Single Technology Assessment

Tisagenlecleucel (Kymriah) for the treatment of relapsed/refractory acute lymphoblastic leukaemia (ALL) in paediatric and young adult patients

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PREFACE

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

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

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

NoMA evaluates the relative efficacy and incremental costs in relation to a relevant comparator. NoMA does not assess the benefit risk balance already assessed under the market-authorization procedure. Information about this is provided by EMA (1).

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

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

EXECUTIVE SUMMARY

Rationale
Single technology assessment (STA) of tisagenlecleucel (Kymriah) for the treatment of paediatric and young adult patients up to 25 years of age with B-cell acute lymphoblastic leukaemia (ALL) that is refractory, in relapse post-transplant or in second or later relapse. NoMA has assessed the relative effectiveness, safety and cost-effectiveness of tisagenlecelucel, as well as the severity of the condition. NoMAs´s assessment is based on the documentation presented by Novartis.

Background
Tisagenlecleucel is a CAR-T cell therapy, a novel cancer therapy which involves reprogramming patient's own T cells with a transgene encoding a chimeric antigen receptor (CAR) to identify and eliminate CD19 expressing cells. The CD19 antigen is exclusively expressed on B cells, including the cancer cells in B-cell ALL. When tisagenlecleucel is given to the patient, the modified T cells attach to and kill the cancer cells, thereby helping to clear the cancer from the body.

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

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

According to Novartis, manufacturing and release of tisagenlecleucel usually takes about 3-4 weeks. The majority of patients require some form of bridging chemotherapy to stabilize the cancer while waiting for the tisagenlecleucel infusion. During that time period, some of the patients will die, while others become too sick to tolerate treatment with the CAR-T cell therapy. In addition, the manufacturing process occasionally fails to produce an sufficient number of CAR-T cells for infusion.

Patient population
About 5 paediatric and young adult patients with relapsed/refractory B-cell ALL will be candidates for treatment with tisagenlecleucel each year in Norway.

Severity and shortfall
Paediatric and young adult ALL-patients who are refractory, in relapse post-transplant or in second or later relapse have a poor prognosis. The degree of severity can affect whether the costs are considered to be in reasonable proportion to the benefit of the treatment. NoMA has estimated that paediatric patients with relapsed/refractory ALL have an absolute shortfall (AS) of approximately 51 Quality Adjusted Life Years (QALYs).

Treatment in the Norwegian setting
Treatment of ALL in children is described in national guidelines from The Norwegian Directorate of Health and follows common Nordic guidelines decided by NOPHO (Nordic Society of Paediatric Haematology and Oncology). With frontline conventional chemotherapy the overall cure rate of ALL in children is as high as

80 – 85%. Patients with relapse will be offered new treatment with chemotherapy alone or chemotherapy followed by allogenic stem cell transplant (alloSCT) after obtaining a new remission.

For patients who are refractory, in relapse post-transplant or in second or later relapse, there is no agreed treatment in Norway or the Nordic countries. Today clofarabine (Evoltra) in combination with etoposide and cyclophosphamide (CEC) or blinatumomab (Blincyto), both followed by alloSCT in eligible patients, are used according to clinical experts.

NoMA considers CEC, followed by alloSCT in eligible patients, to be the most relevant comparator in the STA.

Clinical efficacy
The clinical efficacy and safety of tisagenlecleucel was demonstrated in one main study (ELIANA) and two supportive studies (ENSIGN and B2101J) in about 190 paediatric and young adult patients with relapsed/refractory B-cell ALL.

Of 97 patients enrolled in ELIANA, 79 (81%) received infusion with tisagenlecleucel. Reasons for discontinuation prior to tisagenlecleucel infusion included: tisagenlecleucel could not be manufactured (n=8), death (n=7), and adverse events (n=3). The median time from enrollment to CAR-T administration was 45 days (range 30 to 105 days).

Results of the ELIANA, ENSIGN and B2101J trials demonstrated high remission rates following a single infusion of tisagenlecleucel. The overall remission rate within 3 months was 82% among the patients who received the tisagenlecleucel infusion in the ELIANA trial (79 patients). In intention-to-treat (ITT) analyses of the full enrolled population (97 patients) the rates of event-free survival (EFS) and overall survival (OS) were 65% and 78%, respectively, at 6 months and 46% and 70% at 12 months. The median EFS and OS was not reached.

All the tisagenlecleucel clinical trials had single arm study designs, and Novartis has conducted matching-adjusted indirect comparisons (MAIC) with historical controls for documentation of relative efficacy. For the CEC comparison, Novartis pooled together a prospective cohort study by Miano 2012 (children with advanced ALL, N=24), a phase II, open label clinical trial by Locatelli 2009 (children with advanced ALL, N=25), and a phase II clinical trial by Hijiya 2011 (children with r/r ALL, N=25). The results of the MAIC are very uncertain due to the small sample size and heterogeneity of the CEC comparator, and too few matching variables to adjust for differences between the patient populations in the comparison. Consequently, although the superior efficacy of tisagenlecleucel over CEC seems clear, the relative effect of tisagenlecleucel vs. CEC cannot be reliably established.

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

Another important adverse event is hypogammaglobulinemia due to B-cell aplasia. Patients without the immunoglobulins produced by B cells are at risk for infections and may need monthly supplemental treatment with intravenous infusions of immunoglobulins (IVIG). The duration of B cell aplasia is unknown but may persist as long as tisagenlecleucel is present. In paediatric and young adult B-cell ALL patients, tisagenlecleucel has been shown to be present in the blood and bone marrow beyond 2 years (study B2101J).

The most common non-haematological adverse reactions in clinical studies were CRS (77%), infections (65%), hypogammaglobulinaemia (47%), pyrexia (40%) and decreased appetite (39%). Grade 3 and 4 adverse reactions were reported in 88% of patients. The most common Grade 3 and 4 haematological laboratory abnormalities were white blood cells decreased (99%), neutrophils decreased (95%), lymphocytes decreased (95%), platelets decreased (77%) and haemoglobin decreased (53%).

Cost effectiveness

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

- OS and EFS data for tisagenlecleucel based on pooled data from ELIANA + ENSIGN as opposed to ELIANA + ENSIGN + B2101J.
- OS and EFS extrapolated with standard parametric functions as opposed to weighted AIC curves
    - OS: Log-normal for tisagenlecleucel, spline model with two knots for CEC.
    - EFS: Log-normal for tisagenlecleucel, derived from the OS curve using an EFS:OS ratio for CEC.
- Health state utilities from the ELIANA trial for the first 5 years and from published literature (Kelly et al 2015) after 5 years, as opposed to Kelly et al only.
- All patients alive after 5 years are assumed to have the quality of life and costs associated with the EFS health state, in line with the assumption of long-term survival after 5 years.
- Age adjustment of health state utility values based on Swedish studies (Sun et al 2012 and Burstrøm et al 2001) as opposed to UK data from Janssen et al. 2014
- Disutility after alloSCT assumed to last for two months as opposed to one year.
- Hospitalisation and ICU costs are derived from Lindemark et al as opposed to SAMDATA.
- Disutility and hospital costs due to bridging chemotherapy included.
- NHS reference costs adjusted for inflation and purchasing power parities.
- Length of hospital stay of 14 days for lymphodepleting therapy for 94.7% of population as opposed to 65.5% of population.
- Leukapherese costs 94 000 NOK based on data from OUS as opposed to 44 000 NOK based on data from Rigshospitalet in Denmark.
- Length of hospital stay for CEC treatment 16.8 days for each cycle as opposed to 28 days
- Price of tisagenlecleucel including pharmacy markup
- ICU costs corrected for double counting of hospital length of stay.
- Follow-up costs after alloSCT included for all patients in year one and for 60% (as opposed to 100%) of the patients in year two.
- Price of IVIG treatment based on Panzyga as opposed to Octagam

- IVIG treatment duration based on extrapolated KM data of B cell recovery from the ELIANA trial and adjusted for survival as opposed to 11.4 months.
- IVIG treatment for 47.1% of the estimated number of patients with B-cell aplasia over time as opposed to 73% of all patients who received tisagenlecleucel infusion.

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

In NoMA's base case analyses, the additional costs for tisagenlecleucel compared to CEC followed by subsequent alloSCT, with public list prices[1] ex. VAT for medicines, are:

- 651 000 NOK per QALY gained in the ITT population (enrolled patients)
- 648 000 NOK per QALY gained in the mITT population (infused patients)

Budget impact

NoMA estimated the budget impact for the specialist healthcare services to be around 15 million NOK including VAT in the fifth year after introduction, if tisagenlecleucel is introduced for the treatment of paediatric and young adult patients with relapsed/refractory B-cell ALL.

NoMA´s overall assessment

NoMA identified multiple important limitations and uncertainties in the analysis that remained. The clinical trials of tisagenlecleucel have single arm study designs, are small, and have short median follow-up time. The studies lack control arms, and it is therefore not possible to compare outcomes from these trials with outcomes from the comparator trials without a high degree of uncertainty. Long-term outcomes - both in terms of efficacy and safety - are currently not known. NoMA considers the estimated gain in overall and quality adjusted survival for tisagenlecleucel compared to CEC followed by subsequent alloSCT to be highly uncertain. Patients with hypogammaglobulinemia due to B cell aplasia are at risk for developing infections and may need prolonged supplemental treatment with IVIG for years after infusion. The proportion of patients that require IVIG treatment and the duration of treatment is still unclear. However, tisagenlecleucel is targeted towards a small patient group with a severe condition in which it is difficult to conduct randomised controlled studies. Therefore, a less stringent requirement for documentation is considered acceptable. The outcomes of alternative scenario analyses are generally within the range of what can be considered a cost-effective use of healthcare resources. Although this does not take away the limitations and uncertainty in the analysis, NoMA considers there may be plausible potential for tisagenlecleucel to be a cost-effective treatment option for relapsed/refractory paediatric and young adult ALL patients, given the degree of severity for the patient group.

[1] Tisagenlecleucel public list price: NOK 3 959 508 (incl. pharmacy markup and VAT)

OPPSUMMERING

Formål
Hurtig metodevurdering av legemiddelet Kymriah (tisagenlekleucel) i henhold til godkjent preparatomtale og bestilling ID2017_093: «Tisagenlecleucel (Kymriah) – Behandling av akutt lymfoblastisk leukemi». Legemiddelverket har vurdert relativ effekt, sikkerhet og kostnadseffektivitet ved bruk av Kymriah, samt alvorlighet av tilstanden. Vurderingen tar utgangspunkt i dokumentasjon innsendt av Novartis.

Bakgrunn
Kymriah er godkjent til behandling av barn og unge voksne pasienter opptil 25 år med akutt lymfoblastisk B-celleleukemi (B-ALL) som er refraktær, i residiv etter transplantasjon eller med to eller flere tilbakefall. Om lag 5 pasienter er aktuelle for behandling med Kymriah hvert år i Norge.

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

Alvorlighet og helsetap
Barn og unge voksne med residivert/refraktær B-ALL har dårlig prognose med dagens behandling. Legemiddelverket har beregnet at absolutt prognosetap er ca. 51 gode leveår for denne pasientgruppen.

Effekt
Av totalt 97 pasienter som ble inkludert i hovedstudien (ELIANA), var det 18 pasienter som ikke fikk infusjon, enten fordi Kymriah ikke kunne lages, eller fordi pasienten døde eller fikk bivirkninger av annen behandling i ventetiden. Av de 79 pasientene som fikk infusjon med Kymriah, var det 82% som oppnådde komplett remisjon innen 3 måneder. Etter ett år var sannsynligheten for å være i live ca. 76% for de pasientene som hadde fått infusjon. Det var ingen kontrollgruppe i studien og oppfølgingstiden er foreløpig kort. Et behandlingsalternativ i dag er klofarabin kombinasjonsbehandling (CEC), etterfulgt av stamcelletransplantasjon. Effekten som er vist for Kymriah er bedre enn det som er sett med dagens behandling, men vi har ikke pålitelige data for hvor stor effektforskjellen er.

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

Kostnadseffektivitet
Legemiddelverket har vurdert om kostnadene ved bruk av Kymriah står i et rimelig forhold til den nytten behandlingen gir. To pasientgrupper er analysert: Innrullerte pasienter (alle pasienter i studien, både pasienter som fikk infusjon med Kymriah og pasienter som falt fra i ventetiden) og Infuserte pasienter (kun pasienter som fikk infusjon med Kymriah). I de analysene Legemiddelverket mener er mest sannsynlige, med dagens maksimalpriser[2] for legemidlene, er merkostnad for Kymriah sammenlignet med CEC etterfulgt av stamcelletransplantasjon:

- 651 000 NOK per vunnet kvalitetsjusterte leveår (QALY) i analysen med innrullerte pasienter
- 648 000 NOK per vunnet kvalitetsjusterte leveår (QALY) i analysen med infuserte pasienter

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

Budsjettkonsekvenser
Legemiddelverket har estimert at budsjettvirkningen for sykehusene vil være om lag 15 millioner NOK per år i år fem, hvis Kymriah innføres til behandling av barn og unge voksne med residivert/refraktær B-ALL.

Legemiddelverkets vurdering
Langtidsvirkning av Kymriah – både når det gjelder effekt og sikkerhet – er foreløpig ikke kjent. Så langt har ingen studier av CAR-T celleterapi fulgt pasientene lenge nok til å fastslå om pasienter i vedvarende remisjon kan anses å være kurert. Vi har heller ikke pålitelige data for effektforskjellen mellom Kymriah og dagens behandling. Hvor mange pasienter som vil trenge immunoglobulinbehandling etter infusjon, og over hvor lang tid, er heller ikke kjent. For denne indikasjonen er imidlertid Kymriah rettet mot en liten pasientgruppe med alvorlig sykdom hvor det kan være vanskelig å gjennomføre kontrollerte studier. Et lavere krav til dokumentasjon kan derfor aksepteres.

