 060 NOK per vunnet QALY (ITT populasjon, metode B)
- 1 085 400 NOK per vunnet QALY (mITT populasjon, metode B)
- 1 396 600 NOK per vunnet QALY (deterministisk vektet scenario)

**Budsjettkonsekvenser**
Legemiddelverket har estimert at budsjettvirkningen for sykehusenes totale budsjett vil være om lag 51 millioner NOK (ITT-analyse) og 74 millioner NOK (mITT-analyse) per år i år fem, hvis tisagenlecleucel innføres til behandling av voksne pasienter med r/r DLBCL.

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# LOG

| | |
|---|---|
| **Bestilling:** | ID2019_141: Tisagenlecleucel (Kymriah) til behandling av diffust storcellet B-cellelymfom. Revurdering. |
| **Forslagstiller:** | Leverandør, Novartis |
| **Legemiddelfirma:** | Novartis |
| **Preparat:** | Kymriah |
| **Virkestoff:** | Tisagenlecleucel (tisa-cel) |
| **Indikasjon:** | Behandling av voksne med residivert eller refraktært diffust storcellet B-cellelymfom (DLBCL) etter to eller flere systemiske behandlinger. |
| **ATC-nr:** | L01XX71 |

## Prosess

| | |
|---|---|
| Dokumentasjon bestilt av Legemiddelverket | 30-03-2020 |
| Fullstendig dokumentasjon mottatt hos Legemiddelverket | 10-05-2021 |
| Klinikere kontaktet for første gang | 28-10-2021 |
| LIS kontaktet for første gang av Legemiddelverket. | 25-02-2021 |
| Legemiddelverket bedt om ytterligere dokumentasjon | 06-07-2021. Svar mottatt: 12-10-2021<br>26-10-2021. Svar mottatt: 25-11-2021<br>02-12-2021. Svar mottatt: 14-12-2021 |
| Rapport ferdigstilt: | 26-05-2022 |
| Saksbehandlingstid: | 375 dager hvorav 157 dager i påvente av ytterligere opplysninger fra legemiddelfirma. Dette innebærer en reell saksbehandlingstid hos Legemiddelverket på 218 dager. |
| Saksutredere: | Ania Urbaniak<br>Mathyn Vervaart<br>Helga Haugom Olsen |
| Kliniske eksperter: | Bjørn Østenstad (OUS)<br>Alexander Fosså (OUS)<br>Unn Merete Fagerli (St. Olav) |

Kliniske eksperter har bidratt med avklaringer av sentrale forutsetninger i analysen (bl.a. sammenlignende behandling, pasientgrunnlag og overførbarhet av studiedata til norsk klinisk praksis). Legemiddelverket er ansvarlig for rapportens innhold. Kliniske eksperter har ikke vært involvert i noen konsensusprosess eller hatt noen «peer-review» funksjon ved utarbeidelse av rapporten.

# 4 UPDATED HEALTH ECONOMIC ANALYSIS

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

- Tisagenlecleucel parametrization is based on the updated overall survival (OS) and progression free survival (PFS) data, adding approximately 20 months to the median follow-up time.
- A new indirect treatment comparison (ITC) has been provided, leveraging the patient-level data from the two CORAL extension studies. OS for the CORAL arm is informed by the hazard ratio (HR) derived from this updated patient-level ITC and has been applied to the extrapolated JULIET OS.
- Cost inputs are updated based on new information and adjusted for inflation.
- All other assumptions are aligned with NoMA's preferred assumptions in the original evaluation.

## 4.1 JULIET DATA

Efficacy results provided in the original submission (1)

The clinical efficacy and safety of tisagenlecleucel was demonstrated in one ongoing, pivotal single-arm phase II study (JULIET) in adult patients with relapsed and refractory (r/r) DLBCL. The original submission was based on a data cut-off date (DCO) of 21-May-2018, with a median time from infusion to last follow-up of 19.3 months (range: 0.4 to 28.9). Data from a later DCO of 11-Dec-2018 were also assessed but remained confidential at the time of the original assessment.

The primary endpoint was the best overall response rate (ORR), defined as the proportion of patients with complete response (CR) and partial response (PR). The primary efficacy analysis was conducted in the modified intention-to-treat (mITT) population including all patients infused with tisagenlecleucel who had had the opportunity to be followed for 3 months. Analyses of the enrolled (ITT) population were also conducted and reported. Secondary endpoints included progression PFS and OS.

Among the 167 patients enrolled in JULIET (ITT population), 115 patients (69%) received infusion with tisagenlecleucel (mITT population). The median time from screening and enrolment to CAR-T administration was 119 days (range: 49 to 396) and 54 days (range: 30 to 357 days), respectively (DCO March 2017). 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 primary endpoint (ORR) was analyzed in patients whose tisagenlecleucel was manufactured at the Novartis US facility (147/167 patients). Among the 147 patients in the ITT population, the best ORR was 37%, with a CR rate of 28%. In the mITT (infused) population (n=99), the best ORR and CR were 54.5% and 41%, respectively.

The PFS and OS analyses included patients from both the US and EU manufacturing sites. In the cost-utility model progression was defined per independent review committee (IRC) according to the Lugano response criteria (3). In the ITT analyses (n=167) the median PFS from enrollment was 4.6 months (95% CI: 3.7 to 5.2) (Figure 1), with a PFS rate of 35% at 6 months and 31% at 12 months. Further, the median PFS in the mITT population was 2.9 months (95% CI: 2.3 to 4.2) (Figure 2).

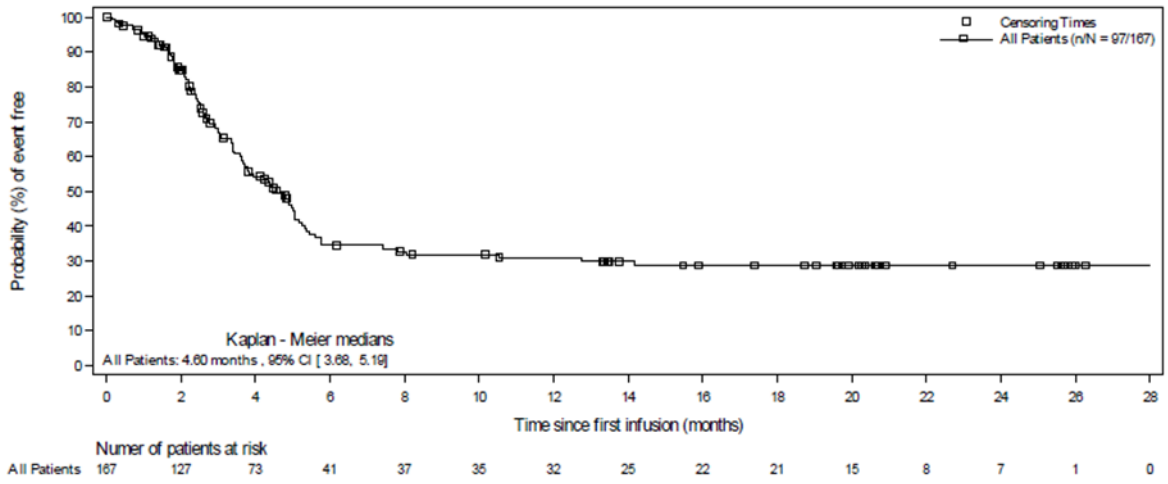



*Figure 1 Kaplan-Meier plot of PFS in the ITT population censoring HSCT from enrolment by IRC assessment (DCO: 21-May-2018).*

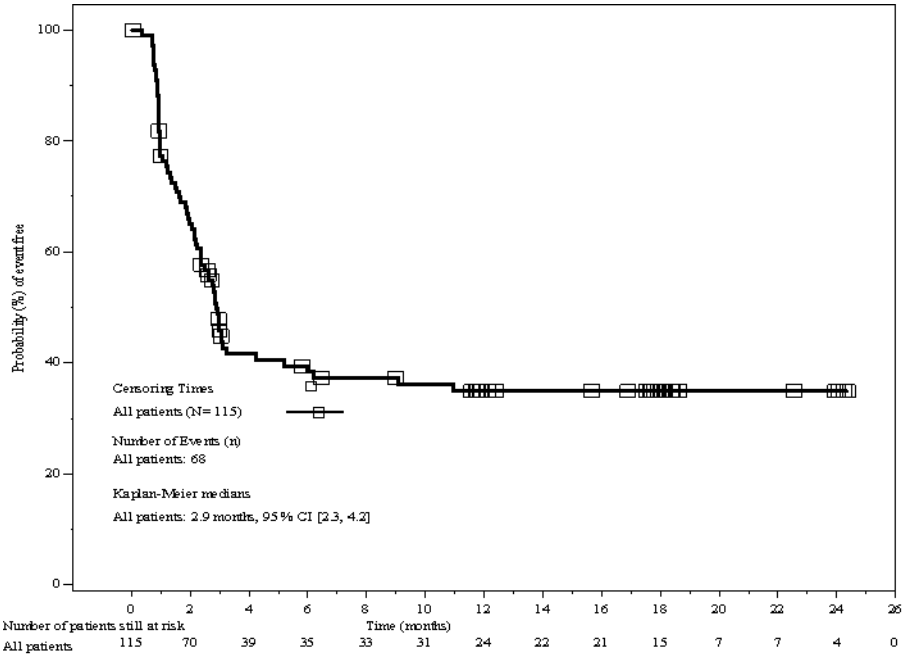



*Figure 2 Kaplan-Meier plot of PFS in the mITT population censoring HSCT by IRC assessment (DCO: 21-May-2018).*

The median OS in the ITT population was 8.2 months (95% CI: 5.8, 11.7), with a survival rate of 57% and 40% at 6 months and 12 months, respectively (Figure 3). In the mITT population the median OS was 11.1 months (95% CI: 6.6, upper range not yet estimable) (Figure 4).

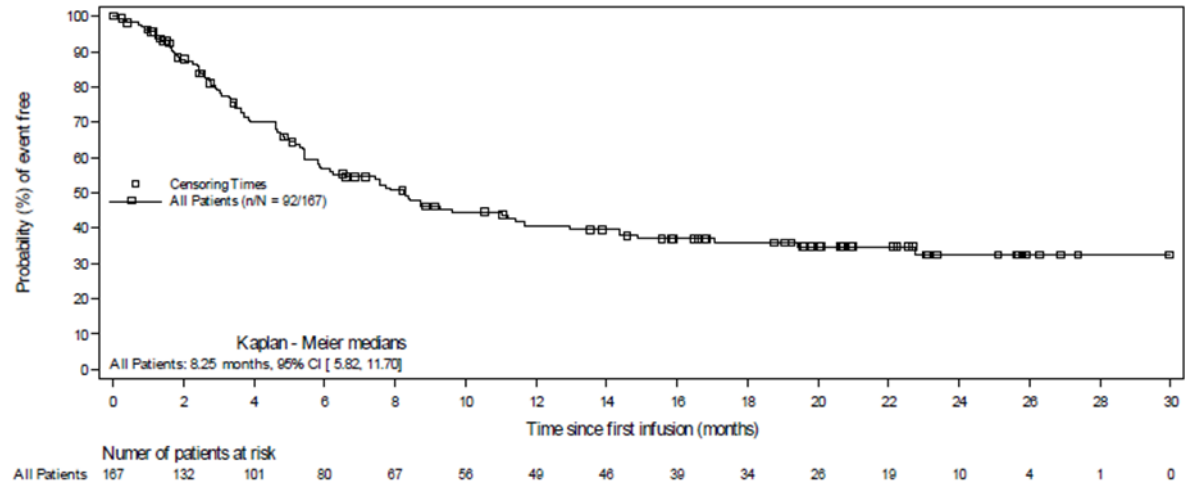



*Figure 3 Kaplan-Meier plot of OS from enrolment in the ITT population (Enrolled set; DCO: 21-May-2018). Time is relative to enrolment, 1 month=30.4375 days.*

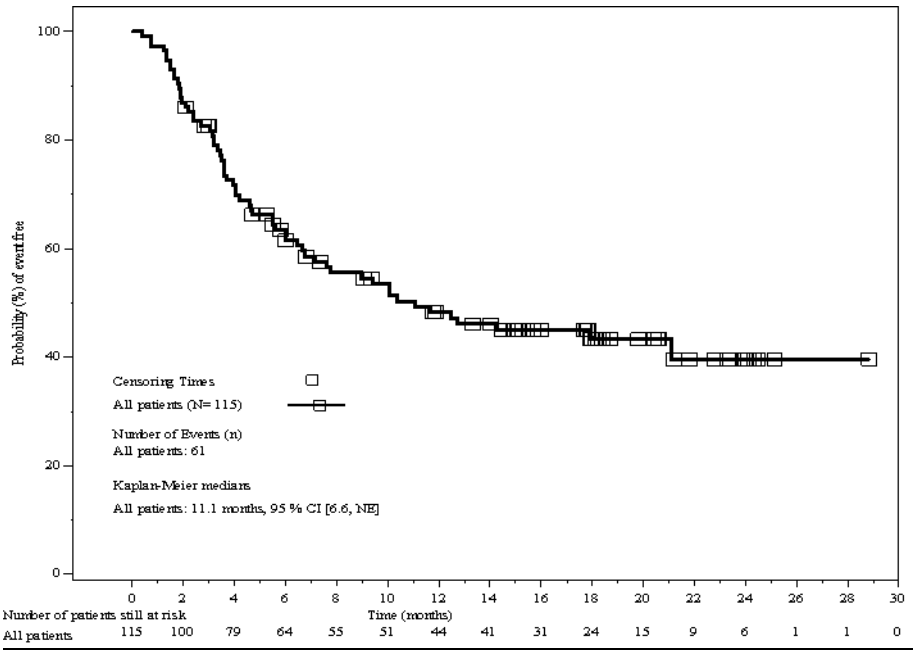



*Figure 4 Kaplan-Meier plot of OS in the mITT population (DCO: 21-May-2018)*

Efficacy results provided in the updated submission

The updated submission used a data cut-off date of February 2020 (unless otherwise specified), with a median follow-up time (defined as the median time from tisagenlecleucel infusion to the data cutoff date) of 40.3 months. At the time of the original submission, the study was closed for enrolment and therefore the patient numbers and baseline characteristics remained unchanged. Best ORR and CR rates were also unchanged (DCO date July 2019). In patients achieving CR either as best objective response (BOR) or at month 3, long-term survival (> 24 months) was just below 80%.

Most progression events occurred early after treatment, with the majority taking place before three months. In the ITT population, the median PFS was 4.8 months (95% CI: 3.7, 5.3) (Figure 5). A total of 70

patients were censored including 18 patients who were censored due to new cancer therapy other than hematopoietic SCT. Novartis has limited information about the reasons for initiation of new cancer therapies. Upon request, Novartis provided KM plots where new cancer therapy other than HSCT is treated as an event. The median PFS decreased to 4.3 months (3.5-5.0). In the infused patients (mITT), the median PFS was 2.9 months (95 % CI: 2.3, 5.2) (Figure 6), with an estimated progression-free probability of 46.1% (95% CI: 36.4, 55.2) and 34.7% (95% CI: 25.7, 43.9) at Months 3 and 18, respectively.

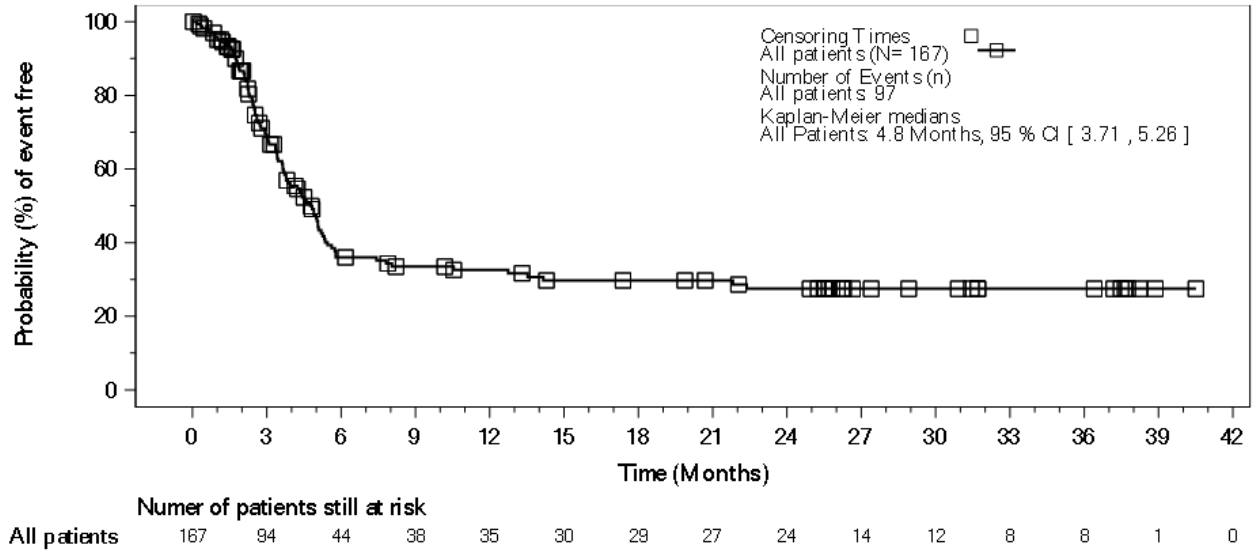



*Figure 5 Kaplan-Meier plot of PFS in the ITT population censoring HSCT from enrolment by IRC assessment (DCO: July 2019). Note: Assessed by an independent review committee, 1 month=30.4375 days.*

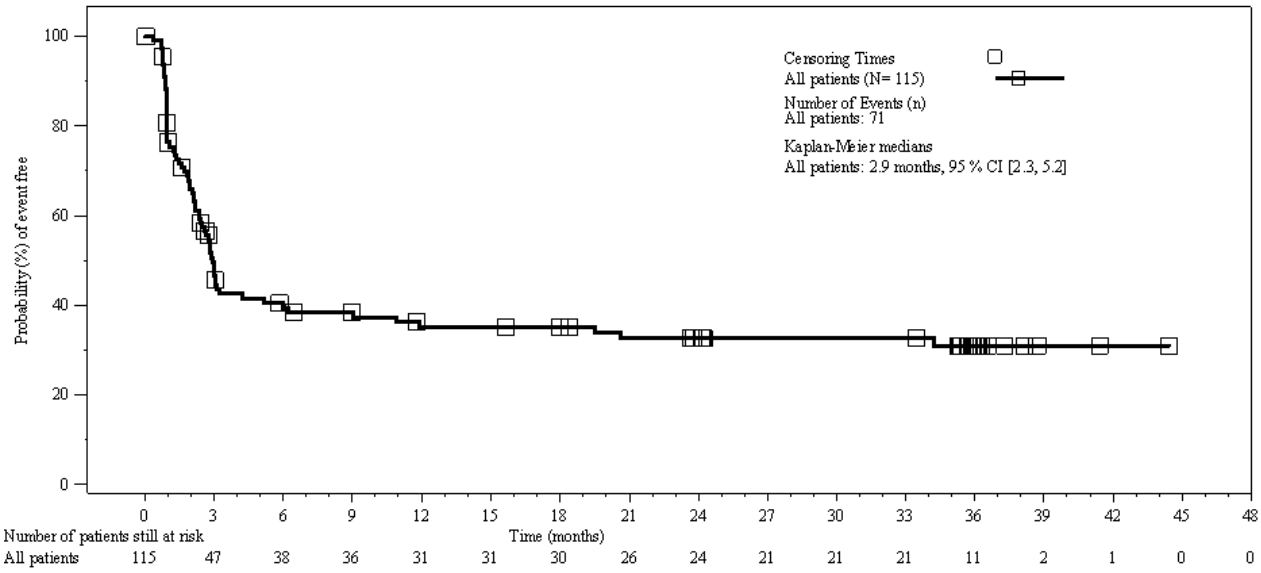



*Figure 6 Kaplan-Meier plot of PFS in the mITT population censoring HSCT by IRC assessment (DCO: Feb 2020).*

The median OS in the ITT population was 8.2 months (95% CI: 5.8, 11.7) with a 60% event rate (Figure 7). For the infused patients (mITT), the median OS was 11.1 months (95% CI: 6.6, 23.9) (Figure 8), with an estimated probability of survival at 24 months of 40.0% (95% CI: 30.7, 49.1).