Analysene har en rekke viktige begrensninger og usikkerheter. Legemiddelverket vurderer at det kan være en rimelig mulighet for at merkostnaden per vunnet kvalitetsjusterte leveår for Kymriah ligger innenfor det som kan anses som kostnadseffektiv behandling, gitt alvorlighetsgraden for den aktuelle pasientgruppen.

[2] Tisagenlekleucel maksimalpris (AUP): 3 959 508 (inkl. mva). I analysene brukes maksimalpris eks. mva.

3-SIDERS SAMMENDRAG

Metode
Hurtig metodevurdering av legemiddelet tisagenlekleucel (Kymriah) til behandling av barn og unge voksne pasienter opptil 25 år med akutt lymfoblastisk B-celleleukemi (B-ALL) som er refraktære, i residiv etter transplantasjon eller med to eller flere tilbakefall. Vurderingen er i henhold til godkjent preparatomtale og bestilling ID2017_093: «Tisagenlecleucel (Kymriah) – Behandling av akutt lymfoblastisk leukemi». Legemiddelverket har vurdert klinisk effekt, sikkerhet og kostnadseffektivitet ved bruk av Kymriah, samt alvorlighet av tilstanden. Vurderingen tar utgangspunkt i dokumentasjon innsendt av Novartis.

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

Den kliniske prosessen starter med leukaferese, hvor pasientens egne mononukleære celler, inkludert T-celler, høstes fra perifert blod. Cellene sendes deretter til et sentralt produksjonslaboratorium hvor CAR-T cellene blir laget ved å bruke et retrovirus til å sette DNA-et for det kimære proteinet inn i DNA-et til pasientens T-celler. De modifiserte cellene blir deretter stimulert og ekspandert, for så å bli fryst ned og sendt tilbake til behandlingsstedet.

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

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

Pasientgrunnlag i Norge
Om lag 5 barn og unge voksne med residivert/refraktær B-ALL er aktuelle for behandling med tisagenlekleucel hvert år i Norge.

Alvorlighet og prognosetap
Barn og unge voksne med residivert/refraktær B-ALL 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 denne pasientgruppen har et absolutt prognosetap (APT) på ca. 51 QALY.

Behandling i norsk klinisk praksis
Behandling av ALL hos barn er beskrevet i «Nasjonalt handlingsprogram med retningslinjer for diagnostikk, behandling og oppfølging av kreft hos barn» fra Helsedirektoratet 2017 og følger felles nordiske retningslinjer vedtatt av NOPHO (nordisk forening for pediatrisk hematologi og onkologi). I dag blir ca. 80 – 85 % av barn med ALL kurert ved behandling med konvensjonell kjemoterapi. Pasienter med tilbakefall vil få ny behandling med kjemoterapi, enten alene eller etterfulgt av allogen stamcelletransplantasjon (alloSCT) etter at ny remisjon er oppnådd.

For pasienter som er refraktære, i residiv etter transplantasjon eller med to eller flere tilbakefall er det ikke noen ensartet behandlingspraksis i Norge eller Norden. Ifølge kliniske eksperter brukes klofarabin (Evoltra) i kombinasjon med etoposid og syklofosfamid (CEC) eller blinatumomab (Blincyto), begge etterfulgt av alloSCT hos pasienter hvor dette er egnet. Legemiddelverket har valgt CEC, etterfulgt av alloSCT, som komparator i metodevurderingen.

Effekt
Klinisk effekt og sikkerhet for tisagenlekleucel er vist i en hovedstudie (ELIANA) og to støttende studier (ENSIGN og B2101J) med om lag 190 barn og unge voksne pasienter med residivert/refraktær B-ALL.

Av 97 pasienter som ble innrullert i ELIANA, fikk 79 (81 %) pasienter infusjon med tisagenlekleucel. Årsaker til frafall før infusjon var at tisagenlekleucel ikke kunne produseres (n=8), død (n=7) eller bivirkninger av annen behandling (n=3). Median tid fra innrullering til CAR-T infusjon i denne studien var 45 dager (fra 30 til 105 dager).

Resultater fra ELIANA, ENSIGN and B2101J viste høye remisjonsrater etter infusjon med tisagenlekleucel. Total remisjonsrate innen 3 måneder var 82 % hos pasienter som fikk infusjon med tisagenlekleucel i ELIANA (79 pasienter). I intention-to-treat (ITT) analysen av alle inkluderte pasienter (97 patienter) var sannsynligheten for hendelsesfri overlevelse (event-free survival, EFS) og totaloverlevelse (OS) henholdsvis 65 % og 78 % ved 6 måneder, og 46 % og 70 % ved 12 måneder. Median EFS og OS var ikke nådd.

Alle studiene med tisagenlekleucel hadde enkeltarmet studiedesign, og Novartis har gjort justerte indirekte sammenligninger (matching-adjusted indirect comparisons, MAIC) med historiske kontroller for å dokumentere relativ effekt. I en sammenligning med CEC, har Novartis slått sammen en prospektiv kohortstudie av Miano 2012 (barn med avansert ALL, N=24), en fase II, åpen klinisk studie av Locatelli 2009 (barn med avansert ALL, N=25) og en fase II klinisk studie av Hijiya 2011 (barn med residivert/refraktær ALL, N=25). Resultatene fra MAIC er svært usikre. Studiepopulasjonene er små og CEC studiene er heterogene. Videre var det altfor få variabler for å kunne justere tilstrekkelig for forskjeller mellom pasientpopulasjonene i sammenligningen. Oppsummert ser det ut til at tisagenlekleucel har en mereffekt sammenlignet med CEC, men vi har ikke et pålitelig estimat for størrelsen på denne effektforskjellen.

Sikkerhet

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

En annen viktig bivirkning er hypogammaglobulinemi på grunn av B-celleaplasi. Pasienter med redusert nivå av immunoglobuliner, som produseres av B-celler. har økt risiko for infeksjoner og kan trenge månedlig substitusjonsbehandling med immunoglobuliner intravenøst (IVIG). Varigheten av B-celleaplasi er ikke kjent, men kan vare så lenge tisagenlekleucel er tilstede i pasienten. Hos barn og unge voksne med B-ALL, har det blitt vist at tisagenlekleucel er tilstede i blod og benmarg lenger enn to år (studie B2102J).

De vanligste ikke-hematologiske bivirkningene var CRS (77 %), infeksjoner (65 %), hypogammaglobulinemi (47 %), feber (40 %) og nedsatt appetitt (39 %). Bivirkinger av grad 3 og 4 ble rapportert hos 88 % av pasientene. De vanligste grad 3 og 4 avvikende hematologiske laboratoriefunnene var redusert antall hvite blodceller (99 %), redusert antall nøytrofile (95 %), redusert antall lymfocytter (95 %), redusert antall blodplater (77 %) og redusert hemoglobinnivå (53 %).

Kostnadseffektivitet

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

- OS og EFS data for tisagenlekleucel er basert på sammenslåtte data fra ELIANA + ENSIGN, og ikke fra ELIANA + ENSIGN + B2102J.
- OS og EFS er ekstrapolert med standard parametriske funksjoner, og ikke med AIC-vektede kurver.
  - OS: Log-normal for tisagenlekleucel, spline modell med to knots for CEC.
  - EFS: Log-normal for tisagenlekleucel, basert på OS-kurven og bruk av en EFS:OS ratio for CEC.
- Livskvalitetsvekter for helsetilstandene er hentet fra ELIANA for første 5 år og fra publisert litteratur (Kelly et al 2015) etter 5 år, og ikke kun fra Kelly et al.
- Alle pasienter som er i live etter 5 år antas å ha samme helserelaterte livskvalitet og kostnader som i helsetilstanden EFS, i tråd med en antagelse om langtidsoverlevelse etter 5 år.
- Aldersjustering av livskvalitetsvekter er basert på svenske studier (Sun et al 2012 og Burstrøm et al 2001), og ikke basert på UK data fra Janssen et al 2014.
- Redusert livskvalitet etter alloSCT antas å vare i to måneder, og ikke i ett år.
- Sykehuskostnader, inkl. innleggelse på intensivavdeling, er hentet fra Lindemark et al, og ikke fra SAMDATA.
- Redusert livskvalitet og sykehuskostnader ved kjemoterapi i ventetiden før infusjon er inkludert.
- NHS referansekostnader er justert for inflasjon og kjøpekraftsparitet.
- Lengde på sykehusopphold ved lymfodepleterende kjemoterapi satt til 14 dager for 94,7 % av pasientene, og ikke for 65,5 % av pasientene.

- Kostnader for leukaferese satt til 94 000 NOK basert på data fra OUS, og ikke 44 000 NOK basert på data fra Rigshospitalet i Danmark.
- Lengde på sykehusopphold ved CEC-behandling satt til 16,8 dager per syklus, og ikke 28 dager.
- Pris for tisagenlekleucel inkludert apotekavanse.
- Kostnader for intensivbehandling korrigert for dobbelttelling av lengde på sykehusopphold.
- Oppfølgingskostnader etter alloSCT inkludert for alle pasienter første år og for 60 % (ikke 100 %) av pasientene andre år.
- Pris for IVIG-behandling basert på Panzyga, og ikke Octagam.
- Varighet av IVIG-behandling basert på ekstrapolerte KM-data fra ELIANA for gjenopprettelse av normalnivå av B-celler (B cell recovery) justert for overlevelse, og ikke 11,4 måneder.
- IVIG-behandling for 47,1 % av estimert antall pasienter med B-celleaplasi over tid, og ikke for 73 % av alle pasientene som hadde fått tisagenlekleucel infusjon.

Legemiddelverket har estimert en inkrementell kostnad-effektbrøk for tisagenlekleucel sammenlignet med CEC. Analysene har en rekke viktige begrensninger og usikkerheter. Legemiddelverket anser derfor at estimatene for kostnadseffektivitet er svært usikre. I Legemiddelverkets base case analyser, med dagens maksimalpriser[3] for legemidlene, er merkostnad for tisagenlekleucel sammenlignet med CEC etterfulgt av alloSCT:

- 651 000 NOK per vunnet QALY i ITT populasjonen (innrullerte pasienter)
- 648 000 NOK per vunnet QALY i mITT populasjonen (infuserte pasienter)

Budsjettkonsekvenser

Legemiddelverket har estimert at budsjettvirkningen for sykehusene vil være om lag 15 millioner NOK per år i år fem, hvis tisagenlekleucel innføres til behandling av barn og unge voksne med residivert/refraktær B-ALL.

Legemiddelverkets totalvurdering

Legemiddelverket har identifisert en rekke viktige begrensninger og usikkerheter i analysene, og disse er fortsatt tilstede. De kliniske studiene av tisagenlekleucel hadde enkeltarmet studiedesign, var små og hadde kort median oppfølgingstid. Studiene manglet kontrollarm, og det er derfor ikke mulig å sammenligne resultater fra disse studiene med resultater fra komparatorstudiene uten stor grad av usikkerhet. Langtidsvirkninger – både når det gjelder effekt og bivirkninger – er foreløpig ikke kjent. Legemiddelverket vurderer at estimert gevinst i totaloverlevelse og kvalitetsjustert overlevelse, for tisagenlekleucel sammenlignet med CEC etterfulgt av alloSCT, er svært usikker. Pasienter med hypogammaglobulinemi på grunn av B-celleaplasi har risiko for infeksjoner og kan trenge substitusjonsbehandling med IVIG i flere år etter infusjon. Andelen pasienter som trenger IVIG og varigheten av behandlingen er foreløpig ikke kjent. For denne indikasjonen er tisagenlekleucel imidlertid rettet mot en liten pasientgruppe med alvorlig sykdom hvor det kan være vanskelig å gjennomføre kontrollerte studier. Et lavere krav til dokumentasjon kan derfor aksepteres. Resultatene av ulike scenarioanalyser er generelt innenfor det som kan anses som kostnadseffektiv behandling. Selv om dette ikke tar bort begrensningene og usikkerhetene i analysene, vurderer Legemiddelverket at det kan være en

[3] Tisagenlekleucel maksimalpris (AUP): 3 959 508 (inkl. mva). I analysene brukes maksimalpris eks. mva.

rimelig mulighet for at tisagenlekleucel er et kostnadseffektivt alternativ for barn og unge voksne med residivert/refraktær ALL, gitt alvorlighetsgraden for den aktuelle pasientgruppen.

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LOGG

Bestilling:	ID2017_093: Tisagenlecleucel (Kymriah) – Behandling av akutt lymfoblastisk leukemi
Forslagstiller:	Metodevarsel fra Legemiddelverket
Legemiddelfirma:	Novartis
Preparat:	Kymriah
Virkestoff:	tisagenlekleucel
Indikasjon:	Behandling av pediatriske og unge voksne pasienter opptil 25 år med akutt lymfoblastisk B-celleleukemi (B-ALL) som er refraktær, i residiv etter transplantasjon eller med to eller flere tilbakefall.
ATC-nr:	L01

Prosess

Dokumentasjon bestilt av Legemiddelverket	13-11-2017
Fullstendig dokumentasjon mottatt hos Legemiddelverket	08-06-2018
Klinikere kontaktet for første gang	29-06-2018
LIS kontaktet for første gang av Legemiddelverket	28-02-2018
Legemiddelverket bedt om ytterligere dokumentasjon	29-06-2018, 14-08-2018, 21-09-2018, 25-10-2018
Ytterligere dokumentasjon mottatt av Legemiddelverket	11-06-2018, 02-08-2018, 09-08-2018, 25-08-2018, 01-09-2018, 11-09-2018, 25-09-2018, 16-10-2018, 31-10-2018
Rapport ferdigstilt:	08-11-2018
Saksbehandlingstid:	153 dager hvorav 95 dager i påvente av ytterligere opplysninger fra legemiddelfirma.
Saksutredere:	Ania Urbaniak Mathyn Vervaart Einar Andreassen Maria Kalland Kirsti Hjelme
Kliniske eksperter:	Heidi Glosli Geir Erland Tjønnfjord

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

GLOSSARY

AE	Adverse event
ALL	Acute Lymphoblastic Leukaemia
alloSCT	Allogenic Stem Cell Transplant
AML	Acute myeloid leukaemia
AS	Absolute shortfall
CAR	Chimeric Antigen Receptor
CEC	Clofarabine in combination with etoposide and cyclophosphamide
CHRIs	Child Health Ratings Inventories
CNS	Central Nervous System
CR	Complete Remission
CRi	Complete Remission with incomplete red blood cell recovery
CRS	Cytokine release syndrome
CTL019	Tisagenlecleucel
DLBCL	Diffuse large B cell lymphoma
DoR	Duration of Remission.
DRG	Dagnoserelaterte grupper
EFS	Event-Free Survival
ELIANA	Study B2202
EMA	European Medicines Agency
ENSIGN	Study B2205J
EQ-5D	EuroQol – 5 dimensions
HR	Hazard ratio
HRQoL	Health-related quality-of-life
HUI2	Health utility index 2
ICER	Incremental cost-effectiveness ratio
ICU	Intensive care unit
IRC	Independent Review Committee
ITT	Intention to treat
IVIG	Intravenous gamma globulins
KM	Kaplan Meier
LOS	Length of stay

MAIC	Matching-Adjusted Indirect Comparison
mITT	Modified intention to treat
MRD	Minimal Residual Disease
NCCN	National Comprehensive Cancer Network
NICE	National Institute for Health and Care Excellence
NoMA	Norwegian Medicines Agency
NOPHO	Nordic Society of Pediatric Hematology and Oncology
ORR	Overall Remission Rate
OS	Overall Survival
OUS	Oslo University Hospital
PartSA	PARTITIONED SURVIVAL ANALYSIS
PD	Progressive Disease
PD/RL	Progressive/relapsed disease
PedsQL	Pediatric Quality of Life Inventory
PH	Proportional hazard
PPP	Purchasing power parities
PROMIS	Patient-reported outcomes measurement information system
QALY	Quality Adjusted Life Year
QC	Quality control
r/r ALL	Relapsed/refractory Acute Lymphoblastic Leukaemia
SAEs	Serious adverse events
Safety analysis set	All patients treated with tisagenlecleucel
SCCSS	Swiss Childhood Cancer Survivor Study
SCT	Stem Cell Transplant
SLR	Systematic Literature Review
SMR	Standardized mortality ratio
STA	Single Technology Assessment

1 BACKGROUND

1.1 SCOPE

This single technology assessment (STA) concerns the treatment of paediatric and young adult patients up to 25 years of age with B-cell acute lymphoblastic leukaemia (ALL) that is refractory, in relapse post-transplant or in second or later relapse with the CAR-T therapy tisagenlecleucel (Kymriah) in Norway.

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 evaluated together and weighed against each other. NoMA´s assessment is primarily based on the documentation presented by Novartis.

1.2 ACUTE LYMPHOBLASTIC LEUKAEMIA (ALL)

Leukaemia is a group of cancers affecting the white blood cells. Leukeamia causes uncontrolled growth of white blood cells and/or precursors of these in the bone marrow. The leukemic cells replace healthy blood cells. Low blood cell counts of white blood cells, red blood cells and platelets can cause infections, anemia and bleeding.

Acute lymphoblastic leukaemia (ALL) is the most common form of leukaemia. The cancer cells arise from immature B or T cells but rarely from mature B cells. Most ALL malignancies are of B-cell origin. ALL can occur at any age and has a bimodal incidence. It is more commonly seen in children with approximately 60% of the cases occurring in patients aged younger than 20 years, with a peak incidence between 2 to 5 years, and rising incidence again after the age of 60 years.

ALL is the most common cancer in children. There were 513 patients diagnosed with ALL in Norway in the period between 2002 and 2016 (2), corresponding to an average of 34 children per year. The ALL-population relevant to this STA consists of patients that are refractory, in relapse post-transplant or in second or later relapse. Clinical experts recruited from the four regional health authorities have estimated that around 5 patients with B-cell ALL will be candidates for treatment with tisagenlecleucel each year in Norway.

1.3 SEVERITY AND SHORTFALL

Paediatric ALL patients generally have a good prognosis with firstline conventional chemotherapy. Five-year relative survival is 89% (95% Confidence Interval, CI, 85 – 92) and ten-year relative survival is 86% (95 %CI, 82 – 90) (2). The ALL-population relevant to this STA consists of patients that are refractory, in relapse post-transplant or in second or later relapse. These patients have a very poor prognosis with the current standard of care.

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

The average age of patients enrolled in the ELIANA and ENSIGN trials was 12 years. NoMA has used this estimate as input for the severity calculation. The prognosis is based on the clofarabine combination therapy arm in the health economic model.

Table 1 Calculation of severity

Age	12
Expected $QALYs_A$ without disease (undiscounted)	58.62
Expected number of $QALYs_A$ with disease (undiscounted)	7.46
Number of lost QALYs with disease (absolute shortfall)	51.16

NoMA estimates the absolute shortfall based on current standard care to be approximately 51 QALYs.

1.4 TREATMENT OF RELAPSED/REFRACTORY ALL

1.4.1 Treatment with tisagenlecleucel

Therapeutic indication
Kymriah (tisagenlecleucel) is indicated for the treatment of:

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

This STA applies to paediatric and young adult patients with relapsed/refractory B-cell ALL. The assessment of DLBCL is presented in a separate report.

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

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

The CAR is comprised of a murine single chain antibody fragment which recognises CD19 and is fused to intracellular signalling domains from 4-1BB (CD137) and CD3 zeta. The CD3 zeta component is critical for

initiating T cell activation and anti-tumour activity, while 4-1BB enhances the expansion and persistence of tisagenlecleucel. Upon binding to CD19-expressing cells, the CAR transmits a signal promoting T cell expansion and persistence of tisagenlecleucel.

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

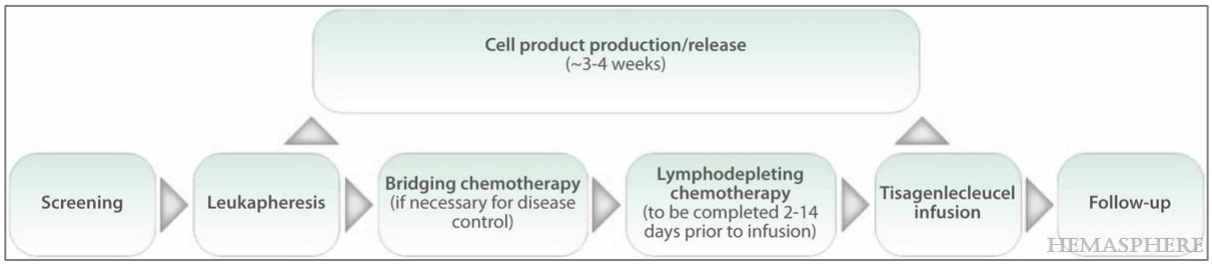


Figure 1 Clinical process flow of tisagenlecleucel therapy. Source: Buechner et al 2018 (3)

Step 1: Leukapheresis
The patient's own peripheral blood mononuclear cells containing T cells are collected by leukapheresis. The cells are then cryopreserved and shipped to a central manufacturing facility in EU (at present Fraunhofer Institut für Zelltherapie, Leipzig, Germany) and the United States (Novartis Morris Plains, New Jersey).

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

Step 3: Pre-treatment conditioning - Lymphodepleting chemotherapy
Lymphodepleting chemotherapy is recommended to be administered before tisagenlecleucel infusion unless the white blood cell count within one week prior to infusion is ≤1,000 cells/µL.

The recommended lymphodepleting chemotherapy regimen for B-cell ALL is fludarabine (30 mg/m2 intravenous daily for 4 days) and cyclophosphamide (500 mg/m2 intravenous daily for 2 days starting with the first dose of fludarabine). If the patient experienced a previous Grade 4 haemorrhagic cystitis with cyclophosphamide, or demonstrated a chemorefractory state to a cyclophosphamide-containing regimen administered shortly before lymphodepleting chemotherapy, then cytarabine (500 mg/m2 intravenous daily for 2 days) and etoposide (150 mg/m2 intravenous daily for 3 days starting with the first dose of cytarabine) should be used.

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

Step 4: Tisagenlecleucel infusion
Dosage in paediatric and young adult B-cell ALL patients:
- For patients 50 kg and below: 0.2 to 5 x 10^6 CAR-positive viable T cells/kg body weight.
- For patients above 50 kg: 0.1 to 2.5 x 10^8 CAR-positive viable T cells (non-weight based).

Tisagenlecleucel treatment is given as a single intravenous infusion.

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

Adverse reactions
As the activated CAR-T cells proliferate in the patient and kill tumor cells, they release inflammatory cytokines. This can cause CRS with symptoms like high fevers, low blood pressure, and respiratory distress. Another common and serious side effect is neurotoxicity. The most common neurologic side effects include encephalopathy, headache, delirium, aphasia, anxiety, and tremors.

Higher-grade CRS and neurotoxicity can be life threatening and require care in an intensive care unit (ICU). CRS management algorithm is given in the SmPC. Tocilizumab (anti-IL-6) is used to treat moderate or severe CRS, and a minimum of four doses of tocilizumab must be on site and available for administration prior to tisagenlecleucel infusion. Corticosteroids may be administered if tocilizumab is insufficient to control a life-threatening CRS.

The most common non-haematological adverse reactions in clinical studies were CRS (77%), infections (65%), hypogammaglobulinaemia (47%), pyrexia (40%) and decreased appetite (39%). Grade 3 and 4 adverse reactions were reported in 88% of patients. The most common Grade 3 and 4 non-haematological adverse reaction was CRS (47%). The most common Grade 3 and 4 haematological laboratory abnormalities were white blood cells decreased (99%), neutrophils decreased (95%), lymphocytes decreased (95%), platelets decreased (77%) and haemoglobin decreased (53%). Grade 3 and 4 adverse reactions were more often observed within the initial 8 weeks post-infusion (83% of patients) compared to the subsequent follow-up phases after 8 weeks post-infusion (46% of patients).

1.4.2 Treatment guidelines

Treatment of ALL in children is described in national guidelines from The Norwegian Directorate of Health: "*Nasjonalt handlingsprogram med retningslinjer for diagnostikk, behandling og oppfølging av kreft hos barn*" (4). Treatment of leukaemia in children follows common Nordic guidelines decided by NOPHO

(Nordic Society of Paediatric Haematology and Oncology). NOPHO has establised its own protocol for ALL in children.

The overall cure rate of ALL in children is as high as 80 – 85% with frontline conventional chemotherapy. Chemotherapy is given in treatment phases: induction, consolidation and maintenance. The treatment goal is to obtain a relatively quick response to treatment and complete remission, then treatment is maintained over a longer period of time to reduce the risk of relapse. The treatment lasts for approximately 2.5 years.

About 15% experience a relapse. This corresponds to 5-10 cases of relapses in Norway annually. Children with progressive or relapsed ALL remain curable despite failing initial treatment. However, the chance of remission and cure is reduced with every subsequent relapse.

If the relapse occurs early (less than 6 months after completion of primary treatment - high risk), the patient will be offered chemotherapy followed by allogenic stem cell transplant (alloSCT) after obtaining a new remission. In the case of late relapses (standard risk), it is most common to use chemotherapy alone, but depending on the therapeutic response assessed by MRD (Minimal Residual Disease), alloSCT may also be an option.

For patients that is refractory, in relapse post-transplant or in second or later relapse, there is no agreed treatment options in Norway or any of the other Nordic countries. Input from clinical experts recruited from the four regional health authorities, is that clofarabine (Evoltra) in combination with etoposide and cyclophosphamide (CEC) or blinatumomab (Blincyto) are the treatment options used to get the patients into remission. Subsequently alloSCT is used for those eligible patients who achieve remission.

1.4.3 Comparator

As mentioned above, CEC and blinatumomab, both followed by alloSCT in eligible patients, are relevant comparators for Norway according to clinical experts.

Blinatumomab (Blincyto) is indicated as monotherapy for the treatment of adults with Philadelphia chromosome negative CD19 positive relapsed or refractory B-precursor acute ALL. NoMA performed a STA for this indication in 2016. Based on this, the four regional health authorities decided not to introduce blinatumomab for adult ALL in the specialist health care system (5). In August 2018, blinatumomab was granted a marketing authorisation as monotherapy for the treatment of paediatric patients aged 1 year or older with Philadelphia chromosome negative CD19 positive B-cell precursor ALL which is refractory or in relapse after receiving at least two prior therapies or in relapse after receiving prior allogeneic hematopoietic SCT. This indication has not yet been evaluated by NoMA.

Clofarabine (Evoltra) is indicated for the treatment of ALL in paediatric patients who have relapsed or are refractory after receiving at least two prior regimens and where there is no other treatment option anticipated to result in a durable response. This corresponds to the population that is relevant to this STA. The European Commission granted a marketing authorisation under exceptional circumstances for Evoltra

in May 2006. Clofarabine is licensed as a single agent but its standard use is in combination with etoposide and cyclophosphamide (CEC).

Sales statistics from Farmastat indicate that the sales of clofarabine have been declining in recent years, whereas there have been some sales of blinatumomab since the launch in 2016. Farmastat does not provide data by indication.

It has not been established whether blinatumomab or CEC are cost effective for the treatment of paediatric and young adult patients with relapsed/refractory B-cell ALL in Norway. However, CEC can be viewed as established treatment practice the last decade, and has documented efficacy for the population relevant to the STA. The total cost of CEC treatment is in line with the total costs for salvage chemotherapy.