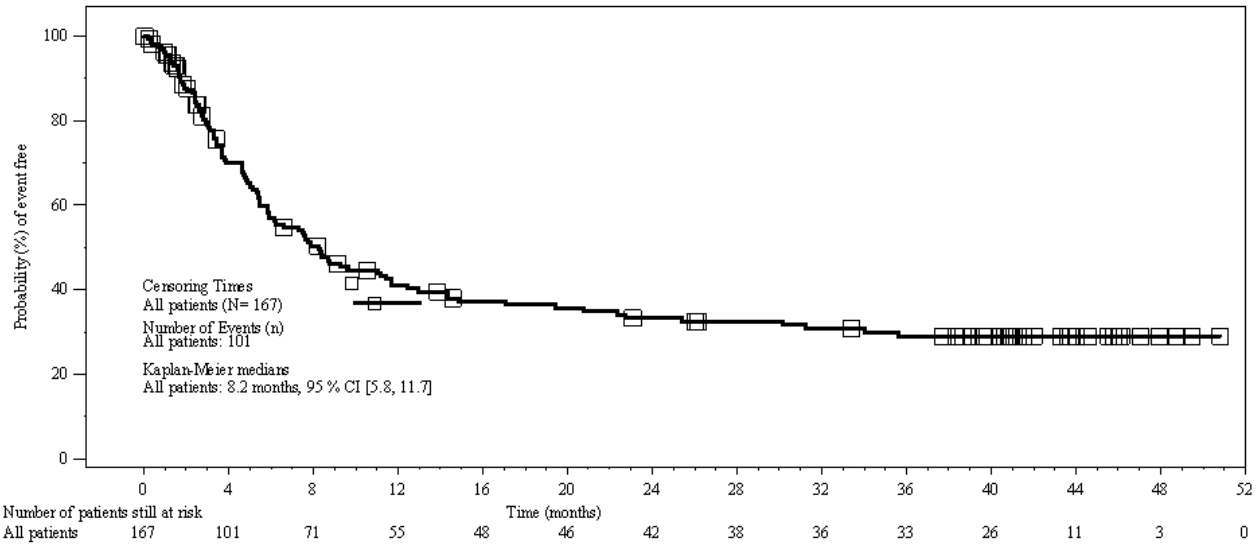



*Figure 7 Kaplan-Meier plot of OS from enrolment in the ITT population (Enrolled set; DCO: Feb 2020). Time is relative to enrolment, 1 month=30.4375 days.*

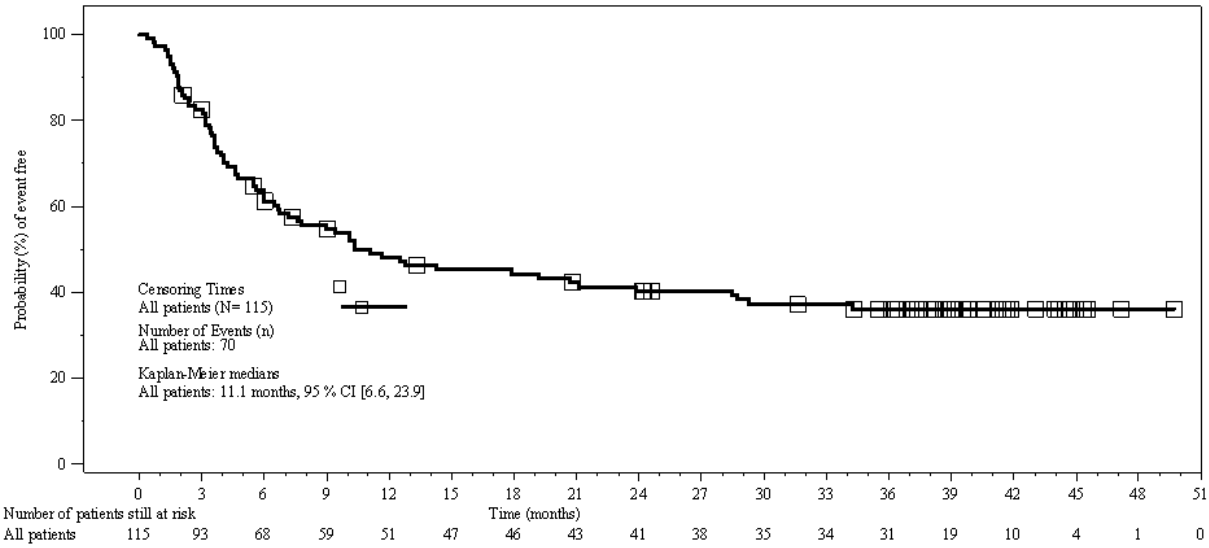



*Figure 8 Kaplan-Meier plot of OS in the mITT population (DCO: Feb2020)*

As a part of the study protocol, OS will be collected up to year 15.

NoMA also requested additional data from JULIET on post-progression survival, which was submitted by Novartis (Figure 9).

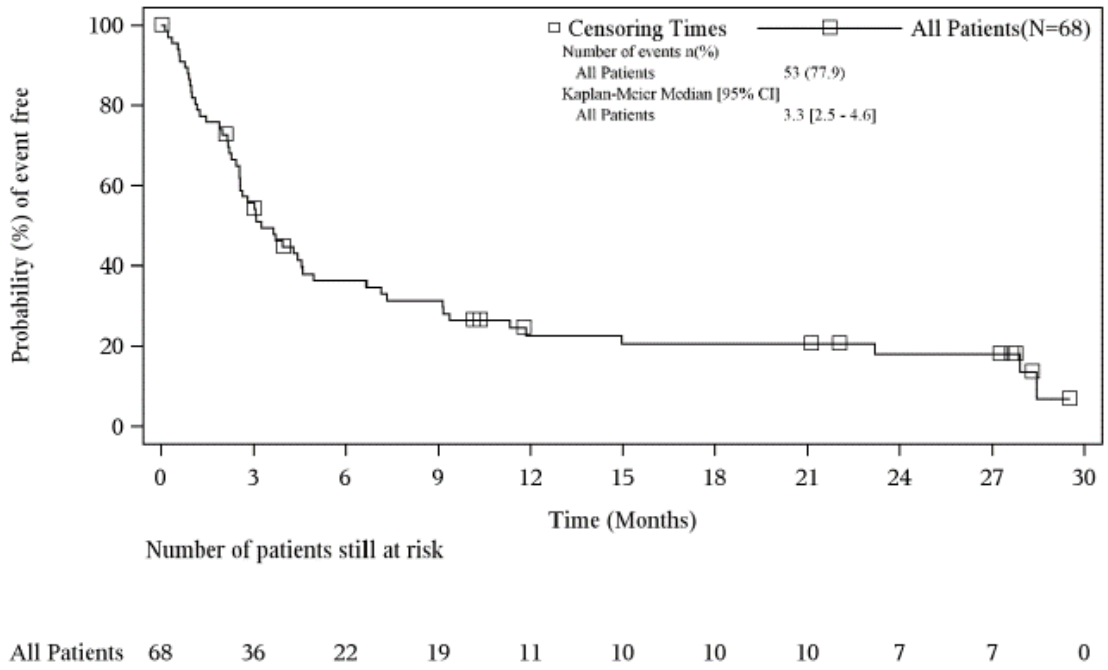



*Figure 9 Kaplan-Meier plot of Overall survival (OS) after progression, mITT population*

*NoMA's assessment*

NoMA welcomes updated PFS and OS data from JULIET. The relatively short follow-up in the original submission was an important source of uncertainty in the cost-utility model. The updated data, reveal an additional 9 deaths compared to the original submission, with an event rate in the enrolled patient population of 60.5%.

NoMA has also requested post-progression survival data for tisagenlecleucel which shows that 10/68 progressed patients survived for 15 months or longer.

## 4.2 THE BELINDA TRIAL (NCT03570892) (7)

The BELINDA trial was an Annex II condition of the tisagenlecleucel marketing authorization (MA).

BELINDA was an international, open-label, phase III randomized controlled trial, comparing tisagenlecleucel (with optional bridging therapy) to salvage chemotherapy and ASCT (standard of care (SOC)), in transplant eligible patients with aggressive lymphoma, refractory to or progressing within 12 months after first-line therapy.

A total of 322 patients were randomized; 95.7% of patients in the tisagenlecleucel group received tisagenlecleucel and 32.5% of the patients in the standard-care group received ASCT. The median time from leukapheresis to tisagenlecleucel infusion was 52 days. The median event-free survival (primary endpoint) in both groups was 3.0 months (hazard ratio for event or death in the tisagenlecleucel group, 1.07; 95% confidence interval, 0.82 to 1.40; P=0.61). A response occurred in 46.3% of the patients in the tisagenlecleucel group and in 42.5% in the standard of care group. Ten patients in the tisagenlecleucel group and 13 in the standard-care group died from adverse events.

*NoMA's assessment*

The MA for the r/r DLBCL indication was based on a single-arm trial. To provide further confirmation of the (long-term) clinical efficacy and safety of tisagenlecleucel, the BELINDA study was included in the MA as a post-authorization efficacy measure. The study, evaluating the efficacy of tisagenlecleucel compared to SOC in an earlier treatment line, failed to meet its primary endpoint (EFS). Data on OS were immature at the time of the primary efficacy analysis. The study therefore does not provide the intended supportive evidence for the r/r DLBCL 3+ line indication and as such cannot contribute to alleviating the uncertainties regarding the relative efficacy estimates in a late line setting.

Of note, 19% of patients in the SOC group proceeded to ASCT following a second regimen of salvage chemotherapy. This is in line with the subsequent ASCT rates for the comparator arm in the two provided ITCs (see section 5.2).

As the BELINDA study was an Annex II condition to the marketing authorization (i.e. a binding condition to the marketing authorization considered key to benefit/risk), the regulatory implications of the negative outcome will be evaluated by the CAT/CHMP.

## 4.3 REAL-WORLD EVIDENCE (RWE) FOR TISAGENLECLEUCEL

Novartis has identified a total of ten publications reporting the real-life efficacy and safety data for tisagenlecleucel and axicabtagene ciloleucel. Of these, one was a review publication (8), and one reported the long- term follow-up of a case-series study (9). The latter study is described separately below. An overview of the eight remaining publications have been provided in Table 1. The results of the JULIET trial have also been included for comparison. The key findings are summarized below:

- Compared to the JULIET trial, r/r DLBCL patients offered tisagenlecleucel in the real-world setting tend to be older, more heavily pre-treated and a larger proportion of patients are in ECOG ≥2.
- Most patients (approx. ≥80%) who underwent apheresis also eventually received tisagenlecleucel (or any CAR-T) infusion.
- The majority of r/r DLBCL patients received bridging therapy in the real-world setting.
- Efficacy results similar to the JULIET trial results have been reported from the US (CIBMTR and CAR-T Cell Consortium), Spain and single centers from France and Germany, whereas the national CAR-T programs from the UK and Germany report slightly inferior results.
- In Europe, data from Spain has the longest follow-up time (14.1 months). Durable responses are confirmed, with 87 % of patients achieving CR being progression free at 12 months.
- The incidence of cytokine release syndrome (CRS) and Immune effector cell-Associated Neurotoxicity Syndrome (ICANS) in the real-world setting is in line with the JULIET clinical trial results. Although any grade CRS appear to be somewhat more common in the real-word setting, severe CRS and ICANS (> grade 3), seem to occur less frequently, likely reflecting current management practice with supportive care (tocilizumab & steroids), increased clinical experience in the management of CAR-T cell therapy as well as changes in the grading system of CRS and ICANS.

*Table 1: Overview of real-world evidence (RWE) publications*

| CAR-T in DLBCL | JULIET Trial | NIS report CCTL019B2401 (10) | | CAR-T Cell Consortium, USA (11) | | National CAR-T Program, UK (12) | | Updated CIBMTR data, USA (13) | Lyon University Hospital, France (14) | | Multi-center CAR-T RWE, Spain (15) | University of Munich, Germany (16) | RWE from German Lymphoma Alliance (17) | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Patient characteristics** | | | | | | | | | | | | | | |
| | **Tisa-cel** | **CIBMTR (Tisa-cel)** | **EBMT (Tisa-cel)** | **Tisa-cel** | **Axi-cel** | **Tisa-cel** | **Axi-cel** | **Tisa-cel** | **Both CAR-Ts** | | **Tisa-cel** | **Both CAR-Ts** | **Tisa-cel** | **Axi-cel** |
| **Apheresis** | 167 | | | 94 | 170 | | | | 70 | | 91 | 37 | | |
| **Infused** | 115 | 307 | 79 | 86 (91%) | 158 (93%) | 50 | 133 | 155 | 61 (87%) | | 75 (82%) | 29 (78%) | 130 | 137 |
| **Age, median** | 56 (22-76) | 66 (19-89) | 62 (20-80) | 67 (29-88) | 59 (18-85) | 61 (30-72) | 56 (18-75) | 65 (18-89) | 59 (27 -75) | | 60 (52 – 67) | 60 (19-74) | 61 (19-83) | 59 (20-83) |
| **Median prior therapies** | 3 (1-6) | 3 (0-11) | | 4 (2-9) | 3 (2-10) | | | 4 (0-11) | 3 | | 3 (2 – 4) | | | |
| **Prior auto** | 49% | 24% | 28% | 26% | 27% | 10% | 15% | 26% | 28% | | 39 % | 34% | 27%[1] | 10%[1] |
| **Bridging tx[2]** | 92% | | | 75% | 61% | 84.8% overall | | | 97% | | | 75 % | 85% | 72% |
| **ECOG 0-1** | 100% | 87% | 86% | 95% | 90% | 54% | 51% | | | | 88 % | 59% | | |
| **ECOG ≥ 2** | 0% | 3% | 14% | | | 12% | 14% | | 30% | | 7 % | 41% | 7% | 16% |
| **Results Efficacy** | | | | | | | | | | | | | | |
| | **Tisa-cel** | **CIBMTR (Tisa-cel)** | **EBMT (Tisa-cel)** | **Tisa-cel** | **Axi-cel** | **Tisa-cel** | **Axi-Cel** | **Tisa-cel** | **Tisa-cel** | **Axi-cel** | **Tisa-cel** | **Both Car-Ts** | **Tisa-cel** | **Axi-cel** |
| **Median FU[3]** | | 6.3 | 3.5 | 6.3 | 7.6 | 9.9 | | 11.9 | 5.7 | | 14.1 | 3.3 | 7.0 | |
| **ORR** | 53% | 60% | 51% | | | | | 62% | | | 60% | | 46% | 77% |
| **CR** | 39% | 39% | 19% | | | | | 40% | | | 32% | | 33% (overall) | |
| **3-month CR** | | | | 42% | 53% | 25% | 30% | | 39% | 40% | | 36% | | |
| **Median PFS[3]** | 2.9 (mITT) | 3.4 | | 3.2 | 6.7 | EFS 3.2, (overall) | | 4.2 | 3.0 | 3.1 | 3.0 | | | |
| **Median OS[3]** | 11.1 (mITT) | 13.0 | | NR | NR | 13.4 (overall) | | 13.1 | 7.4 | NR | 10.7 | | | |

*Table 1 continued: Overview of RWE publications, safety results*

| CAR-T in DLBCL | JULIET Trial | NIS report CCTL019B2401 | | CAR-T Cell Consortium, USA | | National CAR-T Program, UK | | Updated CIBMTR data, USA | Lyon University Hospital, France | | Multi-center CAR-T RWE, Spain | University of Munich, Germany | | RWE from German Lymphoma Alliance | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Tisa-cel | CIBMTR (Tisa-cel) | EBMT (Tisa-cel) | Tisa-cel | Axi-cel | Tisa-cel | Axi-cel | Tisa-cel | Tisa-cel | Axi-cel | Tisa-cel | Tisa-cel | Axi-cel | Tisa-cel | Axi-cel |
| **CRS, any grade** | 57% | 49% | 61% | 41% | 85% | 68% | 93% | 45% | 79% | 93% | 71% | 94% | 89% | 57% | 79% |
| **CRS, ≥ grade 3** | 23% | 5% | 10% | 1% | 8% | 6% | 9% | 5% | 9% | 7% | 5% | 19% | | 11% | 10% |
| **ICANS, any grade** | 23.5% | 20% | 9% | 14% | 53% | 12% | 43% | 18% | 24% | 32% | 15% | 25% | 61% | 22% | 41% |
| **ICANS, ≥ grade 3** | 13% | 4% | 1% | 0% | 33% | 4% | 19% | 5% | 9% | 11% | 1% | 12.5% | 17% | 7% | 13% |
| **ICU Admission** | | | | 7% | 39% | 20% | 37% | | 9% | 25% | 13% | | | 21% (overall) | |

*[1]Not specified if the patients received auto-SCT or allo-SCT; [2]Most studies don't report the type of bridging therapy (chemotherapy, immunotherapy, radiotherapy, steroids and/or their combinations) in more detail; [3]Median follow-up, PFS and OS are given in months; FU= follow up; tx = treatment, NR = Not Reached; ORR = overall response rate; CR = complete response rate; PFS = progression free survival; OS = overall survival; EFS = Event Free Survival; CRS, cytokine release syndrome; ICANS, Immune effector cell-Associated Neurotoxicity Syndrome; ICU, intensive care unit.*

Five-Year Outcomes for Refractory B-Cell Lymphomas with CAR T-Cell Therapy

Chong et al. (2021) (9) recently reported the 5-year outcomes of a case-series study conducted at the Hospital of the University of Pennsylvania, where patients with r/r DLBCL and follicular lymphoma (FL) received CTL019/tisagenlecleucel therapy. In this study, 24 patients with DLBCL received tisagenlecleucel infusion with best overall response (BOR) of 58 % and with CR in 46 % of patients. The PFS was 31 % at 5 years, 60 % of responding patients had a sustained response at 5 years and the median duration of response (DOR) was 61.4 months. OS data were not reported. No new safety concerns emerged, no cases of replication competent lentivirus were detected, 16% of patients presented with secondary malignancy.