For these reasons, NoMA has accepted CEC followed by subsequent alloSCT, as the comparator in the analyses. This is in line with the NoMA guidelines concerning the choice of comparator (6).

2 RELATIVE EFFECTIVENESS

Tisagenlecleucel was granted marketing authorization in Norway by 23 August 2018 for the treatment of paediatric and young adult patients up to 25 years of age with B-cell acute lymphoblastic leukaemia (ALL) who are refractory, in relapse post-transplant or in second or later relapse. The clinical efficacy and safety of tisagenlecleucel was demonstrated in one main study (ELIANA) and two supportive studies (ENSIGN and B2101J) in about 190 paediatric and young adult patients with relapsed/refractory B-cell ALL.

All the clinical trials were designed as single arm studies. Novartis has therefore conducted matching-adjusted indirect comparisons (MAIC) with historical controls in order to document the relative efficacy. MAICs were based on pooled patient level data from the ELIANA, ENSIGN and B2101J trials, or from the ELIANA and ENSIGN trials, or from the ELIANA trial only.

2.1 OVERVIEW OF RELEVANT CLINICAL STUDIES

2.1.1 Tisagenlecleucel efficacy studies

NoMA considers the ELIANA and ENSIGN trials as the most relevant to this STA. This is based on the fact that study design and patient population were largely comparable between the two studies and in line with the licensed indication and posology for tisagenlecleucel. The supportive study B2101J was different with regard to the study design, patient population, posology and efficacy measurements. However, this study has the longest follow-up time.

Table 2 Methods – ELIANA, ENSIGN and B2101J trials

	ELIANA (B2202)	ENSIGN (B2205J)	B2101J
Design	Phase II Single arm Multicenter	Phase II Single arm Multicenter	Phase I/IIa Single arm Single center
Pasients	Relapsed or refractory B-cell ALL ≥3 years ≤ 21 years	Relapsed or refractory B-cell ALL ≥3 years ≤ 21 years	CD19+ B-cell malignancies ≥1 years ≤24 years*
Intervension	Tisagenlecleucel single infusion	Tisagenlecleucel single infusion	Tisagenlecleucel multiple infusions/split dosing
Comparator	none	none	none
Primary endpoint	ORR (CR+CRi) during 3 months after infusion, IRC-assessed	ORR (CR+CRi) during 6 months after infusion, IRC-assessed	Safety, and feasibility of administration and in vivo persistence of tisagenlecleucel
Some secondary endpoints	MRD DoR BOR EFS OS Safety PedsQL, EQ-5D	MRD DoR BOR EFS OS Safety	ORR, IRC-assessed Immunogenicity Determination of the relative subset of tisagenlecleucel (central memory, effector memory and regulatory T cells)

Data cutoff date	25 Apr 2017: Enrolled: N = 92 Infused: N = 75 Median follow-up: 13.1 months 31 Dec 2017: Enrolled: N = 97 Infused: N = 79 Median follow-up: 20.8 months	01 Feb 2016: Enrolled: N = 35 Infused: N = 29 Median follow-up: 11.5 months 06 Oct 2017: Enrolled: N = 73 Infused: N = 58 Median follow-up: 19.6 months	31 Jan 2017: Enrolled: N=73 (ALL) Infused: N=56 (ALL) Median follow-up: 32.3 months

*Patients aged 22-24 were only enrolled if they were treated at CHOP or another paediatric facility/oncologist at the time of enrolment. CR = complete remission. CRi = CR with incomplete red blood cell recovery. DoR = Duration of Remission. EFS = Event-free survival. EQ-5D = EuroQol – 5 dimensions. IRC = Independent Review Committee. MRD = Minimal residual disease. ORR = Overall remission rate. OS = Overall survival. PedsQL = Paediatric quality of life.

The studies (ELIANA and ENSIGN) consisted of the following sequential periods: screening including acceptance of leukapheresis product, enrolment, pre-treatment with bridging- and lymphodepleting chemotherapy, one single dose of tisagenlecleucel infusion, a primary (1-60 months) and a secondary (if applicable, 2-60 months) follow-up, and long-term survival follow-up. All patients were allowed to receive bridging chemotherapy based on the investigators choice to stabilize the disease while waiting for the tisagenlecleucel infusion.

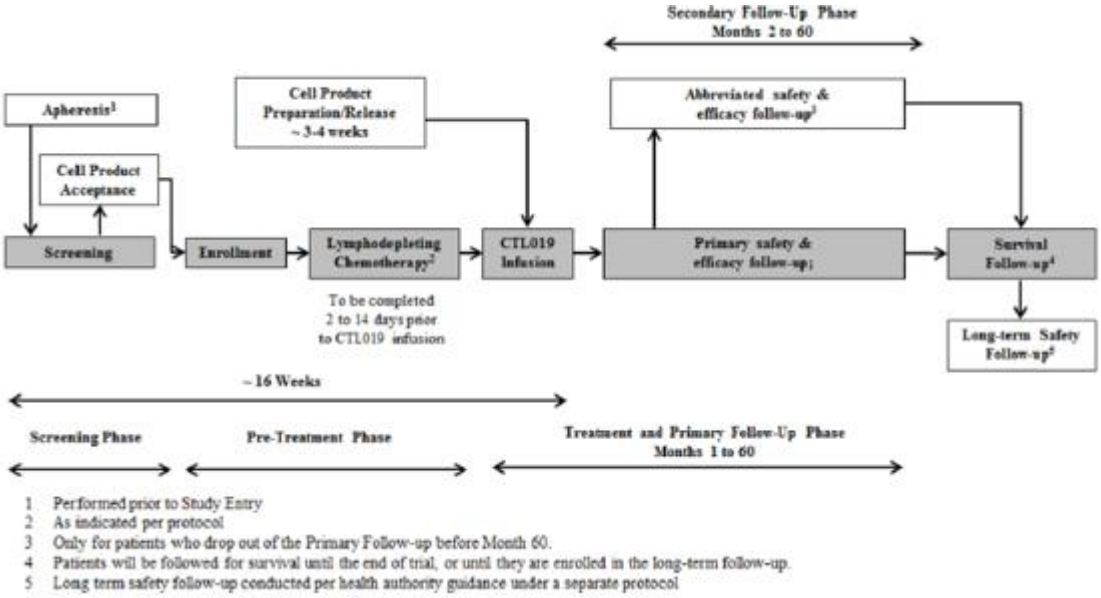


Figure 2 Study periods for ELIANA and ENSIGN

The primary efficacy endpoint was overall remission rate (ORR) within 3 months post infusion in the ELIANA trial and within 6 months in the ENSIGN trial, as determined by Independent Review Committee (IRC) assessment. ORR included complete remission (CR) and complete remission with incomplete blood count recovery (CRi) with minimal residual disease (MRD) < 0.01% evaluated by flow cytometry (MRD-negative). Remission status was required to be maintained for at least 28 days without clinical evidence of relapse.

Event-free survival (EFS) and overall survival (OS) were secondary endpoints in the ELIANA and ENSIGN trials. EFS was defined as the time from date of tisagenlecleucel infusion to the earliest of the following: death from any cause after remission, relapse, and treatment failure (i.e. no response in the study and discontinuation from the study due to death, adverse event (AE), or lack of efficacy, or new anticancer therapy). OS was defined as the time from date of tisagenlecleucel infusion to the date of death due to any cause.

The ELIANA study included 25 study sites across 11 countries, including 1 centre in Norway. In the ENSIGN study 9 US sites participated.

NoMA's assessment of the submitted evidence

The studies of tisagenlecleucel are considered to have considerable shortcomings to inform a STA. The studies lack a controll arm, and therefore it is not possible to compare outcomes from these trials with outcomes from other trials studying relevant comparators without a high degree of uncertainty. Furthermore, the studies have included a relatively small number of patients (97 enrolled patients in the main study ELIANA) with short median follow-up time (20.8 months at the cutoff date of 31 Dec 2017 in ELIANA).

In ELIANA, the primary outcome was the overall remission rate (ORR) within 3 months after infusion, assessed by an Independent Review Committee (IRC). ORR included CR (complete remission) and CRi (CR with incomplete red blood cell recovery). ORR is relevant as it provides a direct measure of the antitumor activity of the CAR-T cell therapy. However, the more clinical relevant time-to-event results (i.e. EFS, OS) are immature and long-term outcomes - both in terms of efficacy and safety - are currently not known. Since CAR-T cell therapy represent a new treatment modality, in which the patient's own T cells are genetically modified, there is a particular uncertainty about long-term efficacy and safety. The key clinical treatment goal from the patient's perspective is curing the cancer. Thus far, none of the trials of CAR-T therapy have followed patients long enough to ascertain whether children with ongoing remission could be considered cured.

The analyses of data from the studies are primarly based on patients who received tisagenlecleucel infusion (mITT – modified intention to treat). Patients who did not receive the infusion because of e.g. manufacturing failures, death prior to infusion, or adverse events (AEs) were excluded from the primary analyses. This gives an optimistic presentation of the results and violates the ITT (intention to treat) principle.

2.1.2 Matching-adjusted indirect comparison (MAIC)

Due to the single arm trial design of the ELIANA, ENSIGN and B2101J trials, Novartis presented an indirect treatment comparison to a historical control using MAIC. MAIC uses individual patient data from trials of one treatment to match baseline summary statistics reported from trials of another treatment. After matching, by using an approach similar to propensity score weighting, treatment outcomes are compared across balanced trial populations. Due to the similar design of ELIANA and ENSIGN, NoMA chose to use the pooled data in our base case analysis.

As described previously, NoMA chose CEC as the main comparator in the STA. Summary-level data for CEC was from the Miano et al. (2012) (7), Locatelli et al. (2009) (8), and Hijiya et al. (2011) (9) manuscripts. In all the studies, CEC was used as a bridge-to transplant therapy. Overall, 28 out of 74 paediatric ALL patients (38%) proceeded to SCT.

After adjusting for prior SCT and gender via MAIC, tisagenlecleucel was estimated to have superior OS and ORR over CEC. The OS HRs were 0.3 (95%CI: 0.192, 0.469) for the mITT population and 0.388 (95%CI: 0.26, 0.579) for the ITT population. The results for the adjusted and naïve comparisons were fairly similar.

Novartis claims that the proportional hazard (PH) assumption was not violated. However, the Schoenfeld residuals and log-cumulative hazard plot do not support the PH assumption . The mechanism of action between tisagenlecleucel and CEC is also very different, and does not provide a rationale for a constant proportional treatment effect. NoMA concludes that there is no evidence to support the use of a constant HR.

In summary, there are many methodological issues underlying the provided comparison. The component studies of the CEC comparison are heterogenous and the overall patient number is small. Furthermore, the matching of ELIANA+ENSIGN to CEC is based on too few prognostic factors and effect modifiers. As result, the comparison vs. CEC is considered more as a naïve comparison rather than an adjusted comparison. Overall, this comparison is subject to potential bias due to unobserved or unmeasurable confounding. At the same time it is noted that the degree of benefit observed was largely consistent regardless of whether the comparison was made using ELIANA only or using the pooled tisagenlecleucel studies and was largely consistent across all the endpoints and between the mITT and the ITT populations. However, although the superior efficacy of tisagenlecleucel over CEC seems clear, the relative effect of tisagenlecleucel vs CEC cannot be reliably established .

A detailed description and evaluation of the methodology and the results can be found in Appendix 2 Matching-adjusted indirect comparison (MAIC): tisagenlecleucel vs. CEC.

2.1.3 Ongoing and initiated studies

Novartis plans to initiate one new trial for paediatric ALL patients in 2019. The CASSIOPEIA trial will study tisagenlecleucel in first line high risk pasients. Oslo University hospital (OUS) will take part in this trial. In addition Novartis has committed to further evaluate the efficacy and safety of tisagenlecleucel in ALL patients below the age of 3 years, and will therefore conduct and submit a study based on data from a disease registry in ALL patients.

3 PICO[4]

3.1 PATIENT POPULATION

Norwegian clinical practice

Tisagenlecleucel is intended to be a treatment option for patients up to 25 years of age with B-cell ALL who are refractory, in relapse post-transplant or in second or later relapse.

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

According to the clinicians contacted by NoMA, about 5 paediatric and young adult patients with relapsed/refreactory B-cell ALL will be candidates for treatment with tisagenlecleucel each year in Norway.

Submitted clinical studies

The ELIANA and ENSIGN studies included paediatric and young adult patients with B-cell ALL between 3 and 25 years of age who were primary refractory, chemo-refractory, relapsed after alloSCT, or were otherwise ineligible for alloSCT. To be eligible for participation in the studies, patients had to have at least 5% lymphoblasts in the bone marrow at screening, adequate organ functions, Karnofsky (age ≥ 16 years) or Lansky (age <16 years) performance status of ≥ 50 at screening and a life expectancy of >12 weeks. Patients with active CNS involvement and patients with prior treatment with any anti-CD19/anti-CD3 therapy (i.e. blinatumomab) were excluded from the studies.

Among 97 patients enrolled in ELIANA, 79 received infusion with tisagenlecleucel. Reasons for discontinuation prior to tisagenlecleucel infusion included: tisagenlecleucel could not be manufactured (n=8), deaths (n=7), and AEs (n=3). The median time from enrollment to CAR-T cell administration was 45 days (range 30 to 105 days).

Among 73 patients enrolled in ENSIGN, 58 received infusion with tisagenlecleucel. Reasons for discontinuation prior to tisagenlecleudel infusion included: tisagenlecleucel could not be manufactured (n=5), and deaths (n=6). At the study cut-off date of 06 Oct 2017, 4 patients were pending infusion.

[4] Patients, Intervention, Comparator, Outcome.

Table 3 Patient characteristics, ELIANA and ENSIGN trials

	ELIANA (B2202)			ENSIGN (B2205J)		
	Infused (n=79)	Not infused (n=18)	Enrolled (i.e. all patients) (n=97)	Infused (n=58)	Not infused (n=15)	Enrolled (i.e. all patients) (n=73)
Age (years)						
Mean	12.0	12.1	12.0	12.2	14.6	12.7
Median (min-max)	11.0 (3-24)	11.0 (3-27)	11.0 (3-27)	12.0 (3-25)	14.0 (5-24)	13.0 (3-25)
Age category (years) - n (%)						
<10 years	32 (40.5)	8 (44.4)	40 (41.2)	19 (32.8)	3 (20.0)	22 (30.1)
≥10 and <18 years	33 (41.8)	7 (38.9)	40 (41.2)	30 (51.7)	8 (53.3)	38 (52.1)
≥18 years	14 (17.7)	3 (16.7)	17 (17.5)	9 (15.5)	4 (26.7)	13 (17.8)
Sex - n (%)						
Female	34 (43.0)	9 (50.0)	43 (44.3)	31 (53.4)	4 (26.7)	35 (47.9)
Male	45 (57.0)	9 (50.0)	54 (55.7)	27 (46.6)	11 (73.3)	38 (52.1)
Disease status - n (%)						
Primary refractory[1]	6 (7.6)	2 (11.1)	8 (8.2)	5 (8.6)	1 (6.7)	6 (8.2)
Relapsed disease[2]	73 (92.4)	16 (88.9)	89 (91.8)	53 (91.4)	14 (93.3)	67 (91.8)
Prior stem-cell transplantation - n (%)						
0	31 (39.2)	8 (44.4)	39 (40.2)	32 (55.2)	9 (60.0)	41 (56.2)
1	42 (53.2)	8 (44.4)	50 (51.2)	24 (41.4)	6 (40.0)	30 (41.1)
2	6 (7.6)	2 (11.1)	8 (8.2)	2 (3.4)	0	2 (2.7)

Submitted health economic analyses

Patients up to 25 years of age with B-cell ALL who are refractory, in relapse post-transplant or in second or later relapse were included in the economic model.

Patient characteristics in the model can be selected from the following sources: ELIANA trial data, pooled data from ELIANA and ENSIGN, or pooled data from ELIANA, ENSIGN, and B2101J. When selecting pooled data from ELIANA and ENSIGN the starting age is 12 years, the proportion of females 47.4%, and average weight 42.2 kg.

Novartis included the mITT population (infused patients only) in the economic analysis. Upon request from NoMA, Novartis submitted a new model that included the ITT population (enrolled patients).

NoMA´s assessment

The patient population for the economic analyses is in line with the indication for tisagenlecleucel and corresponds to the patient population evaluated in the tisagenlecleucel clinical trials ELIANA and ENSIGN.

According to clinical experts, the study population in ELIANA and ENSIGN is similar to the population expected to be treated in the Norwegian clinical practice, although the study population does not fully reflect the variety of patients intended for tisagenlecleucel treatment. The applied inclusion and exclusion criteria selected a patient population likely to benefit from the treatment and unlikely to be at risk of

being harmed if treated with tisagenlecleucel. For example, patients with active CNS involvement (i.e. CNS3) were excluded from ELIANA and ENSIGN. It is likely that tisagenlecleucel will be administered to this patient population in clinical practice, since CAR-Ts have been shown to be present in the cerebrospinal fluid and data from B2101J indicate some benefit to these patients. Thus, some uncertainty remains regarding the safety and efficacy in clinical practice.

Novartis evaluated the mITT population (infused patients) in their base case. NoMA considers both the ITT population (enrolled patients) and the mITT population to be relevant.

In the ITT population, the efficacy of tisagenlecleucel is measured from the time of enrollment to account for the time period required to manufacture the CAR-T cells. It is relevant to include this waiting period in the analysis for several reasons, as following:

- Patients would have received the comparator treatment if they were not waiting for infusion.
- A substantial proportion of the patients who underwent leukapheresis did not receive tisagenlecleucel infusion in the clinical trials. This should be reflected in the economic analysis. In the ELIANA trial 18 (18,6%) of the enrolled patients did not receive the tisagenlecleucel infusion.
- Most patients (84% in ELIANA) received bridging chemotherapy to stabilize the disease while waiting for the tisagenlecleucel infusion. Costs and disutility associated with bridging therapy should be included in the economic analysis.
- The ITT analysis evaluates the efficacy of all the sequential treatment phases connected to this CAR-T cell product, including bridging and lymphodepleting therapy, in addition to tisagenlecleucel (and not only tisagenlecleucel alone). Although the impact of bridging chemotherapy on the efficacy outcomes is likely to be small, bridging therapy should be considered as an essential element of the treatment strategy. There was no assessment of the disease status after bridging therapy and prior to the tisagenlecleucel infusion in the clinical studies.
- The mITT analysis, on the other hand, is likely to introduce important selection bias. The time span from apheresis to the CAR-T administration may have enriched the patient population included in the mITT analysis. Only the patients that survived the waiting period and were able to receive infusion were assessed in the mITT analysis, and it is likely that these patients had a better prognosis than the patients that could not be infused due to for example death or AEs. Consequently it is difficult to separate the influence of patient characteristics and (unobserved) prognostic factors from the treatment effect of tisagenlecleucel in the infused set.

In the mITT population, the effect of tisagenlecleucel is measured only in the infused patients from the time of infusion, i.e. the patients who did not receive the infusion because of manufacturing failures, death prior to infusion, or AEs were excluded from the analysis. NoMA has also considered the mITT analysis due to the following reasons:

- The historical control studies include only patients who received CEC (i.e. mITT population).
- The ITT analysis may be too conservative compared to clinical practice. Median time from enrollment to the CAR-T administration in ELIANA was 45 days (range 30 to 105 days). However, according to Novartis, both manufacturing time and capacity have been improved in the commercial setting, and is

now closer to the 3-4 weeks as specified in the SmPC. It is likely that with increased manufacturing experience a higher proportion of patients may receive successful infusion of CAR-T cells within acceptable timelines in the future.

- The ITT analysis is affected by the timing of enrollment in the clinical trial. In the tisagenlecleucel trials, enrollment started from the time when a leukapheresis product was received and accepted by the manufacturing site. The cells were then cryopreserved until a production slot was available. In other recent CAR-T trials, enrollment and leukapheresis was postponed until production capacity at the manufacturing site was confirmed. This difference in study designs between the CAR-T trials is likely to affect the waiting time and dropout rates in the period from leukapheresis to infusion, and hence the efficacy results in the ITT population. In order to assess the CAR-T products on equal terms, NoMA has also considered the mITT analysis.

NoMA noted that in the ELIANA trial 4 patients satisfied all clinical eligibility criteria, but were not enrolled in the study and are therefore not included in the ITT population. Reasons for discontinuation prior to enrollment included death (n=2), physician decision (n=1), and apheresis product received but not accepted (n=1). These patients are excluded in the economic analyses, and NoMA was not able to explore the impact on the model outcomes. Of note, at least one of the patients underwent leukapheresis with associated costs.

3.2 INTERVENTION

Norwegian clinical practice

The SmPC states that tisagenlecleucel must be administered in a qualified treatment centre.

It is assumed that the posology in the SmPC for lymphodepleting chemotherapy, and the tisagenlecleucel infusion will be followed in clinical practice, as described in chapter 1.4.1.

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

Submitted clinical studies

Tisagenlecleucel:
Planned dosage of tisagenlecleucel in the ELIANA and ENSIGN trials was similar to the dosage that is now recommended in the SmPC. Six (7.6%) patients in the ELIANA trial and 9 (15.5%) patients in the ENSIGN trial received a lower dose of CAR-positive viable T-cells than the minimum specified target dose.

In the B2101J trial a wider range of dose and multiple infusions were allowed. Tisagenlecleucel treatment was administered using an intra-patient dose escalation approach: 10% on day 0, 30% on day 1-4, possibly followed by 60% on day 14 (or later) with a total target dose of ~1.5 $x10^7$ to 5 x 10^9 (~0.3 x 10^6 to 1.0 x 10^8/kg) CAR-positive T-cells. Most patients (98.2%) with non-CNS3 ALL in Study B2101J received tisagenlecleucel within the protocol-specified dose range.

Lymphodepleting chemotherapy:
A standard fludarabin/cyclophosphamide based regiment was used in the clinical studies, except for patients who could not tolerate or were chemorefractory to cyclophosphamide.

In the ELIANA trial, 94.7% of the patients treated with tisagenlecleucel received the fludarabine/cyclophosphamide regimen and 1.33% received the cytarabine/etoposide regimen. The remaining 4% of the patients did not receive lymphodepleting chemotherapy.

Bridging chemotherapy:
The protocol allowed bridging chemotherapy per investigator choice to stabilise the clinical state of the patients during the waiting period from apheresis to CAR-T cell administration.

In the ELIANA trial 84% of the enrolled patients (77 of the 92 patients enrolled at the data cutoff date of 25 Apr 2017) received bridging therapy. The most commonly used concomitant antineoplastic medications before lymphodepleting therapy (in ≥ 50 % of patients) included methotrexate (64.1%), cytarabine (58.7%), and vincristine (50.0%).

Submitted health economic analyses

Tisagenlecleucel:
Tisagenlecleucel infusion is given once.

In the mITT analysis all patients received tisagenlecleucel infusion.

In the ITT analysis (enrolled patients) the proportion of patients who received infusion was informed by the trial data: ELIANA alone 81.4%, pooled ELIANA and ENSIGN 80.6%, pooled ELIANA, ENSIGN and B2101J 81.8%. For the non-infused patients, cost inputs were based on the cost of comparator treatment (i.e. treatment, administration, and hospitalisation).

Lymphodepleting chemotherapy:
The dosing schedule, number of doses and distribution of patients receiving each lymphodepleting regimen are obtained from the ELIANA trial:

- Fludarabine + cyclophosphamide – 94.67% of patients:
  - Fludarabine: 30 mg/m^2 IV daily for 4 days
  - Cyclophosphamide: 500 mg/m^2 IV daily for 2 days
- Etoposide + Cytarabine – 1.33% of patients:
  - Cytarabine: 500 mg/m^2 IV daily for 2 days
  - Etoposide: 150 mg/m^2 IV daily for 3 days

Bridging chemotherapy:
Novartis has included bridging chemotherapy in the ITT analysis (enrolled patients), but not in the mITT analysis (infused patients).

In the ITT analysis bridging treatment costs were added to both infused and non-infused patients. The proportion of patients who recieved bridging chemotherapy is derived from the pooled trial data of ELIANA, ENSIGN and B2101J, and set to 71.3%. The cost of bridging chemotherapy is assumed to be equal to the total drug and administration cost of salvage chemotherapy, and includes fludarabine 5 doses, cytarabine 5 doses, and idarubicin 3 doses.

NoMA´s assessment

The intervention arm for the economic analyses is in line with the SmPC for tisagenlecleucel and corresponds to the intervention in the tisagenlecleucel clinical trials.

3.3 COMPARATOR

Norwegian clinical practice

CEC (Clofarabine in combination with etoposide and cyclophosphamide) and blinatumomab, both followed by subsequent alloSCT in eligible patients, are relevant comparators for peadiatric and young adult patients with refractory/relapsed ALL in Norway according to clinical experts.

Submitted clinical studies

The tisagenlecleucel studies (ELIANA, ENSIGN, and B2101J) are single-arm studies and hence lack comparators.

Novartis presented indirect treatment comparisons using MAIC of tisagenlecleucel versus CEC followed by allogenic SCT (section 2.1.2 and Appendix 2).

Submitted health economic analyses

Novartis included the following comparators in the submitted health economic analysis:

- CEC
- Clofarabine monotherapy
- Fludarabine based chemotherapy (“salvage chemotherapy”)
- Blinatumomab

Subsequent alloSCT for eligible patients are included in the comparator arms.

Novartis selected CEC as the main comparator.

NoMA´s assessment

NoMA chose CEC, followed by subsequent alloSCT in eligible patients, as the main comparator. See section 1.4.3 regarding the selection of comparator.

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

3.4 OUTCOMES

3.4.1 Efficacy

Submitted clinical studies

In the ELIANA, ENSIGN and B2101J trials the median follow-up ranged from 20 to 32 months and the maximum follow-up ranged from 32 to 57 months.

Table 4 Data cut-off dates and follow-up time in the ELIANA, ENSIGN, and B2101J trials

Study	Study cut-off date	Median follow-up	Max follow-up
ELIANA[1)]	31 Dec 2017	20.8 months	31.7 months
ENSIGN	06 Oct 2017	19.6 months	36.5 months
B2101J	31 Jan 2017	32.3 months	57.5 months

1) From the ELIANA trial Novartis has also shared updated results from the clinical data cutoff date of 13-Apr-2018. These data are confidential as they are not yet published.

Results of the ELIANA, ENSIGN and B2101J trials demonstrated high remission rates following a single infusion of tisagenlecleucel in paediatric and young adult patients with relapsed or refractory B-cell ALL.

The overall remission rate within 3 months was 82% among the patients who received tisagenlecleucel in the ELIANA trial. In the intention-to-treat analyses of the full enrolled population (97 patients), the rates of event-free survival (EFS) and overall survival (OS) were 65% (95 %CI: 55 to 74) and 78% (95% CI: 68 to 85), respectively, at 6 months and 46% (95% CI: 35 to 57) and 70% (95% CI: 59 to 78) at 12 months post-infusion. The median EFS or OS were not reached.