*NoMA's assessment*

The real-world efficacy data for tisagenlecleucel have been provided for external validity and are not used in the updated cost-effectiveness model. With the exception of the national CAR-T programs from the UK and Germany (12, 17), the ORR of 46% - 62% is consistent across the real-world studies. The lower response rates in the UK (3-month CR) and German (ORR) national programs compared to the US registries may be driven by several factors, such as differences in patient characteristics, waiting time from treatment decision to infusion, and different modes of data collection (i.e. in the UK registry data were recorded prospectively from the total national cohort as opposed to the retrospective, voluntary US registry inclusion). The PFS (reported in 5 studies) is also consistent across the publications, ranging from 3.0 to 4.2 months. Median OS (5 studies) ranges from 7.4 to 13.4 months. There is a rather large variability across the real-world studies in the proportion of patients experiencing cytokine release syndrome (CRS) and neurotoxicity. However, the proportion of patients with severe events (≥ grade 3) appear relatively low.

Broadly, the real-world results are consistent with the updated data from the JULIET trial. However, as patient characteristics are not consistently published in the real-world studies, it is difficult to draw any strong conclusions about comparability to JULIET. In that regard, it is noted that the CAR-T cell consortium, including 94 tisagenlecleucel treated patients, reported that as many as 29% of patients receiving the treatment in the real-world would not have met JULIET eligibility criteria (18). The median follow-up time of the real-word data is too short to validate long-term OS extrapolation of tisagenlecleucel in the model.

## 4.4 UPDATED COMPARATOR ASSUMPTIONS

The OS comparator data in the cost-utility model are sourced from the two CORAL extension studies (4, 5).

The original CORAL study was a phase III, multicenter, randomized trial that compared two different second-line salvage regimens (R-ICE or R-DHAP), followed by autologous stem cell transplant (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 and constitute the CORAL extension studies. As in JULIET, the original CORAL randomized study enrolled patients without significant co-morbidities, as these were all considered eligible for ASCT at the time of relapse/refractoriness to 1st line of treatment. However, whereas approximately 50% of patients in the JULIET trial had received three or more prior treatment lines, patients in the CORAL extension studies were required to have fail only two lines of prior therapy. Furthermore, all patients in the CORAL

extension studies had a histological diagnosis of DLBCL, as opposed to the JULIET trial where 80% of the infused patients had DLBCL, 18.3% TFL, and 1.7% (i.e. 2 patients) had other types of lymphoma.

In the original submission, matching-adjusted indirect comparisons (MAIC) were conducted matching individual patient data from JULIET to baseline summary statistics reported from the two CORAL extension studies. However, 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)), and thereby failed to address several important differences between the arms.

Furthermore, for the time-to-event endpoints, concerns were raised over the pronounced lead time bias favoring JULIET which would not have been present if JULIET was a randomized controlled trial. Briefly, survival was measured from most recent relapse in the CORAL extension studies and JULIET, thereby introducing 'immortal time bias' as patients in JULIET could not have died during the period between relapse and enrolment/infusion, resulting in an artificial survival benefit for JULIET. Consequently, NoMA's base case was built on a "lead time"-adjusted analysis, aligning the starting time of the survival analysis in both arms to the JULIET trial, and removing CORAL patients who would not be eligible for JULIET. Still, due to several limitations of the MAIC, it was concluded that the magnitude of the clinical benefit of tisagenlecleucel could not be reliably established.

For the current submission, Novartis has acquired patient-level data from the two CORAL extension studies (4, 5), and conducted both an adjusted (Method B) and an unadjusted (Method A) indirect treatment comparison to the JULIET population.

Patient selection for the CORAL follow-up full analyses set (CORAL FU FAS):

From the two CORAL extension studies (n=297), patients for the external control arm (CORAL FU FAS) were selected based on pre-specified inclusion and exclusion criteria, matching those of the JULIET trial (Table 2). The baseline parameters were collected at screening for the JULIET trial and on the treatment index date (i.e. the start of the treatment line to be included in the indirect treatment comparison) for the CORAL FU FAS, unless otherwise specified.

*Table 2 Sample selection flow in CORAL Follow-up FAS*

| Inclusion/exclusion criteria | Number retained |
|---|---|
| 18 years of age or older on potential index date | 297 |
| 18 years of age or older and with non-missing potential index date | 267 |
| Histologically confirmed DLBCL or transformed lymphoma | 267 |
| Relapsed or refractory disease after ? 2 lines of chemotherapy, including rituximab, and previous ASCT was allowed | 264 |
| ECOG performance status that was either 0 or 1 within three months prior to or on the potential index date | 254 |
| Exclude patients with CNS involvement on the potential index date | 249 |
| Exclude patients with primary mediastinal large B-cell lymphoma | 249 |
| Patients with a potential index treatment of 3L or above. Unknown treatment, ASCT, mono immunotherapy and BSC only are not considered as appropriate comparators. Records with unknown treatment, ASCT, mono immunotherapy or BSC only were excluded | 162* |
| Method A - unadjusted line selection | 162 |
| Method B - PS mediated line selection | 132 |

*ECOG performance status was assessed within a month prior to or on the index date for CORAL FU FAS. A large proportion of patients in CORAL follow-up did not have an ECOG and/or CNS assessment; those with a missing or unknown status were not be excluded in the analyses to reserve the sample size.*

**212 patients (method A) and 160 patients (method B) were retained when patients with ASCT as index treatment were included.*

All patients had to have received a qualifying third or later line index treatment. Qualifying index treatments were chemotherapy, +/- rituximab and lenalidomide administered as mono- or combination therapy. Best supportive care and immuno-monotherapy were not considered as appropriate comparators by NoMA. The immuno-monotherapy category comprised therapies not approved in the r/r DLBCL setting. Furthermore, based on the inclusion criteria, the JULIET trial population was considered medically fit for more intensive treatment regimens. Thus, to preserve the internal validity of the indirect comparisons, this was considered applicable also to the comparator arm. Unknown treatments were also excluded, as it could not be assessed whether these patients had received an appropriate comparative therapy.

Since the JULIET trial enrolled patients who either had failed ASCT or were ineligible for or not consenting to ASCT, to match to these criteria, Novartis did not consider treatment with ASCT as a potential index treatment in the CORAL FU FAS. Similar to the JULIET trial design, ASCT prior to or after a potential index treatment was allowed. Patients who received allogenic stem cell transplant (alloSCT) after an index treatment (but not before) in the CORAL extension studies were also retained in the analysis. Upon request, Novartis provided an additional analysis where patients who received ASCT as an index treatment were retained in the CORAL FU FAS (see also NoMA's assessment of the updated comparator assumptions).

Assignment to index treatment line:

As patients in the CORAL FU FAS could have received multiple qualifying index treatments, two methods (Method A and Method B) were used to assign patients to an index treatment line/index date for the indirect treatment comparisons. The index date was defined as the date of enrollment (JULIET) or the initiation date of the index treatment (CORAL). In the unadjusted comparison, the goal was to balance the number of prior treatment lines and thus CORAL patients were assigned to the index treatment line that was most overrepresented among JULIET patients without adjustment for confounders (Method A). The date of initiation of the index treatment (i.e index date) was the starting point of survival analysis for that patient in the CORAL extension studies. In the adjusted comparisons (Method B), the index treatment line was selected with the goal of reducing the cross-study differences in confounders via propensity score (PS) methodology (described below).

Line distribution in JULIET and CORAL FU FAS before and after line selection is presented in Table 3.

*Table 3 Line Distribution for JULIET ITT and CORAL FU FAS Before and After Line Selection. ASCT as index treatment included.*

| | Before Line Selection | | Method A – Unadjusted After Line Selection[1] | | Method B - PS Mediated After Line Selection[2] | |
|---|---|---|---|---|---|---|
| **Line Distribution** | **JULIET (N=166)** | **CORAL Follow-up (N=250)** | **JULIET (N=166)** | **CORAL Follow-up (N=212)** | **JULIET (N=163)** | **CORAL Follow-up (N=160)** |
| Number of patients with unique line | 166 | 187 | | | | |
| Number of patients with multiple lines | 0 | 25 | | | | |
| 2L | 6 (3.6%) | 0 (0.0%) | 6 (3.6%) | 0 (0.0%) | 6 (3.7%) | 0 (0.0%) |
| 3L | 72 (43.4%) | 208 (83.2%) | 72 (43.4%) | 184 (86.8%) | 72 (44.2%) | 139 (86.9%) |
| 4L | 52 (31.3%) | 27 (10.8%) | 52 (31.3%) | 18 (8.5%) | 50 (30.7%) | 14 (8.8%) |
| 5L | 20 (12.0%) | 9 (3.6%) | 20 (12.0%) | 6 (2.8%) | 20 (12.3%) | 4 (2.5%) |
| 6L | 11 (6.6%) | 4 (1.6%) | 11 (6.6%) | 3 (1.4%) | 10 (6.1%) | 2 (1.2%) |
| 7L | 2 (1.2%) | 2 (0.8%) | 2 (1.2%) | 1 (0.5%) | 2 (1.2%) | 1 (0.6%) |
| 8L | 2 (1.2%) | 0 (0.0%) | 2 (1.2%) | 0 (0.0%) | 2 (1.2%) | 0 (0.0%) |
| 9L | 1 (0.6%) | 0 (0.0%) | 1 (0.6%) | 0 (0.0%) | 1 (0.6%) | 0 (0.0%) |

*[1] For the CORAL follow-up patients that have multiple potential index lines, the index line will be selected based on the relative demand for controls of each line, which is determined by the relative difference of marginal distribution for treatment lines between JULIET and CORAL follow-up.*

*[2] For the CORAL follow-up patients that have multiple potential index lines, a PS model is used to select the index line based on the following baseline characteristics: age at diagnosis, Ann Arbor disease stage, extranodal site involvement, serum LDH level, status of disease, time to initiation of 2L after diagnosis, prior HSCT, and number of relapses.*

## Identification of confounding factors

Potential confounders were identified in a systematic search of literature and therapy guidelines. These were subsequently ranked by clinical experts in terms of importance. Confounders that were not available in the CORAL dataset or with >20% missing values were excluded by Novartis, resulting in the inclusion of five covariates in the adjusted analyses. Upon request from NoMA, confounders with ≤30% missing values were allowed, increasing the number of covariates in the adjusted analyses to eight: age at initial diagnosis (≤60 vs. >60); status of disease (refractory to all prior lines, refractory to last line, relapse after last line); time to second-line treatment after diagnosis (< 12 vs. ≥ 12 vs. > 24 months); number of relapses and previous HSCT (yes, no), serum LDH level (normal vs. > 1 to ≤ 3 vs. > 3 upper limit of normal [ULN]), Ann Arbor disease stage (I, II vs. III, IV) and extranodal (EN) site involvement (0 - 1 vs. ≥ 2 extranodal organs) (Table 4). ECOG status was not included among the covariates due to >60% missing data in the CORAL FU FAS; those with a missing or unknown status were however retained in the analyses to reserve the sample size. Although 4 out of 5 risk factors evaluated in the IPI score were included, the actual IPI score was excluded from the analyses due to missing data. Other important factors such as ethnicity, race, primary site of cancer, predominant histology/cytology, molecular DLBCL subtypes, cytogenetic changes (double/triple hits in MYC [MYC-Proto-Onkogen], B-cell lymphoma 2 protein [BCL2], B-cell lymphoma 6 protein [BCL6]), bulky disease, baseline total metabolic tumor volume, central nervous system-/bone marrow involvement and two not important prognostic factors i.e. hepatitis B infection and vitamin-D-deficiency were not available in CORAL follow-up, and thus not included in the analyses.

*Table 4 Overview of identified confounders and their use in the PS model.*

| Potential confounders (identified by systematic literature research) | Relevance[1] for adults with r/r DLBCL (by medical experts) | Included in the PS model? |
|---|---|---|
| Factors considered under IPI | | |
| Age at initial diagnosis (>40 to ≤ 60 vs. > 60 to < 75 vs. ≥ 75) | very important | Yes |
| Performance Status (ECOG 0 - 1 vs. 2 - 4) | very important | No, >30% missing values |
| Serum LDH level (normal vs. > 1 to ≤ 3 vs. > 3 upper limit of normal [ULN]) | very important | Yes |
| Ann Arbor disease stage (I, II vs. III, IV) | very important | Yes |
| Extranodal site involvement (0 - 1 vs. ≥ 2 extranodal organs) | very important | Yes |
| Status of disease (refractory to all prior lines, refractory to last line, relapse after last line) | very important | Yes |
| Time to first relapse after diagnosis (< 12 vs. ≥ 12 vs. > 24 months) | very important | Yes |
| Number of relapses | very important | Yes |
| Double/Triple Hits (MYC/BCL2/BCL6), MYC-IG rearrangement | very important | No, not available in CORAL FU |
| Previous HSCT (yes, no) | very important | Yes |
| Bulky disease (yes, no) | very important | No, not available in CORAL FU |
| Molecular subtype (GCB, ABC) | less important | No, not available in CORAL FU |
| Hepatitis B infection | not important | No, not available in CORAL FU |
| Vitamin-D-deficiency | not important | No, not available in CORAL FU |

1"Relevant" confounders were defined as "very important" or "less important" by clinical experts

Adjusted indirect treatment comparison (Method B)

For the adjusted indirect treatment comparison (Method B) the identified confounders were used in two steps: 1) for selecting treatment line and/or index date (as described above) and 2) as covariates for adjusted comparisons. For step 1) all CORAL follow-up FAS patients were included, and all potential index treatments were considered. A Generalized Linear Model (GLM) with the logit link was used to estimate the propensity score (PS) for a patient to be in JULIET full analysis set (FAS). Once the per-patient per-line PS was estimated, the therapy line with the highest PS was selected as the index treatment for a given patient. Subsequently comparisons were made between JULIET and CORAL follow-up adjusting for the same selected confounders based on fine stratification PS weight as well as standardized mortality ratio weight (SMRW).

Distributions of PS for JULIET vs CORAL FU FAS are presented in Figure 10 and show reasonable overlap. In other words, the predicted probability of participating in the JULIET trial (based on 8 covariates) was similar between JULIET and CORAL FU FAS patients. Baseline characteristics prior to- and after PS weighting are presented in Table 5. Characteristics that remained imbalanced after PS weighting are marked in orange. Use of a threshold of 0.1 in standardized mean difference between JULIET's patient characteristics and PS weighed patient characteristics from CORAL follow-up FAS indicates meaningful imbalance (19, 20).

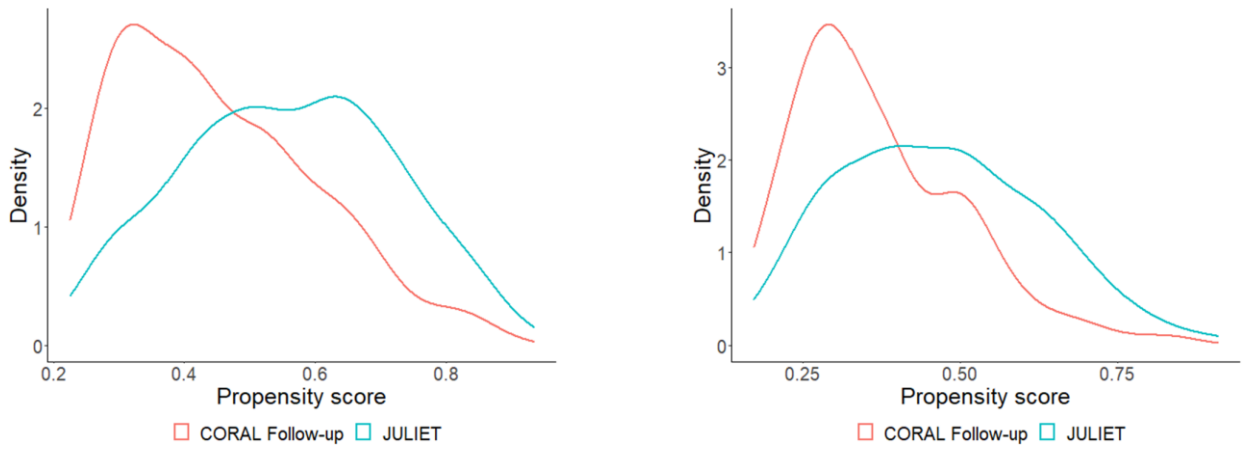



*Figure 10 Distributions of Propensity Score for JULIET ITT (N=163) vs. CORAL Follow-up FAS (N=160), left, and JULIET mITT (N=111) vs. CORAL Follow-up FAS (N=160), right. ASCT as index treatment included.*

*Table 5 Patient Characteristics for JULIET ITT and CORAL Follow-up FAS for Method A, Method B (Prior PS weighting, but after missing data exclusion) and Method B (Post Propensity Score Weighting). ASCT as index treatment included. Characteristics that remained in imbalance between JULIET and Method B (after PS weighting) are marked in orange (19, 20).*

| | JULIET ITT (N=163) | CORAL Follow-up FAS (N=212), Method A | CORAL Follow-up FAS, prior to PS Weighting (N=160) | CORAL Follow-up FAS, post PS Weighting (N=160), Method B | |
|---|---|---|---|---|---|
| | | | | Fine stratification weight | SMRW |
| **Prognostic Factors Included (Relevant for Method B)** | | | | | |
| ***Demographics*** | | | | | |
| Age at initial diagnosis (years) | | | | | |
| ? 60, n (%) | 106 (65.0%) | 173 (81.6%) | 128 (80.0%) | 62,7% | 62,9% |
| > 60, n (%) | 57 (35.0%) | 38 (17.9%) | 32 (20.0%) | 37,3% | 37,1% |
| Missing, n (%) | | | | | |
| n | 163 | 212 | 160 | | |
| Mean (SD) | 53.2 (12.7) | 49.9 (11.2) | 50.1 (11.7) | 53,0 | 52,7 |
| Median (min, max) | 56.0 (14.3, 75.7) | 53.1 (12.0, 64.2) | 53.5 (12.0, 64.2) | | |
| ***Disease characteristics*** | | | | | |
| Status of disease, n (%) | | | | | |
| Relapsed after last line | 67 (41.1%) | 103 (48.6%) | 76 (47.5%) | 43,6% | 45,0% |
| Refractory to all lines | 28 (17.2%) | 33 (15.6%) | 25 (15.6%) | 13,7% | 16,7% |
| Refractory to last line but not to all lines | 68 (41.7%) | 76 (35.8%) | 59 (36.9%) | 42,7% | 38,3% |
| Time to 2L start after diagnosis (months)[5], n (%) | | | | | |
| < 12 | 94 (57.7%) | 106 (50.0%) | 79 (49.4%) | 54,3% | 57,3% |
| ? 12 and ? 24 | 41 (25.2%) | 55 (25.9%) | 42 (26.2%) | 25,9% | 22,8% |
| > 24 | 28 (17.2%) | 50 (23.6%) | 39 (24.4%) | 19,8% | 19,8% |
| Missing | 3 (1.8%) | 1 (0.5%) | 0 (0.0%) | | |
| Serum LDH level[6], n (%) | | | | | |
| Normal | 59 (36.2%) | 57 (26.9%) | 55 (34.4%) | 38,9% | 37,5% |
| Elevated | 104 (63.8%) | 104 (49.1%) | 105 (65.6%) | 61,1% | 62,5% |
| Missing | 0 (0.0%) | 51 (24.1%) | 0 (0.0%) | | |
| Ann Arbor disease stage, n (%) | | | | | |
| I or II | 35 (21.5%) | 58 (27.4%) | 54 (33.8%) | 24,9% | 22,1% |
| III or IV | 128 (78.5%) | 108 (50.9%) | 106 (66.2%) | 75,1% | 77,9% |
| Missing | 0 (0.0%) | 46 (21.7%) | 0 (0.0%) | | |
| Extranodal site involvement, n (%) | | | | | |
| 0 - 1 | 93 (57.1%) | 133 (62.7%) | 123 (76.9%) | 57,5% | 55,0% |
| ? 2 extranodal organs | 70 (42.9%) | 35 (16.5%) | 37 (23.1%) | 42,5% | 45,0% |
| Missing | 0 (0.0%) | 44 (20.8%) | 0 (0.0%) | | |
| ***Prior therapies*** | | | | | |
| Prior HSCT[7], n (%) | | | | | |
| Yes | 74 (45.4%) | 75 (35.4%) | 71 (44.4%) | 48,3% | 48,7% |
| No | 89 (54.6%) | 137 (64.6%) | 89 (55.6%) | 51,7% | 51,3% |
| Number of relapses (excluding refractory)[8] | | | | | |
| 0, n (%) | 28 (17.2%) | 33 (15.6%) | 25 (15.6%) | 13,7% | 16,7% |
| 1, n (%) | 60 (36.8%) | 79 (37.3%) | 59 (36.9%) | 38,9% | 35,2% |
| 2, n (%) | 57 (35.0%) | 87 (41.0%) | 67 (41.9%) | 41,1% | 40,3% |
| 3, n (%) | 16 (9.8%) | 12 (5.7%) | 8 (5.0%) | 4,4% | 4,7% |
| 4, n (%) | 2 (1.2%) | 0 (0.0%) | 0 (0.0%) | -- | -- |
| 5, n (%) | 0 (0.0%) | 1 (0.5%) | 1 (0.6%) | 1,9% | 3,2% |
| Mean (SD) | 1.4 (0.9) | 1.4 (0.8) | 1.4 (0.9) | 1,4 | 1,5 |
| Median (min, max) | 1.0 (0.0, 4.0) | 1.0 (0.0, 5.0) | 1.0 (0.0, 5.0) | | |
| **Prognostic Factor Excluded Due to Missing (Relevant for Method B)[9]** | | | | | |
| ECOG[10], n (%) | | | | | |
| 0 - 1 | 163 (100.0%) | 70 (33.0%) | 68 (42.5%) | 100,0% | 100,0% |
| Missing | 0 (0.0%) | 142 (67.0%) | 92 (57.5%) | | |

**Other Baseline Variables**

| | | | | | |
|---|---|---|---|---|---|
| ***Demographics*** | | | | | |
| Age (years) | | | | | |
| < 40, n (%) | 21 (12.9%) | 35 (16.5%) | 25 (15.6%) | 10,3% | 10,8% |
| ? 40 and < 65, n (%) | 98 (60.1%) | 165 (77.8%) | 125 (78.1%) | 81,6% | 81,8% |
| ? 65, n (%) | 44 (27.0%) | 12 (5.7%) | 10 (6.2%) | 8,1% | 7,3% |
| Mean (SD) | 55.7 (12.9) | 52.4 (11.4) | 52.8 (11.6) | 55,6 | 55,3 |
| Median (min, max) | 58.0 (22.0, 76.0) | 55.7 (19.1, 68.7) | 56.2 (19.1, 67.8) | | |
| Gender, n (%) | | | | | |
| Female | 62 (38.0%) | 77 (36.3%) | 57 (35.6%) | 34,8% | 33,6% |
| Male | 101 (62.0%) | 135 (63.7%) | 103 (64.4%) | 65,2% | 66,4% |
| ***Disease characteristics*** | | | | | |
| Ann Arbor disease stage at diagnosis, n (%) | | | | | |
| I or II | 42 (25.8%) | 90 (42.5%) | 66 (41.2%) | 36,5% | 35,5% |
| III or IV | 115 (70.6%) | 120 (56.6%) | 93 (58.1%) | 63,5% | 64,5% |
| Missing | 6 (3.7%) | 2 (0.9%) | 1 (0.6%) | | |
| IPI at diagnosis[11], n (%) | | | | | |
| < 2 risk factors | 35 (21.5%) | 92 (43.4%) | 68 (42.5%) | 39,0% | 38,1% |
| ? 2 risk factors | 100 (61.3%) | 106 (50.0%) | 80 (50.0%) | 61,0% | 61,9% |
| Missing | 28 (17.2%) | 14 (6.6%) | 12 (7.5%) | | |
| IPI[11], n (%) | | | | | |
| < 2 risk factors | 33 (20.2%) | 20 (9.4%) | 19 (11.9%) | 7,6% | 7,0% |
| ? 2 risk factors | 130 (79.8%) | 119 (56.1%) | 117 (73.1%) | 92,4% | 93,0% |
| Missing | 0 (0.0%) | 73 (34.4%) | 24 (15.0%) | | |
| BM involvement at diagnosis, n (%) | | | | | |
| Yes | 28 (17.2%) | 16 (7.5%) | 11 (6.9%) | 6,5% | 5,8% |
| No | 126 (77.3%) | 169 (79.7%) | 131 (81.9%) | 93,5% | 94,2% |
| Missing | 9 (5.5%) | 27 (12.7%) | 18 (11.2%) | | |
| BM involvement, n (%) | | | | | |
| Yes | 14 (8.6%) | 13 (6.1%) | 12 (7.5%) | 25,9% | 26,1% |
| No | 149 (91.4%) | 45 (21.2%) | 46 (28.7%) | 74,1% | 73,9% |
| Missing | 0 (0.0%) | 154 (72.6%) | 102 (63.7%) | | |
| CNS involvement, n (%) | | | | | |
| No | 163 (100.0%) | 77 (36.3%) | 77 (48.1%) | 100,0% | 100,0% |
| Missing | 0 (0.0%) | 135 (63.7%) | 83 (51.9%) | | |
| Histological subtype, n (%) | | | | | |
| DLBCL | 126 (77.3%) | 212 (100.0%) | 160 (100.0%) | 100,0% | 100,0% |
| Transformed lymphoma | 37 (22.7%) | 0 (0.0%) | 0 (0.0%) | -- | -- |
| Time since most recent relapse / progression to index date (month)[12], n (%) | | | | | |
| ? Median of JULIET | 82 (50.3%) | | 158 (98.8%) | 99,0% | 99,1% |
| > Median of JULIET | 81 (49.7%) | | 2 (1.2%) | 1,0% | 0,9% |
| Missing | 0 (0.0%) | | 0 (0.0%) | | |
| Mean (SD) | 2.7 (1.6) | | 0.9 (1.3) | 0,9 | 0,8 |
| Median (min, max) | 2.4 (0.0, 11.6) | | 0.5 (0.0, 12.1) | | |
| ***Prior therapies*** | | | | | |
| Number of prior lines of therapies | | | | | |
| Mean (SD) | 2.8 (1.2) | 2.2 (0.6) | 2.2 (0.6) | 2,3 | 2,4 |
| Median (min, max) | 3.0 (1.0, 8.0) | 2.0 (2.0, 6.0) | 2.0 (2.0, 6.0) | | |

***Abbreviations:*** *BM: bone marrow; CNS: central nervous system; DLBCL: diffuse large B cell lymphoma; ECOG: Eastern Cooperative Oncology Group; FAS: full analysis set; HSCT: hematopoietic stem cell transplantation; IPI: International Prognostic Index; ITT: intent-to-treat; LDH: lactate dehydrogenase; SMRW: standardised mortality ratio weight*

**Notes:**

[1] Ethnicity, race, primary site of cancer, predominant histology/cytology, molecular DLBCL subtypes, cytogenetic changes (double/triple hits in MYC [MYC-Proto-Onkogen], B-cell lymphoma 2 protein [BCL2], B-cell lymphoma 6 protein [BCL6]), bulky disease, baseline total metabolic tumor volume and two not important prognostic factors hepatitis B infection and vitamin-D-deficiency were not available in CORAL follow-up, and thus not included in the analyses.

[2] Unless otherwise indicated, variables were assessed at screening for JULIET and at the index date for CORAL.

[3] Three patients from JULIET were excluded due to missingness in the covariates used in the propensity score model.

[4] Use a threshold of 0.1 in standardized mean difference to indicate meaningful imbalance: Austin, P.C. "Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples." Statistics in medicine vol. 28 (2009): 3083-3107, and Austin, P.C. "The use of propensity score methods with survival or time-to-event outcomes: reporting measures of effect similar to those used in randomized experiments." Bone marrow transplantation vol. 33 (2014): 1242-1258.

[5] For the JULIET patients who had one prior line, the second-line start date was defined as the JULIET enrollment date. For the JULIET patients with more than one prior lines, the second-line start date was defined as the second-line initiation date. For the CORAL follow-up group, the second-line start date was defined as the second-line initiation date.

[6] Normal serum LDH level was defined as LDH less than or equal to upper limit of normal (ULN), while elevated serum LDH level was defined as LDH greater than ULN.

[7] Prior HSCT only included prior ASCT because records with an allogeneic stem cell transplantation (allo-SCT) prior to index date were excluded.

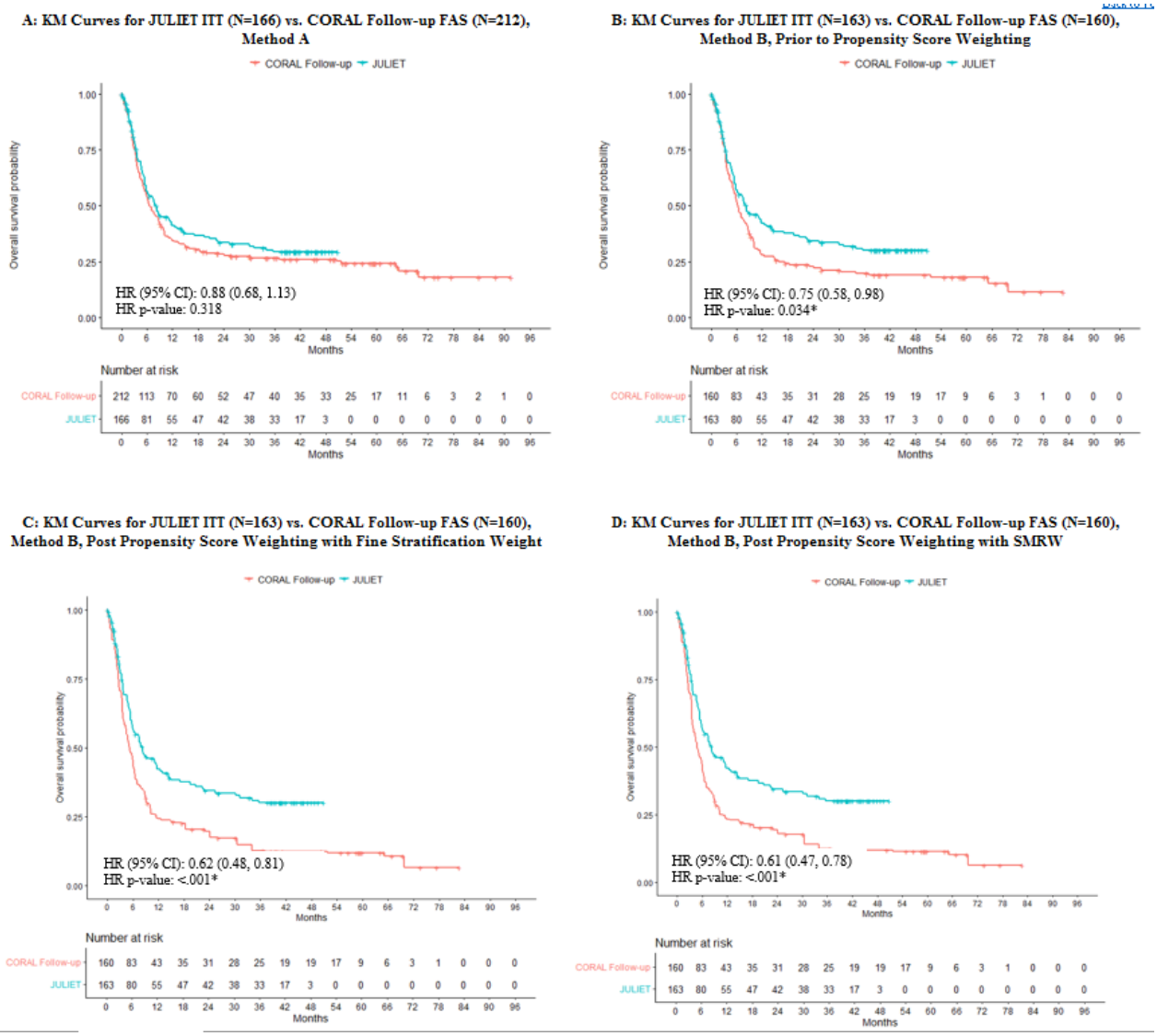
[8] The number of relapses was defined as the total number of lines prior to the index treatment where patient had a CR or PR as the response and relapsed later.

[9] ECOG was not included in method B adjustment due to missing percentage >30%.

[10] ECOG performance status were assessed within three months prior to or on the index date for CORAL follow-up.

[11] The IPI includes the following risk factors: age > 60 years, elevated lactate dehydrogenase level, stage III or IV disease, ECOG performance status ≥2, and two or more extranodal sites. "≥ 2 risk factors" means that a subject has equal to or greater than 2 non-missing risk-factors. "< 2 risk factors" means that a subject has 0 or 1 risk factor if all five factors are non-missing OR 0 risk factor among the 4 non-missing factors and one missing factor. "Missing" means that a subject has insufficient information to be classified into any of the above two categories.

A weighed Cox (for OS) or logistic regression model (for ORR) based on PS weights was next used to calculate the average treatment effect in the treated (ATT) between tisagenlecleucel and salvage therapy. The bootstrapping approach was used to estimate the standard error (SE) of treatment effect after weighting for all study endpoints, as it provided the most accurate SE estimates according to Austin et al. (2016) (21). The summary of the results is presented in Figure 11 and Table 6.