Table 5 Efficacy results from the ELIANA and ENSIGN trials. mITT population (infused patients) and ITT population (enrolled patients). Data cut-off dates: ELIANA: 31 Dec 2017; ENSIGN: 06 Oct 2017

	ELIANA (B2202)		ENSIGN (B2205J)	
	Infused (n=79)	Enrolled (n=97)	Infused (n=58)	Enrolled (n=73)
Best overall response				
ORR, n (%) (95 % CI)	63/77 (81.8%) (71.4, 89.7)	63/95 (66.3%) (55.9, 75.7)	34/50 (68.0) (53.3, 80.5)	34/61 (55.7%) (42.4, 68.5)
CR	47/77 (61.0%)	47/95 (49.5%)	28/50 (56.0%)	28/61 (45.9)
CRi	16/77 (20.8%)	16/95 (16.8)	6/50 (12.0%)	6/61 (9.8%)
Event free survival				
Events/Total, n (%)	31/79 (39.2%)	49/97 (50.5%)	24/58 (41.4%)	35/73 (47.9%)
% event free probability at 6 months	72.5%	65.5%	61.7%	55.9%
% event free probability at 12 months	55.0%	46.3%	44.0%	38.7%
Median (months) (95 % CI)	NE (9.2, NE)	11.7 (7.0, NE)	7.9 (4.4, NE)	7.7 (4.2, NE)
Overall survival				
Events/Total, n (%)	23/ 79 (29.1%))	37/ 97 (38.1%)	19/ 58 (32.8%)	25/73 (34.2%)
% event free probability at 6 months	88.4%	77.5%	79.3%	76.3%
% event free probability at 12 months	75.9%	69.6%	62.6%	60.0%
Median (months) (95 % CI)	NE (NE, NE)	NE (17.6, NE)	23.8 (8.8, NE)	16.2 (10.0, NE)

CR: complete remission. CRi: CR with incomplete blood count recovery. NE: Not estimable. ORR: Overall remission rate.

The swimmer plot of individual durations of remission (DoR) in patients who obtained a best disease control rate of CR or CRi in the ELIANA trial suggests that sustained remissions can be achieved in these patients.

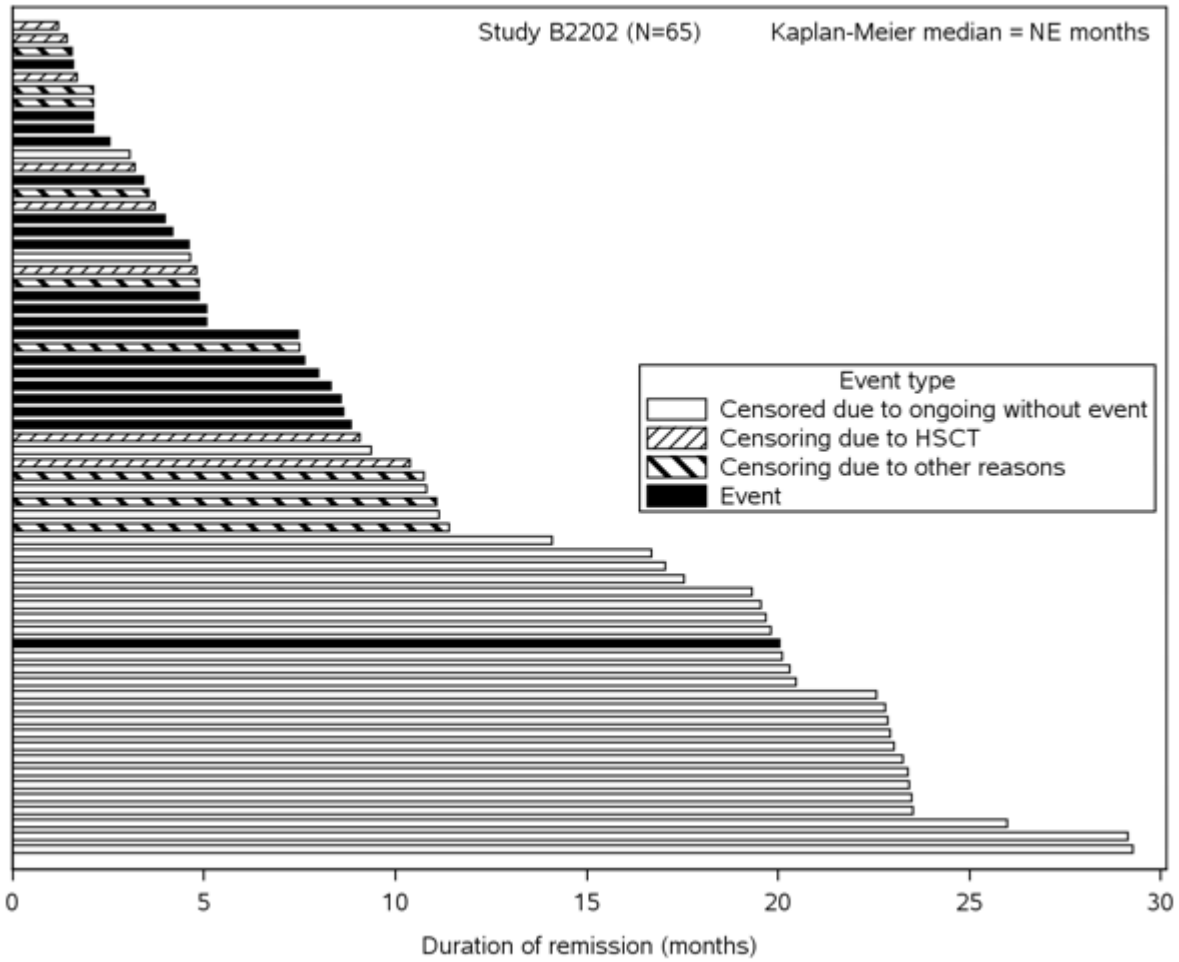


Figure 3 Swimmer plot of individual DoR (Duration of Remission) in patients with CR or CRi within 3 months (ELIANA study)

Patients with active CNS involvement were excluded from ELIANA and ENSIGN. Four patients with active CNS leukaemia (i.e. CNS3) were included in study B2101J. Three of these patients experienced CRS (Grade 2-4) and transient neurological abnormalities (Grade 1-3) that resolved within 1-3 months after inititaion of treatment with tisagelecleucel. One patient died due to disease progression and the remaining three patients achieved a CR or CRi and remain alive 1.5-2 years after infusion.

Submitted health economic analyses

Efficacy inputs for tisagenlecleucel are based on the ELIANA trial data, pooled ELIANA and ENSIGN trial data, or pooled data using all three trials (Data cut-off dates: ELIANA 31 Dec 2017, ENSIGN 06 Oct 2017, B2101J 30 Jan 2017). NoMA chose to use pooled ELIANA and ENSIGN data as the source of efficacy data for tisagenlecleucel due to similar trial design of the two studies (see 2.1.2 for more details). Patient data for EFS and OS separately for the mITT and ITT populations were used to estimate the number of patients in each respective health state in the model.

Efficacy inputs for CEC were based on the pooled data from Hijiya 2011, Miano 2012 and Locatelli 2009. Only aggregate OS data were available in these publications. Data were extracted from the published Kaplan-Meier (KM) curves using the digitization software Engauge. Pseudo-patient level data were then derived based on the KM data using algorithm outlined in Guyot et al (2012) (10). EFS curves were based on the EFS:OS ratio derived from the literature (see the details presented below).

3.4.2 Extrapolation of efficacy

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

Base case OS estimates are based on parametric curves for up to 5 years fitted individually to unmatched KM curves for tisagenlecleucel and CEC. As a scenario analysis, Novartis also provided an option of using a hazard ratio (HR) as derived from MAIC as an input of the relative efficacy. Novartis based its modelling of effect in this scenario on the assumption that the proportional hazard (PH) holds. Long-term survival over 5 years could either be modelled by incorporating a standardized mortality ratio (SMR) from the literature, or based on the parametric extrapolation.

The economic model allows for a wide selection of standard parametric functions, a series of flexible cubic spline models or cure models. Selection of the function is based on goodness-of-fit tests (the Akaike Information Criterion, AIC; Bayesian Information Criteria, BIC) and visual inspection of the KM data.

The fit of standard parametric functions as well as a series of one-, two-, three-, and four-knot spline models to the KM data is presented in

Table 6 and Table 7 and Figure 4- Figure 6. To account for the uncertainty of choosing specific survival distribution, Novartis used a model averaging approach in the base case following the recommendations of the NICE mock appraisal (11) and using the methods described in Jackson et al (2009) (12). This technique includes all plausible survival functions as part of a weighted distribution to estimate the joint distribution of uncertainty around the parameter estimates and the choice of survival function. The weights were calculated based on AIC score using the following equation: $Wgt = Ak/(\sum Ak)$, where $Ak = e^{-(0.5 \times AIC)}$. The weighted distribution was then applied in the base case analysis.

Table 6 Distributions used to estimate overall survival for tisagenlecleucel (ELIANA+ ENSIGN), mITT and ITT populations

	mITT population			ITT population		
	AIC[2]	BIC[2]	AIC based weight[3]	AIC[2]	BIC[2]	AIC based weight[3]
Exponential	400,37	403,29	13,1%	559,27	562,40	0,7%
Weibull	401,40	407,24	7,9%	555,42	561,70	4,7%
Gompertz	399,48	405,32	20,5%	551,28	557,55	37,2%
Log-Normal	399,20	405,04	23,6%	552,57	558,84	19,5%
Log-Logistic	400,13	405,97	14,8%	553,02	559,29	15,6%
Gamma	401,18	409,94	8,7%	554,44	563,85	7,7%
Spline with single knot[1]	401,77	410,53	6,5%	554,19	563,60	8,7%
Spline with two knots[1]	403,56	415,24	2,7%	555,88	568,43	3,7%
Spline with three knots[1]	404,65	419,25	1,5%	557,70	573,38	1,5%
Spline with four knots[1]	406,39	423,91	0,6%	558,96	577,78	0,8%

[1]Cubic spline models with one, two, three, and four knots expressed on the proportional hazard scale are fitted based on the method developed by Royston and Parmar (13) . [2]AIC - Akaike information criterion. A smaller AIC value represents a better goodness of fit; BIC - Bayesian information criterion. A smaller BIC value represents a better goodness of fit. [3]The weights are calculated based on AIC scores using the method outlined in Jackson 2009. The weights represent the adequacy of each distribution in predicting the efficacy and are used in the calculation for the weighted distribution.

*Table 7 Distribitions used to estimate overall survival for CEC, mITT population**

	AIC	BIC	AIC based weight
Exponential	349,24	351,54	0,0%
Weibull	343,31	347,92	0,0%
Gompertz	325,94	330,54	25,3%
Log-Normal	330,02	334,63	3,3%
Log-Logistic	330,43	335,03	2,7%
Gamma	328,55	335,46	6,8%
Spline with single knot[1]	326,02	332,94	24,2%
Spline with two knots[1]	326,84	336,06	16,1%
Spline with three knots[1]	328,07	339,59	8,7%
Spline with four knots[1]	327,28	341,11	12,9%

**OS was measured from the initiation of treatment*

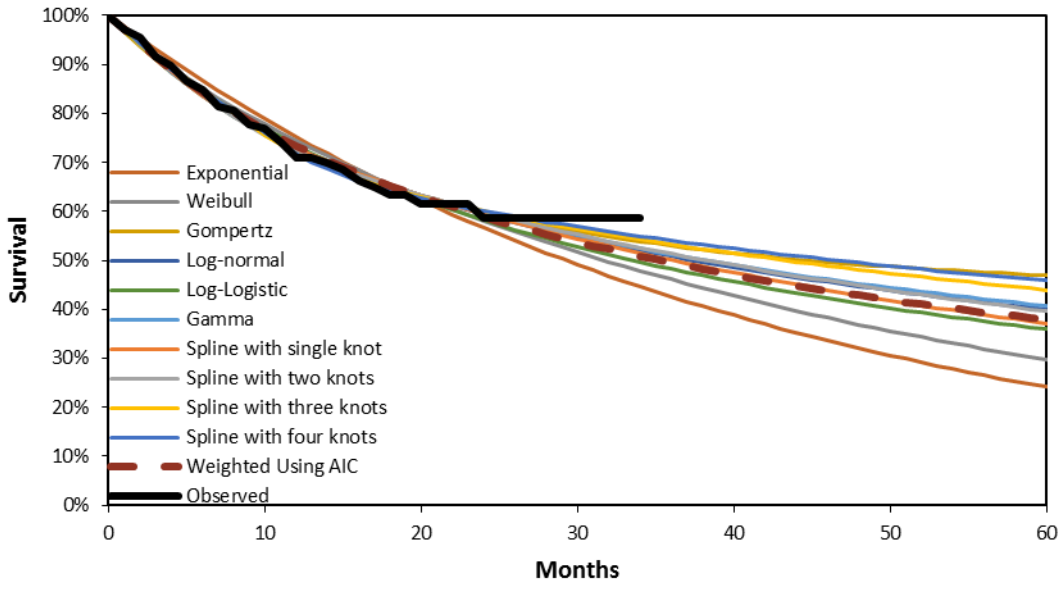


Figure 4 OS parametric models for tisagenlecleucel (ELIANA+ ENSIGN), mITT population