**corresponding HRs (95%CI) for mITT population, ASCT as index included in CORAL FU FAS: A: 0.74 (0.55, 0.98), B: 0.61 (0.45, 0.82), C: 0.53 (0.39, 0.74), D: 0.55 (0.39, 0.75)*

***corresponding HRs (95%CI) for ITT population, ASCT as index excluded from CORAL FU FAS: A: 0.68 (0.52, 0.88), B: 0.65 (0.49, 0.85), C: 0.56 (0.41, 0.73), D: 0.54 (0.41, 0.70)*

*** corresponding HRs (95%CI) for mITT population, ASCT as index excluded from CORAL FU FAS: A: 0.56 (0.42, 0.76), B: 0.53 (0.39, 0.72), C: 0.48 (0.35, 0.66), D: 0.50 (0.35, 0.68)*

*Figure 11 Summary of ITC overall survival (OS) results, ITT population*, ASCT as index included** in CORAL FU FAS.*

*Table 6 Summary of ITC objective response rate (ORR) results*

| Method | JULIET | CORAL Follow-up | Risk Ratio (JULIET vs. CORAL Estimate | 95% CI | P-value |
|---|---|---|---|---|---|
| **JULIET ITT vs CORAL follow-up FAS (including ASCT as index treatment)** | | | | | |
| *CORAL follow-up index line selected using method A - Unadjusted line selection* | | | | | |
| Univariable Logistic regression | | | **0,94** | **(0.71, 1.26)** | **0.699** |
| N | 146 | 212 | | | |
| ORR, (%) | 37 % | 39 % | | | |
| *CORAL follow-up index line selected using method B - PS mediated line selection (post PS weighting)* | | | | | |
| Logistic regression with fine stratification weight based on PS | | | **1,39** | **(0.97, 2.20)** | **0.119** |
| N | 143 | 160 | | | |
| ORR, (%) | 38 % | 27 % | | | |
| Logistic regression with SMRW based on PS | | | **1,53** | **(1.04, 2.31)** | **0.038*** |
| N | 143 | 160 | | | |
| ORR, (%) | 38 % | 25 % | | | |
| **JULIET mITT vs CORAL follow-up FAS (including ASCT as index treatment)** | | | | | |
| *CORAL follow-up index line selected using method A - Unadjusted line selection* | | | | | |
| Univariable Logistic regression | | | **1,41** | **(1.08, 1.83)** | **0.012*** |
| N | 98 | 212 | | | |
| ORR, (%) | 55 % | 39 % | | | |
| *CORAL follow-up index line selected using method B - PS mediated line selection (post PS weighting)* | | | | | |
| Logistic regression with fine stratification weight based on PS | | | **2,03** | **(1.48, 3.16)** | **<.001*** |
| N | 95 | 160 | | | |
| ORR, (%) | 57 % | 28 % | | | |
| Logistic regression with SMRW based on PS | | | **2,20** | **(1.56, 3.33)** | **<.001*** |
| N | 95 | 160 | | | |
| ORR, (%) | 57 % | 26 % | | | |
| **JULIET ITT vs CORAL follow-up FAS (excluding ASCT as index treatment)** | | | | | |
| *CORAL follow-up index line selected using method A - Unadjusted line selection* | | | | | |
| Univariable Logistic regression | | | **1,25** | **(0.89, 1.75)** | **0.200** |
| N | 146 | 162 | | | |
| ORR, (%) | 37 % | 30 % | | | |
| *CORAL follow-up index line selected using method B - PS mediated line selection (post PS weighting)* | | | | | |
| Logistic regression with fine stratification weight based on PS | | | **1,72** | **(1.17, 3.02)** | **0.025*** |
| N | 143 | 132 | | | |
| ORR, (%) | 38 % | 22 % | | | |
| Logistic regression with SMRW based on PS | | | **1,91** | **(1.25, 3.16)** | **0.006*** |
| N | 143 | 132 | | | |
| ORR, (%) | 38 % | 20 % | | | |
| **JULIET mITT vs CORAL follow-up FAS (excluding ASCT as index treatment)** | | | | | |
| *CORAL follow-up index line selected using method A - Unadjusted line selection* | | | | | |
| Univariable Logistic regression | | | **1,86** | **(1.35, 2.56)** | **<.001*** |
| N | 98 | 162 | | | |
| ORR, (%) | 55 % | 30 % | | | |
| *CORAL follow-up index line selected using method B - PS mediated line selection (post PS weighting)* | | | | | |
| Logistic regression with fine stratification weight based on PS | | | **2,39** | **(1.69, 4.11)** | **<.001*** |
| N | 95 | 132 | | | |
| ORR, (%) | 57 % | 24 % | | | |
| Logistic regression with SMRW based on PS | | | **2,64** | **(1.83, 4.29)** | **<.001*** |
| N | 95 | 132 | | | |
| ORR, (%) | 57 % | 22 % | | | |

*NoMA's assessment*

ITT (enrolled) vs mITT (infused) population in JULIET

In the original assessment, Novartis evaluated the mITT population in their base case but NoMA considered both populations (enrolled and infused) of JULIET to be relevant for the STA. In the updated submission, Novartis chose the ITT population for their base case. The company claims that the mITT population presents a lower end of the expected population treated, as the proportion of patients receiving infusion has increased significantly since the JULIET trial. This is due to two reasons. The production capacity has increased and in the trial period, patients with pedALL were chosen before DLBCL patients, if only one production slot was available. On the other hand, a 100% infusion rate is still not possible, as patients can die before Kymriah is produced and further, the production might not (in rare cases) yield a product that meets the T-cell count requirement per bag.

*NoMA chooses to present the results for both populations in this updated report in order to remain consistent with the original assessment. Moreover, none of the populations on their own provide a*

*sufficient picture of the clinical efficacy likely to be observed in Norwegian clinical practice. In the JULIET study, limited manufacturing capacity in the early phases of the trial, caused treatment delays. Patient who could not tolerate such a delay dropped out of the trial or died prior to receiving tisagenlecleucel (approximately one third). This enriched the mITT analysis set for patients with a less severe prognosis, meaning that the efficacy estimates from the mITT population would likely be overestimated. In the recently published BELINDA trial, evaluating the efficacy of tisagenlecleucel for aggressive lymphoma patients in an earlier treatment line (see section 4.2), 95.7% of patients enrolled in the tisagenlecleucel group were infused. Furthermore, data from the real-world setting indicates that >80% of patients who undergo apheresis will also receive tisagenlecleucel. This suggests that, with the improved manufacturing capacity, loss of patients prior to infusion may be less pronounced also in clinical practice. The ITT population, comprising a large proportion of non-infused patients may as such not be fully representative for Norwegian clinical practice, and efficacy estimates for this population are likely to be conservative. Thus, both costs and effects are believed to lie somewhere in between the ITT and mITT population estimates.*

ITT vs FAS population in CORAL

In the original assessment, Novartis had access only to aggregated data from the CORAL extension studies where survival was measured from the most recent relapse. This was a major limitation of the comparison with JULIET where survival was measured from enrollment or infusion. The misalignment of the survival starting points resulted in an immortal time bias that benefitted tisagenlecleucel.

In this updated submission, Novartis gained access to individual patient level data from the CORAL extension studies that allowed them to select a more comparable survival starting point. Novartis selected the FAS population as a base case, whereas the ITT population was used in sensitivity analyses. The FAS population included patients who received a third line or above (3L+) treatment and survival was measured from the initiation of the index treatment. The ITT population included patients who were "candidates" to receive a 3L+ treatment. For those patients without a documented 3L+ treatment, the index date (i.e. the starting date of the survival analysis) was date of relapse from last line.

*NoMA agrees that the FAS population of CORAL extension studies is more aligned with the JULIET trial.*

With or without ASCT

Novartis's base case analysis excluded patients who received ASCT as index treatment in the CORAL FU FAS, as patients ineligible for ASCT were recruited in JULIET. As a result, 50 ASCT patients were excluded from CORAL FU FAS and only patients who received a subsequent alloSCT were retained (18/162 (11.11%, unadjusted analysis) and 14/132 (10.61%, adjusted analysis).

NoMA disagreed that patients with ASCT as index should be excluded from CORAL FU FAS. The eligibility criteria for JULIET ensured the enrolment of patients with a particular fitness and life expectancy (i.e. patients with no major co-morbidities, no major organ dysfunction and a life expectancy of 12 weeks or more). As per inclusion criteria and reported age (median 56.1 (max 75.7)), it can be expected that there would be considerable overlap in terms of patient fitness required for JULIET and patient fitness required for ASCT (i.e. patients who were fit enough for enrollment in the JULIET trial could also be fit enough for ASCT).

Transplant ineligibility was not defined in the JULIET trial. It is thus understood that patients were considered transplant ineligible (as per inclusion criteria) simply due to being relapsed/refractory (or having failed to mobilise stem cells) to two or more prior treatment lines. NoMA does not agree to this

assumption, which would suggest that in clinical practice 3rd or later line salvage chemotherapy is administered only with a palliative intent. Rather, in clinical practice patients who are fit enough might receive a non-cross resistant salvage therapy at third (or later) line, with a view to proceed to ASCT. This is supported by several publications (4-6, 22), demonstrating that responses to salvage chemotherapy can be achieved also beyond the 2nd line setting, with the possibility of offering ASCT in 3rd or later line. In both the SCHOLAR-1 study (described in the original submission(6)) and the CORAL extension trial of patients failing 2nd line salvage (5), the subsequent SCT rates were approximately 30%, whereas in the post-ASCT setting a subsequent SCT rate of 21% was reported (4). Whereas it is understood that the anticipated transplant rate in clinical practice would be substantially lower, such a "real world estimate" reflects the whole r/r DLBCL 3rd and later line population (including older and sicker patients, such as those with ECOG grades 2-4). It is however, considered unlikely to accurately reflect the specific patient population enrolled in the JULIET trial.

Furthermore, in the JULIET trial tisagenlecleucel was not intended as a bridge to transplant, and none of the responding patients were subsequently transplanted. Still, a total of seven non-responding patients proceeded to transplant (6 allo-SCT), indicating that the JULIET population may indeed comprise a population fit for SCT.

Since the submission relies on non-randomised comparisons, it is essential that the external control arm reflects the population enrolled in JULIET as closely as possible. In this regard, Novartis' focus on a population whom treatment at a 3rd or greater line is given solely with palliative intent is considered overly restrictive. Furthermore, consideration should be given to which patients are likely to be candidates for tisagenlecleucel in Norwegian clinical practice. In this regard, it is noted that the approved indication for tisagenlecleucel does not restrict the population in terms of transplant eligibility.

Hence the uncertainty surrounding the choice of comparator data may also take into account the generalizability to the population who would potentially receive tisagenlecleucel if made available. This includes patients eligible for SCT.

Thus, NoMA requested an updated analysis for the following scenario:

- Salvage chemotherapy+HDCT+ASCT should be counted as one treatment line, and patients receiving such treatment as their index line should be retained in CORAL FU FAS. Endpoints should be measured from the time of initiation of salvage therapy.

In the updated analysis, 50/212 patients (23.58%, unadjusted analysis) and 28/160 patients (17.50%, adjusted analysis) who received ASCT as index or later line were retained in the CORAL follow-up FAS population. There were also 18 (8.49%) and 14 (8.75%) patients, respectively, who received alloSCT as subsequent treatment. In total, 32% and 26% of patients, respectively, received SCT in CORAL follow-up FAS.

*NoMA chooses to retain patients who received ASCT as an index treatment in CORAL FU FAS.*

<u>Unadjusted vs adjusted comparisons, ASCT as index treatment retained</u>

In the CORAL FU FAS, a total of 25 patients received more than one treatment line and could thus be distributed to different index lines in the indirect comparisons. Two comparisons were conducted using different criteria to assign patients to their index treatment. For Method A (unadjusted line selection), the goal was to align the number of prior treatment lines as closely as possible. All patients in the CORAL FU FAS were thus retained (n=212), without adjustment for confounding factors. For Method B (Propensity score (PS) mediated line selection), the goal was to reduce the differences in confounders (based on PSs),

with subsequent adjusted comparisons being conducted between the two cohorts. Method B excludes 52 patients from the CORAL FU FAS (n=160, based on JULIET ITT vs CORAL FU FAS, including ASCT) due to missing data on one or more of the confounders selected for PS weighting (LDH, n=51, Ann Arbour stage, n=46, EN site involvement, n=44 and time to 2L start after diagnosis, n=1).

For both methods; method A and method B prior to PS weighting, there is an imbalance between the JULIET ITT population and the CORAL FU FAS population for many reported baseline characteristics. According to the clinical experts consulted by NoMA, mainly these imbalances indicate that the CORAL FU FAS population have more favorable disease characteristics compared to the JULIET ITT population, thus suggesting the efficacy outcomes for the comparator arm may be overestimated. Following PS adjustment (Method B), these differences are reduced, although some imbalances remain (Table 5). The parameters included in the PS weighting are considered relevant by the clinical experts and are considered to capture the most important disease related prognostic factors. The lack of adjustment for ECOG status is however considered a limitation. In addition to ECOG status, data on several other inclusion/exclusion criteria used for the JULIET trial (including data on co-morbidities) are to a large extent missing for the CORAL FU FAS. The importance of these factors has been recently highlighted in publications documenting CD19 directed CAR-T therapies in the real-word setting. Such studies indicate that up to 50% of patients receiving CAR-T therapy in clinical practice would not fulfill the inclusion criteria implemented in the pivotal CAR-T trials. For patients with comorbidities (assessed by the Cumulative Illness Rating Scale (CIRS)) and/or patients not fulfilling the pivotal trial eligibility criteria, overall response rates appear similar but complete response rates and time to event endpoints are inferior (23, 24). Thus, the inability to compare and adjust for such comorbidities in the indirect treatment comparisons is considered a major limitation.

The baseline characteristics for the two CORAL FU FAS populations (Method A and Method B after missing data removal and prior to PS weighting) are mostly comparable, particularly when assessing the proportion of patients with non-missing data from Method A. This indicates that redistribution of patients (to a different main treatment line) by PS mediated line selection (Method B) had limited impact in terms of reducing the differences in baseline characteristics between the CORAL FU FAS and JULIET populations.

The main difference between the two methods is related to the exclusion of patients with missing data as well as the possibility to conduct subsequent PS adjusted comparisons (Method B). The exclusion of patients with missing data would be acceptable if data were missing at random. In this regard, there is a concern that, compared to the overall CORAL population, a somewhat larger proportion of the excluded patients were aged less than 60 years at diagnosis (i.e. 86.5% of excluded patients compared to 81.6% in the CORAL Method A cohort). Furthermore, there is a concern that, when moving from method A to B, only 56% (28/50) of patients having ASCT as their index line is retained in the analysis.

The KM plots for OS demonstrate that when moving from Method A to Method B the HR is reduced from 0.88 (95% CI: 0.68, 1.13, JULIET ITT vs CORAL FU FAS) to 0.75 (95% CI: 0.58, 0.98), prior to PS adjustment (Figure 11). Acknowledging the uncertainty due to limited patient numbers, this magnitude of change in HR is similar to that observed following the PS weighting of method B (HR 0.62 (95% CI: 0.48, 0.81), fine stratification weight), thus indicating that the excluded patients have a similar impact on the relative efficacy estimates as does the adjustment for confounders. In the analyses excluding patients having ASCT as their index line, there is no such difference in the HR between method A and method B (prior to PS weighting). Thus, overall this indicates that the excluded patients (method B) constitute a subset of patients with a more favorable prognosis, including a large proportion of the transplanted patients.

This concern is further substantiated by the somewhat pessimistic OS KM curves for the CORAL Method B (post PS matching) cohort. The five year survival of < 10% (as modelled) is lower than the long-term

survival reported in a published retrospective cohort of patients with refractory DLBCL (SCHOLAR-1) (25) and lower than that reported in the Oslo University Hospital (OUS) Lymphoma Register for DLBCL patients after second relapse (approximately 18%) (1). Again, whereas the adjustment for important disease characteristics may partly explain the pessimistic CORAL estimate, there is no adjustment for the multimorbidity encountered in the real-world setting but not being present in JULIET. Thus, it is considered implausible that the RWE would provide substantially more optimistic results compared to the CORAL external control.

**In summary**, there is an imbalance in reported baseline disease characteristics between the JULIET populations (ITT and mITT) and the CORAL FU FAS population. Mostly these imbalances favor CORAL, thus indicating that any naïve comparisons could be too conservative. PS adjustment for these imbalances could reduce bias in the indirect treatment comparisons, and potentially provide a more reliable estimate of relative efficacy. However, the adjusted comparison provided (Method B) has two major limitations.

First, whereas the method is able to adjust for relevant disease characteristics, data on other important inclusion/exclusion criteria (including comorbidities) are to a large extent missing. The JULIET population was selected based on certain fitness and life expectancy criteria (i.e. ECOG 0-1, no major organ dysfunction, no major co-morbidities, no CNS involvement, life expectancy of ≥12 weeks etc.). It is therefore likely that lack of adjustment for the missing characteristics will introduce bias in favor of tisagenlecleucel.

Second, the PS method required the exclusion of 25% of the CORAL FU FAS cohort, due to missing data. Notwithstanding the limited patient numbers, the KM OS plots indicate a large sensitivity of the relative treatment effect to the removal of these patients. Thus, there is a concern that data was not missing at random, but rather the excluded patients may represent a subset with a more favorable prognosis. Again, this would bias the comparison in favor of tisagenlecleucel. In addition, the comparator OS curves estimated by method B were more pessimistic that those reported in the real-world setting. The main advantage of method A compared to method B is that the subset of patients with a more favorable prognosis are not excluded from the analysis, thereby avoiding an important source of selection bias introduced by method B. NoMA also notes that the long-term OS curves of the comparator arm appear more clinically plausible, as they are better aligned with reported RWD (SCHOLAR- 1 and OUS Lymphoma Register for DLBCL patients). However, method A does not adjust for the known imbalances in baseline disease characteristics.

According to the clinical experts consulted, there is a concern that none of the two methods will provide sufficiently reliable relative efficacy estimates, and preferably none of the methods should be used for the CUA. Instead, the clinical experts would prefer an indirect treatment comparison based on more recent real-world data, including an age adapted approach. If having to choose between Method A and Method B, Method B would be considered the preferred option, as it allows adjusting for baseline characteristics.

NoMA agrees there are major limitations associated with both the provided comparisons. However, NoMA anticipates that patient level data from the real-world setting would be difficult to derive and would likely be hampered by the same limitations as those observed for CORAL.

Concerning the provided comparisons, due to the major limitations highlighted above, the magnitude and direction of bias for the two methods cannot be readily ascertained. Both methods are therefore considered complementary, providing a rough quantification of the uncertainty of the relative efficacy estimates.

*Thus, NoMA chooses to use both methods (Method A and Method B) for the estimation of relative efficacy.*

*Table 7 Simplified overview of the limitations associated with the two indirect comparisons (Method A and Method B). Orange = indicates relative efficacy for tisagenlecelucel vs comparator could be overestimated. Green = indicates relative efficacy for tisagenlecleucel vs comparator could be underestimated.*

| **CORAL FU FAS** | **Method A, no PS weighting** | **Method B, pre PS weighting** | **Method B, post PS weighting** |
|---|---|---|---|
| Sample size | 212 | 160 | 160 |
| Bias due to imbalance in baseline disease-related characteristics between CORAL and JULIET[a] | Yes | Yes | Yes, but reduced |
| Bias due to imbalance in patient-related baseline characteristics between CORAL and JULIET[b] | Unknown | Unknown | Unknown |
| Potential bias due to the exclusion of patients with missing data.<br><br>HR between CORAL FU FAS and JULIET ITT, ASCT as index treatment retained. | No, all patients were retained in the analysis.<br><br>HR for OS: 0.88<br>(95% CI: 0.68, 1.13) | Yes, 25% of patients were excluded due to missing data.<br><br>HR for OS: 0.75<br>(95% CI: 0.58, 0.98 | Yes, 25% of patients were excluded due to missing data.<br><br>HR for OS: 0.62<br>(95% CI: 0.48, 0.81) |
| Consistency of the CORAL long-term survival estimates compared to:<br>SCHOLAR-1 (about 20% long term survival)<br>OUS lymphoma registry (about 18% long term survival). | Yes,<br>About 20% long term survival. | No<br>About 10% long term survival. | No<br><10% long term survival. |

*[a] Disease characteristics adjusted for in the PS weighting: age at diagnosis, Ann Arbor disease stage, extranodal site involvement, serum LDH level, status of disease (relapsed vs. refractory to all lines vs. refractory to last line), time to initiation of 2L after diagnosis, prior HSCT, and number of relapses.*

*[b] Inclusion/exclusion criteria of the JULIET trial not included in the PS weighting: Inclusion criteria: Life expectancy ≥ 12 weeks, ECOG 0 or 1, adequate renal, hepatic, pulmonary, and cardiac functions, adequate bone marrow reserve without transfusions. Exclusion criteria: Active neurological auto immune or inflammatory disorders, active CNS involvement by malignancy, active replication of or prior infection with hepatitis B or active hepatitis C, human immunodeficiency virus-positive patients, uncontrolled acute life threatening bacterial, viral or fungal infection, unstable angina and/or myocardial infarction within 6 months prior to screening, cardiac arrhythmia not controlled with medical management, previous or concurrent malignancy.*

Fine stratification vs SMRW

Novartis chose the SMRW approach for their base case. The reasoning behind this, is that fine stratification uses quintiles of propensity score and is useful to avoid large weights of extreme values, whereas SMRW uses propensity scores as continuous variables. In these datasets, there are no variables with extreme values and the precision and better matching obtained through SMRW is therefore favorable.

*NoMA accepts the use of SMRW.*

Conclusions

*The access to patient-level data from CORAL extension studies and the PS-adjusted analysis did not resolve the imbalance in patient characteristics between JULIET and the comparator study. The ITC presented in the updated submission addresses, however, the issue of a lead time bias. Overall, NoMA accepts this comparison but points out that uncertainties around the size of the relative effect between tisagenlecleucel and salvage therapy remain due to issues of comparability of the studies' populations. NoMA chooses to use both methods (Method A and Method B, SMRW) for the estimation of relative efficacy.*

## 4.5 EXTRAPOLATION OF TISAGENLECLEUCEL OS AND PFS BASED ON UPDATED JULIET DATA

### 4.5.1 Original submission

*Overall survival (OS)*

In the original submission (1), Novartis chose to use the standardized mortality ratio (SMR) applied to the end of KM data or a mixture cure model (MCM) to extrapolate OS. The cure model is based on the assumption that the patient population consists of a mix of patients who end up cured and patients who are bound to die (26-28). 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. 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 the comparator.

NoMA did not accept these approaches as the application of SMR or MCM implied the beginning of a survival plateau after 28.9 months, i.e. the duration of JULIET's follow-up at DCO of 21-May-2018. Although both the CORAL extension studies and SCHOLAR-1 (6) provide support for a long-term prognosis for a proportion of the patients in this disease setting, a survival plateau was not observed as early as after 28.9 months as assumed in the analysis by Novartis. Therefore, NoMA did 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 the data. Instead, NoMA chose a spline model with two knots to extrapolate OS in the tisagenlecleucel arm. The mortality from the comparator arm was applied to the tisagenlecleucel arm at the end of follow-up time in JULIET in order to prevent a situation where the long-term mortality in JULIET is higher than in the CORAL extension studies. The Gompertz function was selected to extrapolate OS in the salvage therapy arm as this was the only function that reflected a mortality rate that converges to the mortality rate in the general population over a longer time horizon as observed in the literature (6, 29, 30). The maximum between the mortality rate as predicted by the Gompertz function and the general Norwegian population was selected.

*Progression-free survival (PFS)*

To extrapolate PFS in the tisagenlecleucel arm, Novartis chose log-logistic MCM. Since PFS data were not available in the CORAL extension studies, PFS was derived from OS by applying a ratio of 0.65. The PFS:OS ratio was estimated based on the average of R-ICE and R-DHAP arms in the CORAL randomised trial (31). 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.

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 the salvage therapy arm, NoMA preferred to use a PFS:OS ratio based on parametric functions for PFS and OS selected by NoMA in the tisagenlecleucel arm. NoMA considered the lack of direct evidence on PFS in the CORAL extension studies to result in considerable uncertainty with regards to the magnitude of the correlation and the changes in magnitude over time.

*Table 8 Novartis's base case in the original and updated submission together with NoMA's preferred assumptions.*

| Parameter | Novartis's base case in the original submission (1) | NoMA's base case in the original submission (1) | Novartis's base case in the updated submission |
|---|---|---|---|
| **Based on:** | ***DCO 21.05.2018*** | | ***DCO July 2019 for PFS<br>DCO Feb 2020 for OS*** |
| **Population tisagenlecleucel** | Infused set (mITT) | Enrolled (ITT) and infused set (mITT) | Enrolled set (ITT) |
| **Source of comparator data** | Pooled CORAL extension studies data, not adjusted for "lead-time" bias | Pooled CORAL extension studies data, adjusted for "lead-time" bias | Patient-level data from CORAL extension studies |
| **OS tisagenlecleucel** | Log-logistic mixture cure model (MCM).<br><br>After year 5, mortality rate from projected CORAL extension studies was considered for both treatment arms | Spline model with 2 knots constrained by the PFS curve<br><br>Mortality rate as modelled for the comparator arm from point of convergence<br><br>Long-term survivors experience excess mortality as observed in DLBCL studies with longer follow-up | The relative effect expressed as a HR of 0.5 derived from a propensity score-adjusted comparison, method B using SMRW.<br><br>Mortality rate from the projected comparator arm from month 44. |
| **PFS tisagenlecleucel** | Log-logistic MCM<br><br>No convergence with OS during time horizon, i.e. a high proportion of progressed patients were predicted to be alive after 20 years | Spline model with 2 knots.<br><br>Convergence with OS before month 50 post-treatment. | Spline model with 2 knots.<br><br>PFS was constrained by OS from year 5. |
| **OS chemotherapy** | Log-logistic MCM | Gompertz function | Spline model with 2 knots. |
| **PFS chemotherapy** | Based on the modelled ratio between OS and PFS from the CORAL randomised study (31). | Based on the modelled ratio between OS and PFS for tisagenlecleucel | Based on the modelled ratio between OS and PFS for tisagenlecleucel |

### 4.5.2 Updated submission

The current updated submission is based on updated PFS (DCO July 2019) and OS (DCO Feb 2020) data from JULIET as well as updated relative effect vs salvage therapy based on individual patient data from the CORAL extension studies. Novartis selected the comparison between the ITT JULIET population vs the CORAL FU FAS population for their base case. In the submitted cost-utility model, the relative effect is expressed in terms of hazard ratios (HR) obtained from the propensity score-adjusted ITC (i.e. method B) using SMRW. Patients with ASCT as index treatment were excluded from CORAL FU FAS.

Novartis chose a spline model with 2 knots to extrapolate OS in the salvage therapy arm. A HR of 0.5 is then applied to derive OS in the tisagenlecleucel arm. Similarly, a spline model with 2 knots is used to extrapolate PFS in the tisagenlecleucel arm. A HR between tisagenlecleucel's PFS and OS is used to model PFS in the salvage therapy arm. The mortality rate from the CORAL extension studies was applied from month 44. PFS was constrained by OS from year 5. The maximum between the mortality rate as predicted by spline models and the general UK population was selected. The resulting long-term extrapolation is presented in Figure 12 below.

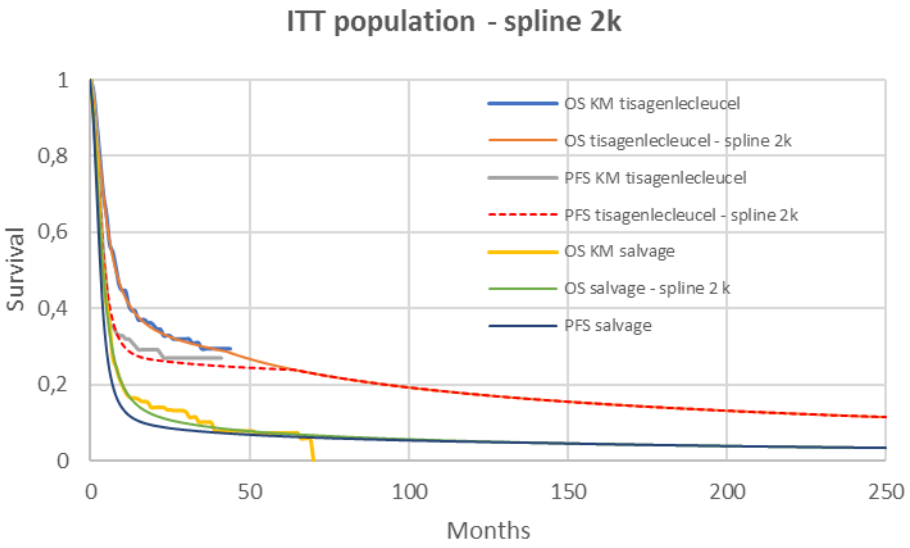
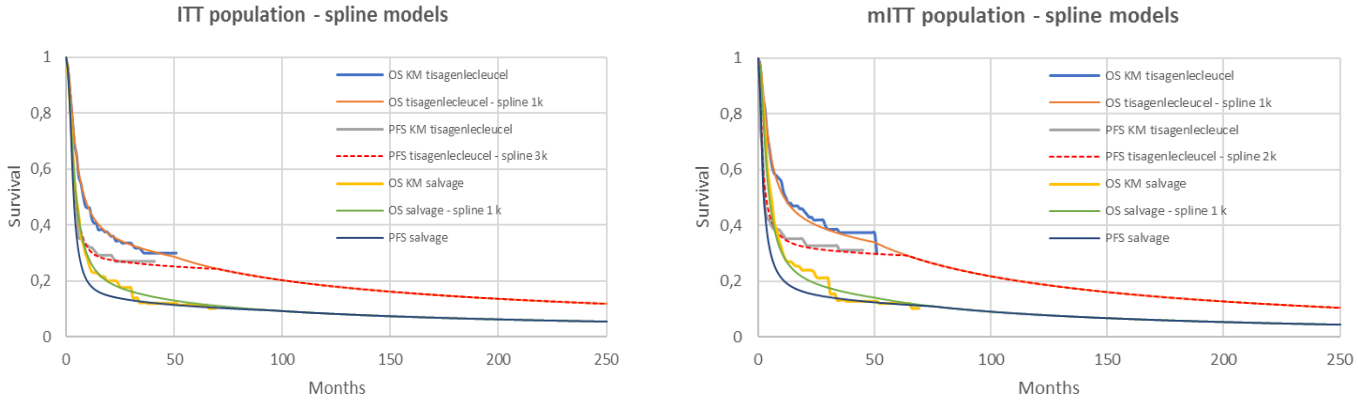



*Figure 12 Parametric functions chosen in Novartis's base case. OS relative effect is based on a HR of 0.5 (method B, SMRW). The PFS curve for the salvage therapy arm is based on the PFS:OS ratio from JULIET. ASCT as index excluded from CORAL FU FAS.*

Upon request from NoMA, Novartis submitted a second version of the cost-utility model where parametric functions were fitted individually to each treatment arm, i.e. without applying a HR. An updated model was requested for both the ITT and mITT population, with survival curves derived from Method A as well as Method B, SMRW. In addition, NoMA requested that patients with ASCT as index treatment are retained in the CORAL FU FAS, as well as patients with 30% missing data on covariates (see chapter 4.4). For these scenarios, Novartis used spline models for each parametrisation as these had the best statistical fit and a good visual fit. The mortality rate from the CORAL extension studies was applied from month 51. PFS was constrained by OS from year 5. The maximum between the mortality rate as predicted by spline models and the general UK population was selected. The resulting long-term extrapolation is presented in Figure 13.

*Method B, PS-adjusted ITC, SMRW*




*Method A, unadjusted ITC*

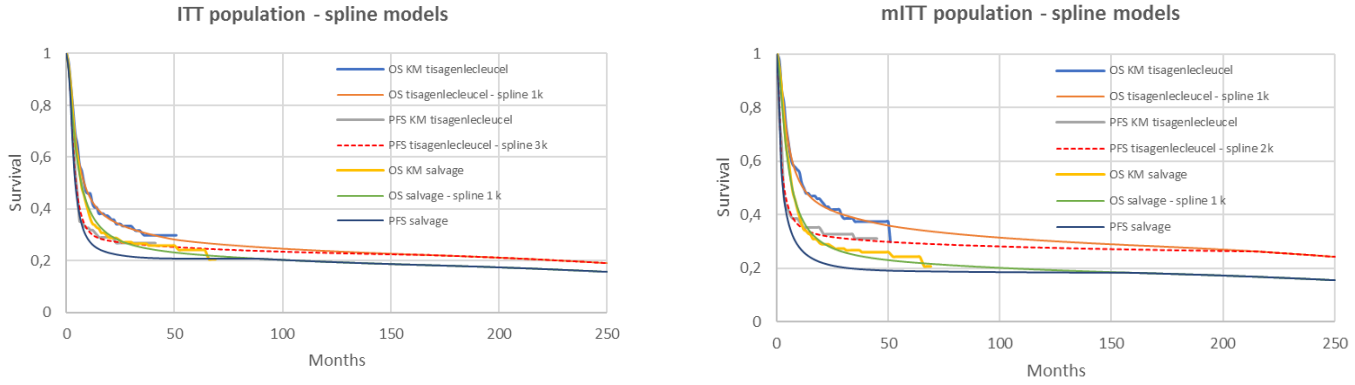



*Figure 13 Individually fitted parametric functions to survival data based on CORAL FU FAS with ASCT as index retained. ITC via method B, SMRW (top panel) and method A (bottom panel). JULIET ITT, left, JULIET miTT, right. Mortality rate from the CORAL extension studies was applied from month 51. PFS was constrained by OS from year 5. Specifications chosen by Novartis.*

*NoMA's assessment*

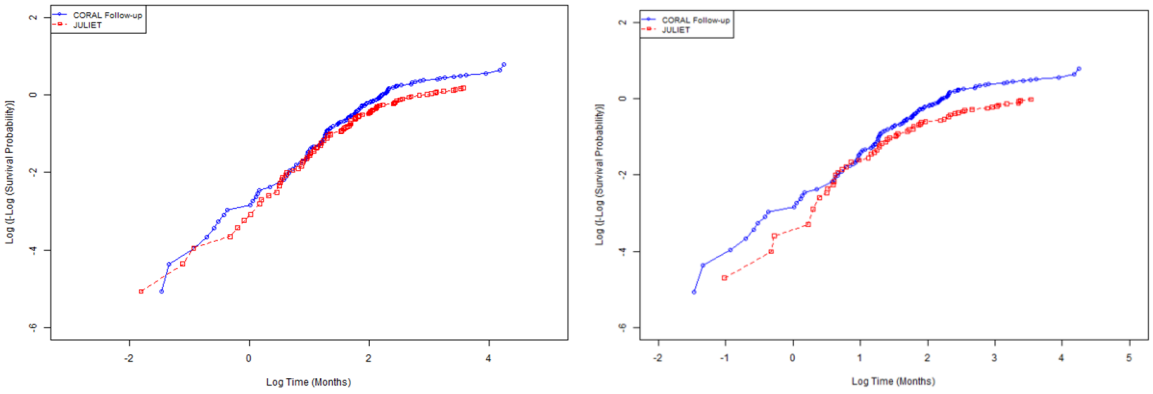
NoMA's selection of parametric curves is based on survival data from the CORAL FU FAS dataset which includes patients who received ASCT as index treatment. Survival data based on adjusted ITC (Method B, SMRW) as well as unadjusted ITC (Method A) were assessed. Both the ITT and mITT populations were considered. Novartis's choice of parametric functions for their preferred dataset (i.e. CORAL FU FAS without ASCT as index) is not assessed here, but the ICER results are presented in chapter 5.1.

*Proportional effect assumption*

Novartis provided log cumulative hazard plots (Figure 14), Schoenfeld residual plots and global p test results in order to assess whether the proportional hazard (PH) for OS holds. Although the horizontal pattern of Schoenfeld residuals and non-significant global p test (not shown) do not indicate a violation of the PH assumption for all the scenarios, the log cumulative hazard curves are not straight, and the hazard cannot be considered proportional. As per NoMA's guidelines, Novartis has also submitted diagnostic

plots for the acceptability of jointly fitted accelerated failure time (AFT) models, but the constant time effect assumption was not fulfilled either. Due to the different mechanisms of action as well as for improving consistency with the original assessment, NoMA selected independent modelling of the treatment arms.

*Method B, PS-adjusted ITC, SMRW*




*Method A, unadjusted ITC*

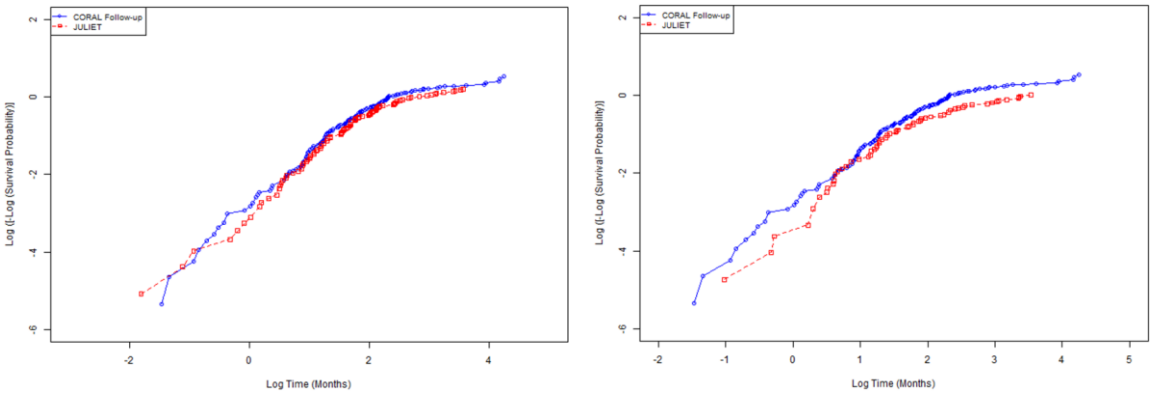



*Figure 14 Log cumulative hazard plots for OS. CORAL FU FASwith ASCT as index treatment retained, ITC via method B, SMRW (top panel) and method A (bottom panel). JULIET ITT, left, JULIET mTT, right.*

*<u>The choice of parametric functions</u>*

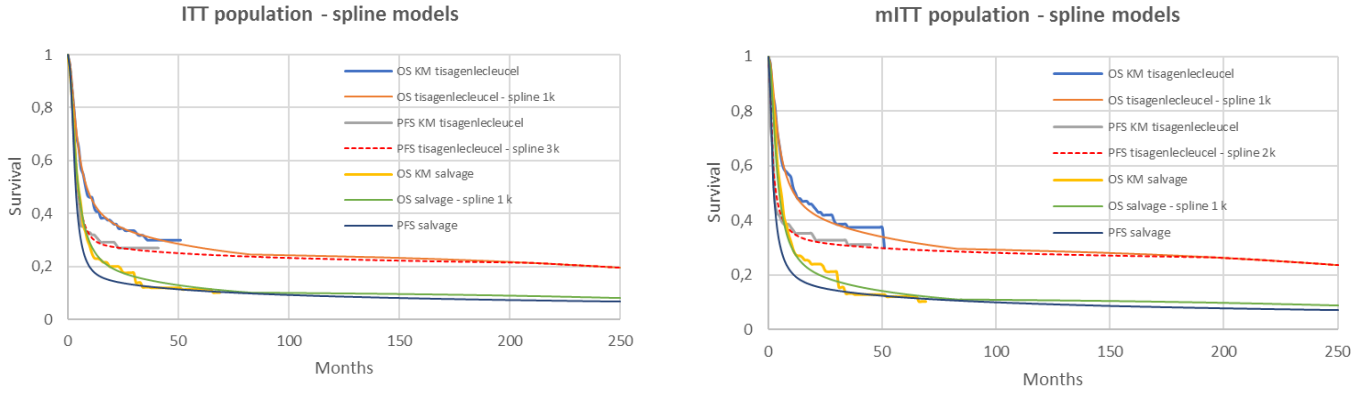
Novartis used spline models for OS and PFS parametrisation due to the best mathematical fit to the observed data according to AIC and BIC and good visual fit (Figure 13). The log cumulative hazard plots are not linear (Figure 14), which supports the use of more flexible functions than standard parametric functions. The AIC and BIC statistics supports the selection of a spline model with single knot for OS extrapolation in each arm and the visual fit is acceptable. For PFS in the tisagenlecleucel arm, Novartis selected a spline model with 3 knots for the ITT population and a spline model with 2 knots for the mITT population. These functions have the best mathematical fit in terms of AIC and a good visual fit.