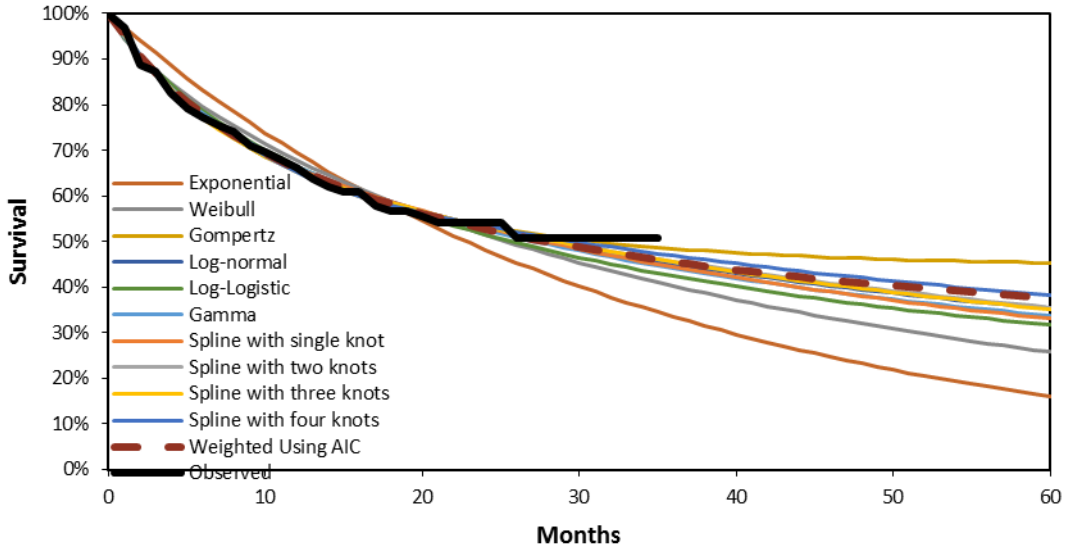
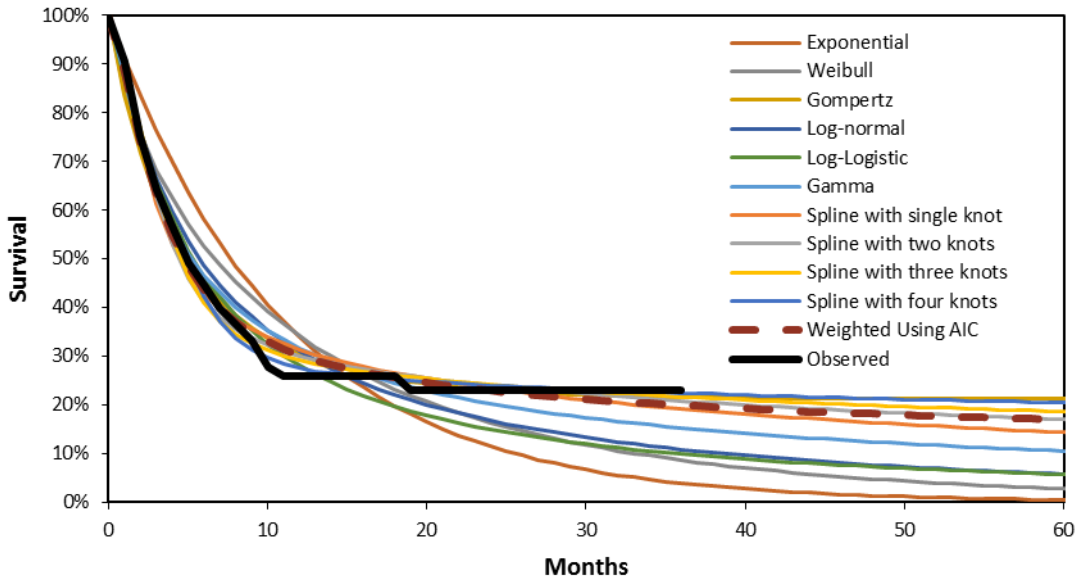


Figure 5 OS parametric models for tisagenlecleucel (ELIANA+ ENSIGN), ITT population



**OS was measured from initiation of treatment*

*Figure 6 OS parametric models for CEC, mITT population**

Patients who remained alive at 5 years were subsequently assumed to be long-term survivors of ALL. The long-term ALL survival was modelled using Norwegian life tables, with a mortality adjustment for 5-year ALL survivors, using the SMR adjustment published in the literature (14-17) (Table 8). The estimated SMR-adjusted survival rate was applied to all patients who remain alive from year 5 onwards in the model. A literature review was conducted to identify publications to inform long-term survival for the study target population (registry or SMR studies). Four SMR publications for ALL long-term survivors were identified as the most relevant evidence. MacArthur et al. (2007) (16) was used in the base-case to be consistent with the NICE mock appraisal (11). SMR inputs from the three other studies were evaluated in the sensitivity analysis. The same mortality risk was applied to all treatments. This assumption reduced some of the long-term uncertainties arising from the extrapolation of data beyond the maximum reported follow-up.

Table 8 Long-term survival input sources

Publication	Population	Sample Size	SMR Measure
Base-case			
MacArthur et al., 2007[7]	Individuals less than 20 years of age diagnosed with cancer who survived 5 years or more after diagnosis.	Overall sample size: 2,354; Sample size for ALL patients: 429	SMR for childhood cancer 5-year survivors: 9.05
Sensitivity analysis			
Armstrong et al., 2016[28]	All childhood cancer survivors diagnosed with cancer before age 21 (paediatric and adolescent) and alive at least 5 years after diagnosis	Overall sample size: 34,033; Sample size for ALL patients: 8,500	SMR for ALL 5-year survivors: 15.2
Bhatia et al., 2005[29]	Paediatric, adolescent, and adult patients who survived two or more years after autologous HSCT for hematologic malignancies	Overall sample size: 854; Sample size for ALL patients: 59	SMRs for ALL: 6-10 years from HSCT: 26.5; 11 or more years from HSCT: 4.2
Socie et al., 1999[30]	Paediatric, adolescent, and adult patients who received allogenic HSCT between 1980 to 1993 and were disease-free 2 years post procedure; 22% of patients were diagnosed with ALL, and among those, 45% received HSCT in CR1, 45% in CR2, and 10% not in remission	Overall sample size: 6,691; Sample size for ALL patients: 1,458	Relative mortality rate for ALL patients vs. general population: 5 years after HSCT: 25.9; 10 years after HSCT: 15.4
Abbreviations: ALL, acute lymphoblastic leukaemia; CR1, first complete remission; CR2, second complete remission; HSCT, haematopoietic stem cell transplant; SMR, standardised mortality ratio			

An option of fitting a mixture cure model individually to each arm was also available. The cure model is based on the assumption that the patient population consists of a mix of patients who are cured and patients who are not cured. 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 the standard parametric survival distributions. When estimating the cure model, no covariate was adjusted given the data used were all from single-arm studies and there was no individual patient level data available for OS of CEC.

NoMA's assessment of OS extrapolation

Both the proposed modelling approaches: 1) parametrization based on unadjusted OS curves (base case), and 2) relative effect based on a HR applied to an unadjusted tisagenlecleucel arm (scenario analysis) suffer from severe limitations. As stated in 2.1.2, the results of the MAIC are very uncertain due to the small sample size and heterogeneity of the CEC comparator, and too few matching variables. There is, therefore, a large amount of uncertainty surrounding the estimated HRs and a high risk of bias, and it is unclear whether the adjusted estimates are more reliable for decision making than the unadjusted estimates. Furthermore, the Schoenfeld residuals and log-cumulative hazard plot (Figure 15 in Appendix 2) do not support the proportional hazard assumption. The mechanism of action between tisagenlecleucel and CEC is also very different, and does not provide a rationale for a constant proportional treatment effect. NoMA concludes that there is no evidence to support the use of a constant HR in the model. Instead, NoMA has focussed on the individual parametrization in this assessment. The

economic model offers the option of fitting parametric curves to unadjusted KM curves. Despite NoMA's request, the individual adjusted curves were not included in the model. Using an unadjusted (naïve) comparison of OS data is highly unreliable and generally not recommended, as it is not possible to determine whether the effect is attributable to tisagenlecleucel only, or to the differences in the studies. NoMA noted however, that due to very few matching variables, the unadjusted OS curves for tisagenlecleucel do not deviate much from the adjusted curves (Figure 14 in Appendix 2). Therefore, it is not expected that using adjusted curves would change the conclusions of this assessment. Furthermore, the adjusted tisagenlecleucel curves are based on smaller patient numbers as they represent patients who were matched to the CEC comparator. NoMA considers the analyses based on unadjusted curves to be highly uncertain.

The long-term survival estimates vary greatly between the scenarios where either individual parameterizations or the HR were used in the model, highlighting the large amount of uncertainty surrounding the model predictions. NoMA identified limitations in the application of the weighted AIC curves in the submission by Novartis. NoMA acknowledges that weighted AIC curves can account for the uncertainty resulting from choosing a specific survival distribution. However, the position of the weighted AIC curve is dependent on the number and the type of parametric functions considered and the plausibility of individual functions has not been discussed. Furthermore, Novartis has averaged survival probabilities as opposed to averaging expected costs and effects resulting from each parametric function in its submission. Choosing a specific parametric model does not only affects survival outcomes, but also for example quality of life and costs. As the model outcomes are highly non-linear functions of the survival parameters, the approach taken by Novartis introduces bias due to non-linearity. This is also explained in the literature, where it is described that the correct approach for model-averaging is to weigh model outcomes in terms of costs and effects (12, 18, 19).

Instead, NoMA has used the weighted AIC curve position together with the individual AIC scores to guide the selection of parametric functions. In the ITT population, Gompertz, log-normal and log-logistic offer the best mathematical fit to the KM data. The log-normal gives a tail that is closely aligned with the weighted AIC curve and is preferred. The application of the Gompertz function gives the most optimistic tail and because of the good mathematical and visual fit to the data, it has been tested in a scenario analysis (Section 0). In the mITT population, all the standard parametric functions result in similar fits to the KM data. To be consistent with the ITT population and to preclude conflicting results between the ITT and mITT populations, the log-normal is chosen. In addition, the function gives a tail that is closely aligned with the weighted AIC curve.

For the CEC arm, the Gompertz or cubic spline models with one or two knots provide the best fit. The use of the Gompertz function results in the most optimistic tail and in line with the tisagenlecleucel arm, the function is tested in a scenario analysis. The spline model with two knots gives a tail that largely coincides with the weighed AIC model and is, therefore, preferred. Flexible cubic spline models are recommended when the log-cumulative hazard plots are not straight lines (20), which is clearly the case for CEC (Figure 15 in Appendix 2). The choice of different functions per arm is justifiable due to the different mechanism of action.

NoMA also considered the selection of a mixture cure model given the curative potential of tisagenlecleucel. The efficacy results from the supportive study B2201J with median follow-up of 32.3 months (max 57.5 months) showed the estimated proportion of patients alive at 48 months of 48.1%. The data is, however, immature with a high censoring rate of 61%. According to Farewell (1986)(21) the mixture cure model generally requires long-term follow-up and large samples, and censoring from loss to follow-up during the period when events can occur must not be excessive. This is not the case for the tisagenlecleucel trials as the data are highly immature and highly censored. It is therefore not possible to robustly estimate the cure fraction as input for the mixture cure model, and the timing of the cure is also highly uncertain. Lastly, Novartis assumes that the "cured" fraction will follow the normal population survival, while evidence suggests that long-term survivors continue to experience excess mortality from both cancer and noncancer causes (14-17). The cure model was, therefore, only explored in a scenario analysis, section 0.

The application of a standardized mortality ratio (SMR) for all arms from year 5 onwards was used by Novartis and various long-term survival input sources were presented. NoMA accepts this approach given the immaturity of the OS and the curative potential of tisagenlecleucel. The source studies for SMR could not be reliably pooled due to a high degree of heterogeneity (I^2 of 94% to 95%, random effects meta-analysis conducted by Novartis). Consequently, MacArthur et al (2007) was selected to derive the SMR in NoMA's base case. The model is not very sensitive to the choice of an alternative input.

Submitted health economic analyses - projection of event-free survival (EFS)

Parametrization of the tisagenlecleucel arm

The fit of standard parametric functions as well as a series of cubic spline models to the tisagenlecleucel KM data is presented in Table 9 and Figure 7. A weighted distribution based on various parametric survival curves was then derived and applied in the base case analysis.

Table 9 Distributions used to estimate event-free survival for tisagenlecleucel (ELIANA+ ENSIGN), mITT and ITT populations

	mITT			ITT		
	AIC[2]	BIC[2]	AIC based weight[3]	AIC[2]	BIC[2]	AIC based weight[3]
Exponential	450,80	453,72	0,0%	638,58	641,72	0,0%
Weibull	391,65	397,49	29,6%	436,36	442,63	1,1%
Gompertz	424,15	429,99	0,0%	571,01	577,28	0,0%
Log-Normal	393,08	398,92	14,5%	427,33	433,60	96,7%
Log-Logistic	393,01	398,85	15,0%	434,85	441,12	2,3%
Gamma	393,43	402,19	12,2%			
Spline with single knot[1]	392,49	401,25	19,5%			
Spline with two knots[1]	394,01	405,69	9,1%			

[1] Cubic spline models with one, two, three, and four knots expressed on the proportional hazard scale are fitted based on the method developed by Royston (2002) (13). [2] AIC - Akaike information criterion. A smaller AIC value represents a better goodness of fit; BIC - Bayesian information criterion. A smaller BIC value represents a better goodness of fit. [3] The weights are calculated based on AIC scores using the method outlined in Jackson 2009. The weights represent the adequacy of each distribution in predicting the efficacy and are used in the calculation for the weighted distribution.