*NoMA accepts the parametric functions selected by Novartis.*

*Long-term mortality assumptions*

Novartis has applied the mortality rate from CORAL FU FAS to the tisagenlecleucel arm from month 51, i.e. after the maximum follow-up time in JULIET. This resulted in pessimistic survival projections in the tisagenlecleucel arm compared to continuing the extrapolation with the spline models. It is understood that Novartis selected this option to be consistent with NoMA's original assessment. However, the current updated submission is based on OS data with 51 months of maximum follow-up compared to 31 months of maximum follow-up the original submission. Therefore, NoMA is of the opinion that the updated JULIET data with a maximum follow-up of 51 months is more informative for the extrapolation than the original submission with a maximum follow-up of 31 months, and that the projections obtained from the spline models should be used beyond month 51. This approach is also consistent with the recent updated Yescarta evaluation (25) where parametric curves were used until month 84 after which the general population mortality was applied. The turning point of month 84 was chosen as the potential "cure point" as the mortality rate in SCHOLAR-1, the source of comparator data in the Yescarta evaluation, converges towards general population mortality at that time. NoMA attempted to take the same approach in the current assessment of tisagenlecleucel but because of the steeper slope of the projected OS for salvage therapy based on CORAL FU FAS rather than on SCHOLAR-1, the convergence of the mortality rate from CORAL FU FAS to the general population mortality occurs at year 21 of follow-up (ITT population, Method B). In order to be consistent across HTAs, NoMA applied the general population mortality from month 84 in both arms (Figure 15).

*Method B, PS-adjusted ITC, SMRW*




*Method A, unadjusted ITC*

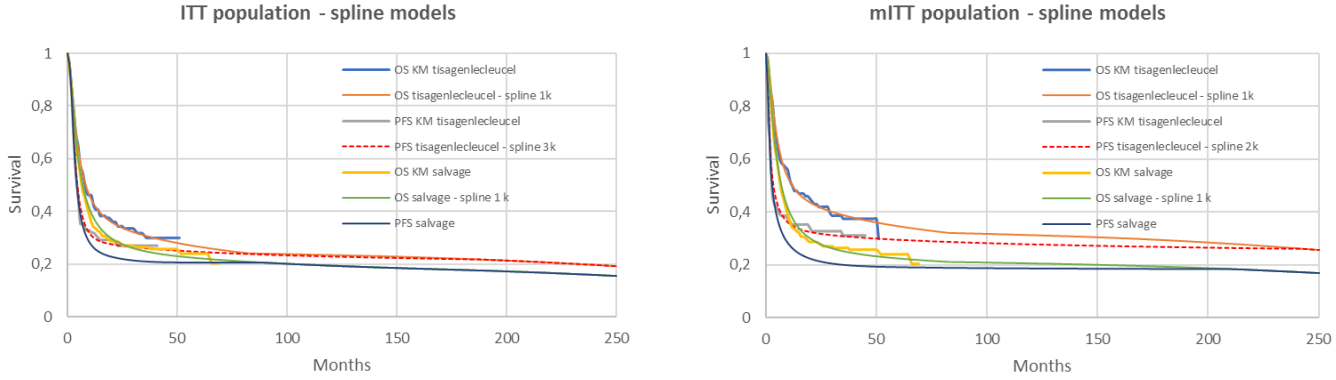



*Figure 15 NoMA's base case extrapolation : general population mortality applied to both arms from month 84. ITC via method B, SMRW (top panel) and method A (bottom panel). JULIET ITT, left, JULIET mTT, right. CORAL FU FAS with ASCT as index treatment retained.*

*Long-term PFS modelling*

When spline models are applied to PFS in the tisagenlecleucel arm, the projected PFS gradually merges with OS (with the exception of mITT population, method A) so that at about 84 months a very small proportion of progressed patients remain alive (post-progression survival equals the area between OS and PFS) (Figure 15). Those projections seem plausible as in JULIET 7/68 patients who progressed (FAS, DCO July 2019) survived up until 27 months. Consequently, NoMA accepts Novartis' assumptions for modelling long-term PFS.

*Summary*

NoMA's selection of parametric curves is based on survival data from the CORAL FU FAS dataset that includes patients who received ASCT as index treatment. In contrast, Novartis used the CORAL FU FAS dataset excluding patients who received ASCT as index treatment. NoMA considers both the mITT and ITT populations relevant for decision making, whereas Novartis used the ITT population in their base case. Lastly, NoMA used both CORAL FU FAS datasets; PS- adjusted (method B) and unadjusted (method A) as the source of OS data, whereas Novartis argues that PS-adjusted CORAL FU FAS dataset is more appropriate.

NoMA accepts the choice of spline models for OS and PFS extrapolation. For long-term mortality in both arms, NoMA prefers to use a more optimistic general mortality rate applied from month 84, rather than the projected CORAL FU FAS mortality from month 51.

## 4.6 UPDATED UTILITY ASSUMPTIONS

Health-state utilities are the same as in the original submission (0.83 for the PFS health state and 0.71 for progressed/relapsed disease). These utility values were derived by mapping SF-36 data from JULIET to utility values using the UK EQ-5D tariff. Disutility due to adverse events is also the same as in the original submission.

*NoMA's assessment*

NoMA accepts the utility inputs used in the updated submission.

## 4.7 UPDATED COST ASSUMPTIONS

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. In the updated submission, Novartis made the following changes to the cost inputs compared to the original submission:

- DRG rates were sourced from the latest DRG list from 2021

- Cost inputs have been adjusted for inflation, by using the change in healthcare-based consumer price index (CPI) change from the original submission (1.02965).
- Per patient hospitalisation cost for patients treated with Kymriah reduced from NOK 282 624 to NOK 98 565. This is based on the assumption that patients on average will spend 7 days in the hospital (general ward), and 7 days in the hospital hotel, whereas the original submission used JULIET trial data on the duration of the hospital stay (27.9 days at the general ward, and 0.9 days at the ICU).
- Duration of bridging chemotherapy for Kymriah patients reduced from 1.7 monthly cycles to 1 cycle, based on the assumption that patients treated with Kymriah are unlikely to receive more than 1 cycle of bridging chemotherapy in clinical practice.
- Cytokine release syndrome (CRS) costs have been reduced from NOK 309 774 to NOK 127 380, based on CIMBTR registry data on the mean ICU stay, ICU costs, tocilizumab use and average doses given.

*NoMA's assessment*

NoMA accepts the assumption that patients will spend 7 days in the hospital, and 7 days in the hospital hotel, which results in reduced hospitalisation costs. Clinical experts have stated that, based on their experience with tisagenlecleucel treatment, patients are unlikely to stay at the ICU for other reasons than severe CRS, which is already accounted for in the calculation of adverse event costs.

NoMA does not accept the assumed reduction in the duration of bridging chemotherapy for Kymriah patients. Bridging chemotherapy is likely to be correlated with the treatment effect as observed in the JULIET trial. Therefore, to retain consistency between costs and effects in the analysis, the duration of bridging chemotherapy should be 1.7 cycles as observed in the JULIET trial.

NoMA accepts the other updated cost assumptions by Novartis.

# 5 UPDATED HEALTH ECONOMICS RESULTS

## 5.1 NOVARTIS'S UPDATED BASE CASE

Results for tisagenlecleucel versus salvage chemotherapy from Novartis's base case analysis are presented in Table 9 for the ITT population, adjusted using method B. Extrapolation of OS is based on a proportional hazard approach, where a spline model with 2 knots is used for salvage chemotherapy, which is combined with a hazard ratio of 0.5 to derive OS for tisagenlecleucel. PFS for tisagenlecleucel was modelled using a spline model with 2 knots, while PFS for salvage chemotherapy was based on the modelled ratio between OS and PFS for tisagenlecleucel. The results are presented given list prices for tisagenlecleucel and salvage chemotherapy excl. VAT and discounted at a rate of 4% per year.

*Table 9 Results from Novartis's updated base case. ITT population (infused patients). List price for tisagenlecleucel and salvage chemotherapy excl. VAT.*

| | Tisagenlecleucel | Salvage chemotherapy | Difference |
|---|---|---|---|
| Total costs | 2 581 623 | 502 672 | 2 078 951 |
| Total QALYs | 3.14 | 1.10 | 2.45 |
| Total life years | 3.86 | 1.41 | 2.05 |
| Incremental cost per QALY gained | | | **1 014 766 NOK** |
| Incremental cost per life year gained | | | **847 160 NOK** |

## 5.2 NOMA'S UPDATED BASE CASE

NoMA has estimated the incremental cost-effectiveness ratios (ICERs) for tisagenlecleucel compared to salvage chemotherapy for the ITT population and the mITT population for both method A and method B resulting in 4 scenarios. Results for the ITT and mITT populations are presented in Table 11 and Table 12 for method A, and in Table 13 and Table 14 for method B, respectively. NoMA has also calculated deterministic model-averaged results, using equal weights (25%) for the 4 scenarios, which are given in Table 15. Results are reported per patient and discounted at a rate of 4% per year. In the ITT population, the efficacy of tisagenlecleucel is measured from the time of enrolment to account for the delay in manufacturing. 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. The summary of NoMA's remaining changes to Novartis's updated base case are presented in Table 10.

*Table 10 NoMA's changes to Novartis's updated base case*

| Parameter | Novartis's updated base case | NoMA's updated base case (only changes presented) |
|---|---|---|
| **Population** | Enrolled ITT | Infused (mITT) and enrolled (ITT) |
| **Comparator** | CORAL FAS excluding ASCT | CORAL FAS including ASCT, adjusted using method A and method B |
| **OS salvage chemotherapy** | Spline model with 2 knots. | Spline model with 1 knot until month 84, general population survival beyond month 84. |
| **OS tisagenlecleucel** | The relative effect expressed as a HR of 0.5 derived from a propensity score-adjusted comparison based on method B using SMRW.<br><br>Mortality rate from the projected comparator arm from month 44. | Spline model with 1 knot until month 84<br><br>General population survival beyond month 84. |
| **PFS tisagenlecleucel** | Spline model with 2 knots, constrained by OS. | Spline model with 3 knots for the ITT population and spline model with 2 knots for the mITT population, constrained by OS. |
| **PFS salvage chemotherapy** | Based on the modelled ratio between OS and PFS for tisagenlecleucel | Based on the modelled ratio between OS and PFS for tisagenlecleucel |
| **Duration of bridging chemotherapy** | 1 cycle | 1.7 cycles |
| **Background mortality** | Based on UK life tables | Based on Norwegian life tables |
| **Subsequent SCT rate salvage chemotherapy** | 29.85% ASCT, 10.46% allo SCT | - Method A: 23.58% ASCT, 8.49% allo SCT<br><br>- Method B: 17.50% ASCT, 8.75% allo SCT |
| **Subsequent SCT rate tisagenlecleucel** | 0.87% ASCT, 6.09% allo SCT | 0.87% ASCT, 6.09% allo SCT |

*Table 11 NoMA´s updated base case (ITT population, method A) per patient, discounted. List price for tisagenlecleucel and salvage chemotherapy excl. VAT.*

| | Tisagenlecleucel | Salvage chemotherapy | Difference |
|---|---|---|---|
| Total costs | 2,659,560 NOK | 640,457 NOK | 2,019,103 NOK |
| Total QALYs | 3.94 | 3.27 | 0.67 |
| Total life years | 4.84 | 4.06 | 0.79 |
| Incremental cost per QALY gained | | | **3,008,975 NOK** |
| Incremental cost per life year gained | | | **2,571,014 NOK** |

*Table 12 NoMA´s updated base case (mITT population, method A) per patient, discounted. List price for tisagenlecleucel and salvage chemotherapy excl. VAT.*

| | Tisagenlecleucel | Salvage chemotherapy | Difference |
|---|---|---|---|
| Total costs | 3,681,840 NOK | 696,832 NOK | 2,985,008 NOK |
| Total QALYs | 4.98 | 3.37 | 1.61 |
| Total life years | 6.17 | 4.20 | 1.97 |
| Incremental cost per QALY gained | | | **1,517,591 NOK** |
| Incremental cost per life year gained | | | **1,852,447 NOK** |

*Table 13 NoMA´s updated base case (ITT population, method B) per patient, discounted. List price for tisagenlecleucel and salvage chemotherapy excl. VAT.*

| | Tisagenlecleucel | Salvage chemotherapy | Difference |
|---|---|---|---|
| Total costs | 2,676,679 NOK | 641,721 NOK | 2,034,958 NOK |
| Total QALYs | 4.01 | 1.86 | 2.15 |
| Total life years | 4.94 | 2.36 | 2.58 |
| Incremental cost per QALY gained | | | **946,059 NOK** |
| Incremental cost per life year gained | | | **789,282 NOK** |

*Table 14 NoMA´s updated base case (mITT population, method B) per patient, discounted. List price for tisagenlecleucel and salvage chemotherapy excl. VAT.*

| | Tisagenlecleucel | Salvage chemotherapy | Difference |
|---|---|---|---|
| Total costs | 3,614,931 NOK | 659,438 NOK | 2,955,493 NOK |
| Total QALYs | 4.72 | 2.00 | 2.72 |
| Total life years | 5.80 | 2.54 | 3.27 |
| Incremental cost per QALY gained | | | **1,085,404 NOK** |
| Incremental cost per life year gained | | | **904,312 NOK** |

*Table 15 NoMA´s updated base case, per patient, discounted. Deterministic model-averaged results using equal weights for the following scenarios: 1) method A, ITT population, 2) method A, mITT population, 3) method B, ITT population, 4) method B, mITT population. List price for tisagenlecleucel and salvage chemotherapy excl. VAT.*

| | Tisagenlecleucel | Salvage chemotherapy | Difference |
|---|---|---|---|
| Total costs | 3,158,252 NOK | 659,612 NOK | 2,498,641 NOK |
| Total QALYs | 4.41 | 2.63 | 1.79 |
| Total life years | 5.44 | 3.29 | 2.15 |
| Incremental cost per QALY gained | | | **1,396,602 NOK** |
| Incremental cost per life year gained | | | **1,162,329 NOK** |

## 5.3 SCENARIO ANALYSES

NoMA has included 1 scenario in addition to the 4 scenarios presented in the previous chapter. The results for this scenario is presented for the deterministic model-averaged analysis.

*Table 16 Scenario analyses performed by NoMA. List price for tisagenlecleucel and salvage chemotherapy excl. VAT*

| | **Parameter** | **NoMA's base case** | **Scenario analyses** | **ICER in scenario analyses (NOK)** |
|---|---|---|---|---|
| | **NoMA's scenarios (Deterministic model-averaged)** | **See 5.2 for all changes** | **-** | **1,396,602** |
| 1 | Hospitalisation for treatment with tisagenlecleucel | Patients spend 7 days in the hospital (general ward), and 7 days in the hospital hotel.<br><br>Source: Clinical expert opinion | Patients spend 27.9 days in the hospital (general ward), and 0.9 days at the ICU.<br><br>Source: JULIET trial data | 1,498,715 |

# 6 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.

## 6.1 ESTIMATION OF THE NUMBER OF PATIENTS POTENTIALLY ELIGIBLE FOR TREATMENT

In the original assessment, clinical experts recruited by the regional health authorities have estimated that around 20 patients with r/r 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 17. The number of patients expected to be treated if Kymriah is not recommended is presented in Table 18.

*Table 17 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 18 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 |

## 6.2 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 using method A (the incremental costs for method B are similar and are therefore not presented). All changes by NoMA as described in chapter 5.2 are incorporated.

Drug costs in NOK per patient per year after treatment initiation according to scenario 1 are presented in Table 19 (ITT population) and Table 20 (mITT population).

*Table 19 Drug costs per patient per year after treatment initiation. List price, including VAT and undiscounted, ITT population, method A*

| | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 |
|---|---|---|---|---|---|
| Kymriah (tisagenlecleucel) | 2,732,223 | | | | |
| Salvage chemotherapy | 246,947 | | | | |

*Table 20 Drug costs per patient per year after treatment initiation. List price, including VAT and undiscounted, mITT population, method A*

| | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 |
|---|---|---|---|---|---|
| Kymriah (tisagenlecleucel) | 3,856,000 | | | | |
| Salvage chemotherapy | 246,947 | | | | |

Healthcare costs in NOK per patient per year after treatment initiation according to scenario 2 are presented in Table 21 (ITT population) and Table 22 (mITT population).

*Table 21 Healthcare costs per patient per year after treatment initiation. List price, including VAT and undiscounted, ITT population, method A*

| | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 |
|---|---|---|---|---|---|
| Kymriah (tisagenlecleucel) | 3,109,890 | 28,939 | 18,107 | 12,351 | 8,645 |
| Salvage chemotherapy | 592,698 | 20,845 | 15,427 | 9,651 | 6,671 |

*Table 22 Healthcare costs per patient per year after treatment initiation. List price, including VAT and undiscounted, mITT population, method A*

| | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 |
|---|---|---|---|---|---|
| Kymriah (tisagenlecleucel) | 4,274,730 | 34,146 | 25,810 | 20,205 | 16,560 |
| Salvage chemotherapy | 604,150 | 2,1922 | 18,391 | 13,405 | 10,925 |

## 6.3 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 23 (ITT population) and Table 24 (mITT population).

*Table 23 Estimated budget impact of drug costs for the eligible patient population. List price, including VAT and undiscounted, ITT population, method A*

| | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 |
|---|---|---|---|---|---|
| Kymriah (tisagenlecleucel) recommended for use | 54,644,458 | 54,644,458 | 54,644,458 | 54,644,458 | 54,644,458 |
| Kymriah (tisagenlecleucel) not recommended for use | 4,938,934 | 4,938,934 | 4,938,934 | 4,938,934 | 4,938,934 |
| **Budget impact of recommendation** | 49,705,524 | 49,705,524 | 49,705,524 | 49,705,524 | 49,705,524 |

*Table 24 Estimated budget impact of drug costs for the eligible patient population. List price, including VAT and undiscounted, mITT population, method A*

| | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 |
|---|---|---|---|---|---|
| Kymriah (tisagenlecleucel) recommended for use | 77,120,000 | 77,120,000 | 77,120,000 | 77,120,000 | 77,120,000 |
| Kymriah (tisagenlecleucel) not recommended for use | 4,938,934 | 4,938,934 | 4,938,934 | 4,938,934 | 4,938,934 |
| **Budget impact of recommendation** | 72,181,066 | 72,181,066 | 72,181,066 | 72,181,066 | 72,181,066 |

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 25 (ITT population) and Table 26 (mITT population).

*Table 25 Estimated budget impact of healthcare costs for the eligible patient population. List price, including VAT and undiscounted ITT population, method A*

| | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 |
|---|---|---|---|---|---|
| Kymriah (tisagenlecleucel) recommended for use | 62,197,805 | 62,776,579 | 63,138,717 | 63,385,740 | 63,558,647 |
| Kymriah (tisagenlecleucel) not recommended for use | 11,853,969 | 12,270,865 | 12,579,410 | 12,772,430 | 12,905,845 |
| **Budget impact of recommendation** | 50,343,836 | 50,505,715 | 50,559,307 | 50,613,309 | 50,652,801 |

*Table 26 Estimated budget impact of healthcare costs for the eligible patient population. List price, including VAT and undiscounted mITT population, method A*

| | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 |
|---|---|---|---|---|---|
| Kymriah (tisagenlecleucel) recommended for use | 85,494,598 | 86,177,513 | 86,693,711 | 87,097,803 | 87,428,998 |
| Kymriah (tisagenlecleucel) not recommended for use | 12,083,002 | 12,521,441 | 12,889,259 | 13,157,368 | 13,375,860 |
| **Budget impact of recommendation** | 73,411,596 | 73,656,072 | 73,804,452 | 73,940,435 | 74,053,139 |

The budget impact of a positive recommendation for Kymriah for the eligible patient population as described in this STA is estimated to be around 51-74 mill. NOK including VAT in the fifth year after introduction.

In this estimation of budget consequences of introducing Kymriah, NoMA has assumed that all CAR-T patients are treated with Kymriah and without considering market shares divided by Kymriah and other potential CAR-T treatments.

# 7 SUMMARY AND CONCLUSIONS

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

*NoMA's updated assessment of the benefit criterion:*
The clinical efficacy and safety of tisagenlecleucel was demonstrated in one uncontrolled, pivotal phase II study (JULIET) in adult patients with r/r DLBCL. Median follow-up time in the original submission was 19.3 months. The updated submission used a later data cut-off date (February 2020) adding approximately 20 months to the median follow up time.

At the time of the original submission, the study was closed for enrolment and therefore the patient numbers and baseline characteristics remain unchanged. Best ORR and CR rates are also unchanged (July 2019 DCO). In the ITT population, the median PFS was stable at 4.8 months (95% CI: 3.7, 5.3, DCO date, July 2019) compared to 4.6 months at the original DCO. Relative to the original submission, nine additional deaths occurred by the updated DCO. The median OS remain unchanged at 8.2 months (95% CI: 5.8, 11.7) in the ITT population and 11.1 months (95% CI: 6.6, 23.9) in the mITT population, with the event rate increasing from approximately 55% to 60% (ITT). The estimated probability of survival at 24 months is also unchanged at 40.0% (95% CI: 30.7, 49.1) for the mITT population.

As the JULIET trial was designed as a single-arm study, the relative efficacy of tisagenlecleucel compared to standard of care was addressed through indirect treatment comparisons to external data. In the original submission, Novartis conducted two matching-adjusted indirect comparisons (MAICs) using published aggregate data from three individual publications (the two CORAL extension studies and SCHOLAR-1). These comparisons had several major limitations and the magnitude of the clinical benefit of tisagenlecleucel relative to standard of care could not be reliably established.

In the present submission, Novartis accessed patient-level data from the CORAL extension studies. An external control arm (CORAL FU FAS) was generated selecting CORAL patients matching the main inclusion and exclusion criteria of the JULIET trial. For their base case analysis, Novartis excluded patients who received ASCT as an index treatment from the CORAL FU FAS, as only transplant ineligible patients were enrolled in the JULIET trial. NoMA noted, however, that patients in the JUIET trial were defined as transplant ineligible based on an assumption that only palliative treatment was offered beyond 2$^{nd}$ line. NoMA did not agree with this assumption, highlighting that in a population fit for SCT, ASCT in the 3$^{rd}$ or later line is still a possible treatment option. Considering the baseline data on ECOG status, median age, and co-morbidities/organ function, it appears likely that a substantial proportion of patients in the JULIET study would have been fit enough for ASCT, and as such, this was considered a relevant comparator treatment option. Furthermore, NoMA noted that the approved indication does not restrict patients in terms of transplant eligibility, thus suggesting tisagenlecleucel may be offered to transplant eligible patients in clinical practice. NoMA therefore elected to retain patients with ASCT as their index treatment in the CORAL FU FAS. It is acknowledged, however, that there is considerable uncertainty regarding the rate of subsequent SCT that could be expected, had the JULIET trial population received existing salvage chemotherapy. Thus, the relevance for the JULIET population of the subsequent transplant rates of the comparator arm produced by the indirect comparisons cannot be verified.

Two different methods were used (Method A and Method B) to conduct indirect comparisons to the JULIET population. Both methods attempted to adjust for differences in the number of prior treatment lines, but Method B also adjusted for differences in certain confounders via propensity score (PS) methodology. Compared to the original submission, more comprehensive patient characteristics were derived from the CORAL studies and an additional four co-variates could be included in the PS-adjusted analysis (Method B). Nevertheless, the access to patient-level data from CORAL extension studies did not fully resolve the imbalance in reported disease characteristics between JULIET and the comparator study. Furthermore, as only cases with complete information were included in the PS weighting (Method B), relative to Method A, a total of 52 CORAL patients were excluded from the analyses due to missing data. The large drop in CORAL's survival following the removal of these patients indicate that data were not missing at random, thus introducing additional bias in the comparisons. Lastly, the estimated comparator OS curves were more pessimistic that those reported in the real-world setting, which was considered implausible.

The direction of bias for the two provided comparisons (Method A and Method B) could not be readily ascertained, and NoMA elected to use both comparisons to provide a rough quantification of the uncertainty in the relative efficacy estimates. The assumptions surrounding these two comparisons together with the inclusion of patients with ASCT as index treatment are a key driver of the estimated incremental life-years and QALYs for tisagenlecleucel compared to standard care.

NoMA adopted a more optimistic approach to modelling long-term mortality for tisagenlecleucel than the basecase by Novartis, as NoMA chose to extrapolate JULIET trial data using spline models until month 84 after which general population mortality was assumed, whereas Novartis applied estimated mortality rates using CORAL data from month 44 to the tisagenlecleucel arm. This resulted in higher estimated life-years and QALYs for tisagenlecleucel in NoMA's scenarios compared to the basecase (ITT population Method B) by Novartis.

*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 discounted healthcare cost was approximately 2.7 million NOK (ITT) and 3.7 million NOK (mITT) per patient for tisagenleucel and 0.7 million NOK (ITT and mITT) per patient for salvage chemotherapy in NoMA's deterministic model-averaged scenario, resulting in a mean incremental healthcare cost of 2 million NOK (ITT) and 3 million NOK (mITT) 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 driver 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 51-74 mill. NOK including VAT in the fifth year after introduction, if all eligible adult patients with r/r DLBCL will be treated with tisagenlecleucel.

*NoMA's updated assessment of quality and uncertainty associated with documentation:*
The pivotal JULIET study is considered to have considerable shortcomings to inform this STA as it is a single-arm study with a small sample size (167 enrolled and 115 infused patients). The original assessment was based on a short follow-up (median 19.3 months, maximum 28.9 months). The updated 20-months longer OS data are welcome as they decrease some uncertainty surrounding OS for tisagenlecleucel, which is an important input in the cost-effectiveness model. The updated OS data do not, however, resolve the uncertainty surrounding the incremental treatment effect of tisagenlecleucel compared to standard of care due to the absence of randomized data. JULIET 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.

For the current updated submission Novartis acquired patient-level data from CORAL follow-up. This allowed the company to adjust for the lead-time bias in JULIET, which is an important advantage over the original submission. In addition, access to patient-level data provided further information on patient characteristics and missing data from CORAL follow-up. Consequently, NoMA was able to explore various scenario analyses for the relative treatment effect through indirect treatment comparisons.

Statens legemiddelverk, 26-05-2022

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# ATTACHMENT 1 COMMENTS FROM THE MANUFACTURER

Denne metodevurderingen er en revurdering av Kymriah til behandling av voksne pasienter med residivert eller refraktært diffust storcellet B-cellelymfom (DLBCL) etter to eller flere systemiske behandlinger. Novartis har sendt inn nye, mer robuste data (på pasientnivå og med langtidsoppfølgning) og en oppdatert helseøkonomisk analyse hvor Legemiddelverkets (SLVs) vurderinger fra første metodevurdering (ID2017_116) er inkludert. **Novartis mener den innsendte analysen er konservativ.**

Siden lanseringen av Kymriah i 2018 har denne CAR-T behandlingen blitt tilgjengelig for behandling av DLBCL i over 20 europeiske land. Mer enn 5000 pasienter har fått behandling og det er tilkommet betydelig mer kunnskap. Klinikere er nå oppmerksomme på utvelgelseskriterier og effektiv behandling av bivirkninger, noe som kommer til uttrykk i den kliniske observerte effekten. Dette understøttes i internasjonale retningslinjer (EBMT, JACIE og EHA), hvor formålet er å støtte helsepersonell i CAR-T behandling[1].

**Kort oppsummert reduserer disse nye data og den oppdaterte helseøkonomiske modellen usikkerheten fra den første metodevurderingen.** Novartis synes SLVs revurdering på mange områder er fornuftig, men stiller seg overraskende til at SLV har gjort en rekke konservative valg i disfavør av Kymriah. Vi vil nedenfor adressere dette nærmere:

1. **Konservative antakelser**

**Novartis' innsendte analyse tok utgangspunkt i SLVs første konservative rapport**, hvor SLV oppjusterte den inkrementelle kostnadseffektivitets ratio (IKER) med om lag 90 %. SLV har videre tatt nye ytterligere konservative valg, noe som er overraskende da vi nå har mer robuste data: Vi reagerer på at SLV ikke har tiltro til vår **«indirekte sammenligning på pasientnivå»,** en sammenligning som tidligere er akseptert av bl.a. G-BA i Tyskland og som også er publisert[2].

SLV mener den innsendte sammenligningen «ikke representerte en korrekt sammenligning av pasienter» og velger å støtte seg til en sammenlikning hvor mono-kjemoterapi og immunmonoterapi ble ekskludert blant behandlingene i komparator armen, mens autolog stamcelle transplantasjon (ASCT) ble inkludert (analyse levert av Novartis spesielt på forespørsel fra SLV).

**Novartis mener inklusjonen av ASCT-pasienter ikke kan supporteres og at slik inklusjon skaper en svært konservativ analyse**. Årsaken er at pasienter som var kvalifisert for ASCT var ekskludert fra den kliniske studien (utprøverbeslutning), og ikke ut fra basale pasientkarakteristika som foreslått av SLV. **SLVs vurdering resulterer i langt lavere inkrementell effekt enn hva Novartis mener er vist.**

2. **Bruk av økonomiske modeller**

Novartis sendte inn en justert analyse i tråd med SLVs retningslinjer for helseøkonomiske vurderinger, og sendte på forespørsel fra SLV også inn en ujustert analyse i løpet av prosessen. SLV har laget 4 scenarier basert på den ujusterte (metode A) og justerte (metode B) analysen og mener disse komplementerer hverandre og gir en «grov kvantifisering» av usikkerheten rundt effekt-estimatene.

**Novartis mener det er korrekt å inkludere metode B, men at metode A ikke reflekterer realistiske scenarier.** Det er særlig tre årsaker til dette:

[1] Ann Oncol. 2022 Mar;33(3):259-275.doi: 10.1016/j.annonc.2021.12.003. Epub 2021 Dec 16
[2] Blood Adv (2022) 6 (8): 2536–2547 https://doi.org/10.1182/bloodadvances.2021006280

a) Pasientpopulasjonen i CORAL-studien er ikke sammenlignbar med pasientpopulasjonene fra SCHOLAR-1 eller OUS register data, **noe som gjør at langtidsoverlevelsen ikke er sammenlignbar mellom disse**. SLV trekker feilaktig slutning at langtidsoverlevelse bør være lik, uavhengig av pasientpopulasjon og data. Denne antakelsen danner basis for SLVs inklusjon av metode A. **Det er Novartis mening at metode A ikke skal inkluderes.**
b) Metodologisk er det vanlig praksis å justere for forskjeller mellom pasientpopulasjoner, da disse kan ha stor innvirkning på effekten av en behandling. Det er nettopp styrken av å ha tilgang på data på pasientnivå som gjør justering/analysene mer presise enn når man bare har tilgang til aggregerte data. **Dette tilsier at metode B, som er justert, må legges til grunn for vurdering av kostnadseffektiviteten.**
c) Klinikerne SLV har konsultert uttaler i rapporten at forskjeller i pasientkarakteristika mellom Kymriah og komparatorarmen overestimerer effekten av komparator. Klinikerne mener **metode B er mest hensiktsmessig å bruke, sammenlignet med metode A**.

**Konklusjon**

DLBCL er en alvorlig diagnose med et absolutt prognosetap i tredjelinje på nesten 18 gode leveår. Selv med konservative antakelser satt av SLV er **Kymriah et kostnadseffektivt alternativ til behandling av tredjelinje DLBCL pasienter i Norge** ved bruk av metode B**.** Novartis mener det er ukorrekt å inkludere metode A i beregningene av kostnadseffektivitet. Det er verken i henhold til SLVs egne retningslinjer, god praksis eller klinikers vurdering at metode A kan eller bør inkluderes.

Klinikere har i lang tid uttrykt et stort ønske om å få tilgjengeliggjort CAR-T til behandling av DLBCL i Norge og mener det vil utgjøre ett viktig behandlingsalternativ for pasienter, som ikke har andre effektive behandlingsalternativer i tredjelinje. Vi er kjent med at norske pasienter har mottatt behandling i utlandet, noe som understreker et udekket medisinsk behov. Klinikere ved Radiumhospitalet har over flere år opparbeidet seg viktig kunnskap gjennom en rekke CAR-T studier og er nå **godt rustet til å velge ut de pasienter som vil ha størst nytte av behandlingen**.

Det er på **høy tid at også norske DLBCL pasienter får tilgang til behandling med CAR-T**. Novartis ønsker best mulig behandling av norske pasienter, noe vi kan bidra til gjennom oppfølgning i allerede etablerte databaser.

# ATTACHMENT 2

# NOMA'S REPLY TO THE COMMENTS FROM THE MANUFACTURER

Novartis har levert kommentarer under to overskrifter, 1) konservative antagelser og 2) bruk av økonomiske modeller. SLV ønsker ikke å kommentere på selve innspillene, men vil herunder korrigere visse påstander vi mener er feilaktige i forhold til det som er beskrevet i rapporten.

1) **Konservative antagelser**
   SLV har ikke manglende tiltro til den leverte indirekte sammenlikningen. SLV har imidlertid foretatt visse justeringer med formål om å optimalisere intern validitet. Begrunnelsen for de justeringer som er gjort er beskrevet på side 25 (eksklusjon av pasienter med beste støttebehandling, ukjent behandling og mono-immunmonoterapi) og på side 33-34 (inklusjon av pasienter med ASCT) i rapporten. SLV har ikke foreslått at pasienter som var kvalifisert for ASCT var ekskludert fra den kliniske studien ut fra basale pasientkarakteristika (side 33-34 i rapporten).
2) **Bruk av økonomiske modeller**
   I den opprinnelige dokumentasjonen for den aktuelle revurderingen sendte Novartis inn to indirekte sammenlikninger, en ujustert (Metode A) og en justert (Metode B), beskrevet på s 25 i rapporten. Metode A ble således ikke spesifikt etterspurt av SLV. SLV mottok imidlertid en CUA modell kun for metode B, og etterspurte derfor CUA modellen også for metode A.

   SLV er enige i at justerte sammenlikninger i all utstrekning er å foretrekke framfor naive sammenlikninger og dette standpunktet reflekteres i SLVs retningslinjer for dokumentasjonsgrunnlag for hurtig metodevurdering av legemidler. Validiteten av slike sammenlikninger vi imidlertid være avhengig av et flertall faktorer, inkl. i hvilken grad man har kunnet justere for alle relevante prognostiske faktorer, samt graden av manglende data.

   SLV har ikke konkludert med at langtidsoverlevelse for CORAL, SCHOLAR-1 og i registeret fra OUS bør være lik, uavhengig av pasientpopulasjon og data. Det er heller ikke korrekt at en slik antagelse danner basis for SLVs inklusjon av metode A. Begrunnelsen for inklusjon av Metode A er beskrevet på s 35 i rapporten.