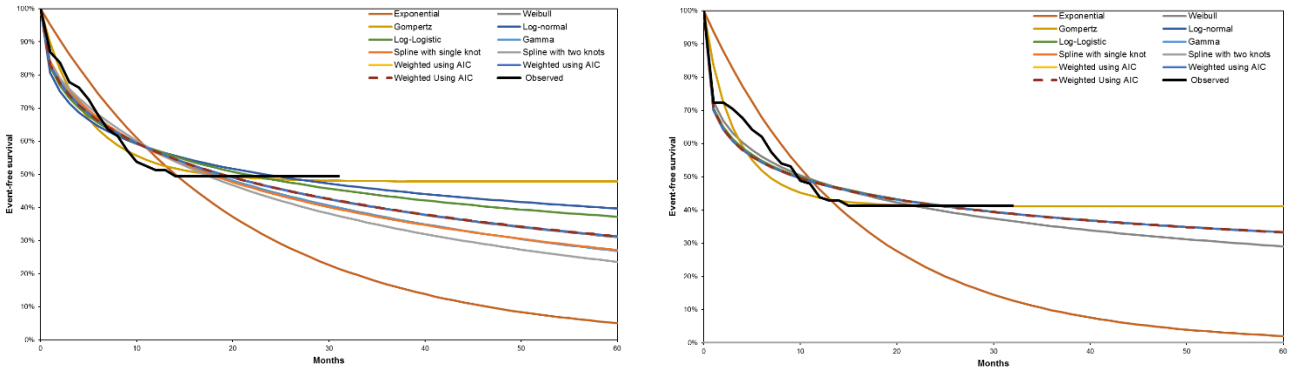


Figure 7 EFS parametric models for tisagenlecleucel (ELIANA+ ENSIGN), mITT (left) and ITT population (right)

Source of EFS for the CEC arm

EFS data was not available in the literature for the comparator arm. In the absence of the data, the EFS curves were derived from the available OS curves. Before year 5, it was assumed that the cumulative hazard function for EFS would be proportional to cumulative hazard function for OS. The ratio between EFS and OS was modelled based on the mitoxantrone arm from the UK ALL study (22). The ratio is first estimated as the natural log of OS probability divided by the natural log of EFS probability at yearly intervals for the first 4 years (Table 10). The overall cumulative hazard ratio between OS and EFS is then calculated as the average of cumulative hazard ratios at all yearly intervals. This assumption is justifiable on the basis that EFS is correlated with OS (23). In this model, the proportional relationship between EFS and OS was assumed to continue up to year 5. After year 5, the cumulative survival probabilities of EFS were assumed to flatten up until they reached OS. The 5-year period is consistently cited in existing ALL studies and represents a clinically important time point for patients to reach given the limited risk of relapses after year 5 (24). EFS was assumed to be less than or equal to OS at all time points.

Table 10 OS and PFS observation from Parker et al. (2010) (22)

	Year 1	Year 2	Year 3	Year 4
PFS (mitoxantrone arm)	74%	67%	65%	61%
OS (mitoxantrone arm)	80%	71%	69%	65%
Cumulative hazard ratio (mitoxantrone, OS vs. PFS)	**0.76**	**0.85**	**0.85**	**0.86**

NoMA's assessment of EFS extrapolation

It is evident that the visual fit of standard parametric functions or more flexible spline functions to the tisagenlecleucel KM data is poor. In the ITT population, the log-normal curve offers the best mathematical

fit and a moderate tail that overlaps the weighted AIC curve which could be seen as an “average” of the tested functions. The log-normal function is therefore preferred. For consistency and comparability, the same function was chosen for the mITT population. The mathematical fit was similar between the functions.

Due to the lack of EFS data for CEC, the EFS curves were derived from the available OS curves using a PFS:OS ratio based on the literature. NoMA does not usually accept survival data based on a ratio from the literature, unless the relationship is well documented and the trial data do not provide the required evidence. Novartis claims that this assumption is justifiable due to a correlation between EFS and OS as observed in an acute myeloid leukaemia (AML) study conducted by Schlenk et al. Although NoMA acknowledges that there is evidence for EFS as a surrogate for OS in AML, it is unknown whether the same applies to paediatric ALL. Novartis conducted a targeted literature review and selected the mitaxontrone arm from the UK paediatric ALL study (Parket *et al*, 2010) as the source of the EFS:OS ratio for CEC. The population in the Parker *et al* study differs from ELIANA and ENSIGN as only patients with first relapse of ALL were included. Furthermore, the Parker study uses PFS as an endpoint and the definition differs slightly from the definition of EFS in ELIANA. In the Parker study, PFS was defined as time from randomisation to the first of induction failure (based on % blasts), relapse, death from any cause, or a second malignancy. In ELIANA, EFS was defined as time from infusion to the earliest date of death due to any cause after remission, relapse, or treatment failure. Treatment failure was defined as no response in the study and discontinuation from the study due to death, AE, lack of efficacy, or new anticancer therapy. NoMA considers the lack of direct evidence on EFS to result in considerable uncertainty surrounding the magnitude of the correlation and the changes in magnitude over time. NoMA recognizes, however, that the correlation between EFS and OS is only applied for 5 years in the analyses. After 5 years, EFS flattens until it reaches OS, i.e., EFS will eventually be equal to OS in the model. It is also noted that it is EFS as opposed to OS, which is the key driver of the model, that is derived from the ratio. The model results are, therefore, not sensitive to this cumulative hazard ratio. Despite the limitations and because of the minimal impact on the results, NoMA accepts the use of the PFS:OS ratio.

Conclusions on efficacy parameters

The key limitations of the submitted documentation are:

- Lack of head-to-head comparator trial data and lack of a common comparator for the indirect comparison
- Immature survival data and uncertainty about the long-term effect
- The CEC comparator arm is based on highly heterogeneous small studies
- Failure to adjust for important prognostic factors and effect modifiers between the patient populations in the tisagenlecleucel and CEC studies
- Poor visual fit of parametric functions to the EFS data for tisagenlecleucel
- Lack of direct evidence on EFS for CEC and the use of external data sources to justify the EFS:OS ratio

Consequently, the relative effect of tisagenlecleucel vs CEC cannot be reliably established. NoMA therefore considers this analyses to be highly uncertain. NoMAs preferred assumptions for the analyses are:

- Use of ELIANA and ENSIGN as the source of OS and EFS data as opposed to ELIANA+ENSIGN+ B2101J
- Use of parametric functions individually fitted to unadjusted KM data as opposed to a HR applied to the tisagenlecleucel arm
- Use of standard parametric functions (mITT OS: Log-normal for tisagenlecleucel, spline model with two knots for CEC; ITT OS: Log-normal for tisagenlecleucel; mITT EFS: Log-normal for tisagenlecleucel, not applicable for the comparator as a ratio from the spline model with two knots is applied; ITT EFS: Log-normal for tisagenlecleucel) as opposed to weighted AIC curves
- Use of a SMR for over 5 years survival projections based on MacArthur *et al.* 2007 (in agreement with Novartis base case)
- Use of PFS:OS ratio from Parker *et al.* 2010 as a source of EFS:OS ratio for CEC (in agreement with Novartis base case)

3.4.3 Safety

Submitted clinical studies

The safety profile of tisagenlecleucel is affected by the cytotoxic chemotherapy combinations used as bridging and lymphodepleting therapy, which the patients receive pre-infusion, as well as the medication needed to treat the AEs post-infusion such as antibiotics, gammaglobulines, antipyretics and anti-IL-6 based therapy (e.g. tocilizumab).

The AE rates for tisagenlecleucel described below are based on the data cut off of the ELIANA (study B2202) of 25-Apr-2017 (median follow-up: 13.1 months) and ENSIGN (study B2205J) of 01-Feb-2016 (median follow-up: 11.5 months), which is consistent with the EMA label. The safety data from both of these multicentre studies were combined. An overview of the most frequently reported AEs regardless of relationship is presented in Table 11 below. Serious adverse events (SAEs) were reported in 77.9% of the infused patients. The most frequently reported SAEs post-tisagenlecleucel infusion were CRS (All grades: 64.4%; Grade 3/4: 43.2%), febrile neutropenia (Grade 3/4: 24.0%), and hypotension (Grade 3/4: 11.5%).

Table 11 AEs post-tisagenlecleucel infusion, regardless of study drug relationship, by preferred term and maximum grade – more than 20% in all patients; all grades (Safety analysis set)

	Study B2202 N=75			Study B2205J N=29			All patients N=104		
Preferred term	**All grades n (%)**	**Grade 3 n (%)**	**Grade 4 n (%)**	**All grades n (%)**	**Grade 3 n (%)**	**Grade 4 n (%)**	**All grades n (%)**	**Grade 3 n (%)**	**Grade 4 n (%)**
Number of patients with at least one AE	75 (100)	17 (22.7)	49 (65.3)	29 (100)	4 (13.8)	20 (69.0)	104 (100)	21 (20.2)	69 (66.3)
Cytokine release syndrome	58 (77.3)	16 (21.3)	19 (25.3)	26 (89.7)	5 (17.2)	6 (20.7)	84 (80.8)	21 (20.2)	25 (24.0)
Pyrexia	30 (40.0)	8 (10.7)	2 (2.7)	13 (44.8)	2 (6.9)	1 (3.4)	43 (41.3)	10 (9.6)	3 (2.9)
Decreased appetite	29 (38.7)	10 (13.3)	1 (1.3)	13 (44.8)	10 (34.5)	0	42 (40.4)	20 (19.2)	1 (1.0)
Hypogammaglobulinaemia	25 (33.3)	4 (5.3)	0	13 (44.8)	1 (3.4)	0	38 (36.5)	5 (4.8)	0
Febrile neutropenia	27 (36.0)	25 (33.3)	2 (2.7)	10 (34.5)	10 (34.5)	0	37 (35.6)	35 (33.7)	2 (1.9)
Vomiting	22 (29.3)	1 (1.3)	0	15 (51.7)	2 (6.9)	0	37 (35.6)	3 (2.9)	0
Headache	27 (36.0)	2 (2.7)	0	8 (27.6)	0	0	35 (33.7)	2 (1.9)	0
Anaemia	23 (30.7)	9 (12.0)	0	11 (37.9)	6 (20.7)	1 (3.4)	34 (32.7)	15 (14.4)	1 (1.0)
Nausea	19 (25.3)	2 (2.7)	0	13 (44.8)	5 (17.2)	0	32 (30.8)	7 (6.7)	0
Platelet count decreased	23 (30.7)	7 (9.3)	7 (9.3)	9 (31.0)	0	6 (20.7)	32 (30.8)	7 (6.7)	13 (12.5)
Hypotension	22 (29.3)	8 (10.7)	7 (9.3)	10 (34.5)	2 (6.9)	7 (24.1)	32 (30.8)	10 (9.6)	14 (13.5)
Aspartate aminotransferase increased	20 (26.7)	8 (10.7)	3 (4.0)	11 (37.9)	3 (10.3)	4 (13.8)	31 (29.8)	11 (10.6)	7 (6.7)
White blood cell count decreased	21 (28.0)	1 (1.3)	13 (17.3)	10 (34.5)	4 (13.8)	4 (13.8)	31 (29.8)	5 (4.8)	17 (16.3)
Hypokalaemia	20 (26.7)	9 (12.0)	2 (2.7)	11 (37.9)	3 (10.3)	1 (3.4)	31 (29.8)	12 (11.5)	3 (2.9)
Neutrophil count decreased	22 (29.3)	5 (6.7)	15 (20.0)	8 (27.6)	0	7 (24.1)	30 (28.8)	5 (4.8)	22 (21.2)
Diarrhoea	18 (24.0)	1 (1.3)	0	11 (37.9)	1 (3.4)	0	29 (27.9)	2 (1.9)	0
Alanine aminotransferase increased	18 (24.0)	7 (9.3)	0	11 (37.9)	7 (24.1)	0	29 (27.9)	14 (13.5)	0
Tachycardia	17 (22.7)	2 (2.7)	1 (1.3)	8 (27.6)	2 (6.9)	0	25 (24.0)	4 (3.8)	1 (1.0)
Fatigue	16 (21.3)	0	0	9 (31.0)	1 (3.4)	0	25 (24.0)	1 (1.0)	0
Hypoxia	18 (24.0)	10 (13.3)	4 (5.3)	7 (24.1)	3 (10.3)	3 (10.3)	25 (24.0)	13 (12.5)	7 (6.7)
Cough	17 (22.7)	0	0	7 (24.1)	0	0	24 (23.1)	0	0
Hypophosphataemia	18 (24.0)	8 (10.7)	1 (1.3)	4 (13.8)	3 (10.3)	0	22 (21.2)	11 (10.6)	1 (1.0)
Lymphocyte count decreased	16 (21.3)	10 (13.3)	5 (6.7)	5 (17.2)	3 (10.3)	1 (3.4)	21 (20.2)	13 (12.5)	6 (5.8)

A patient with multiple occurrences of an AE is counted only once in the AE category at the maximum toxicity grade.
Preferred terms are presented in descending frequency of all grades column, as reported in the All patients column.
Source: [SCS Appendix 1-Table.3-1.1]

The safety profile of tisagenlecleucel was observed to be more severe during an initial acute toxicity phase that encompasses the first 8 weeks post-infusion, due to the rapid T cell expansion and cytotoxic effect on CD19-positive B-cells. Accordingly, both the AEs and SAEs were more frequently reported within the first 8 weeks after tisagenlecleucel infusion (All Grades AEs: 98.1%; Grade 3/4 AEs: 82.7%; All grades SAEs: 71.2%; Grade 3/4 SAEs: 63.5%) compared to the subsequent follow-up phases from >8 weeks to 1 year (All Grades AEs: 92.3%; Grade 3/4 AEs: 45.1%; Grade 3/4 SAEs: 31.9%) and beyond 1 year (All Grades AEs: 27.6%; Grade 3/4 AEs: 10.3%). The most frequently reported AE of special interest (AESI) >8 weeks to 1 year post-tisagenlecleucel infusion was infections (52.7%). Other AESIs were reported in 1-5% of the patients.

In total, 3 deaths were considered related to tisagenlecleucel. Two of these deaths occurred more than 30 days after tisagenlecleucel infusion in ELIANA and were reported to be due to encephalitis and systemic mycosis. Another death registered within 30 days post-infusion, was also considered related to tisagenlecleucel. This patient got several SAEs including CRS, and had a fatal cerebral haemorrhage on Day 15.

The most serious and life-threatening AE related to tisagenlecleucel is CRS, which was observed in 80.8% (Grade 3: 20.2%; Grade 4: 24%) of the paediatric ALL patients with a median time of onset of 3 days (range: 1 to 22 days) post-infusion. CRS is an on-target toxicity that results from tisagenlecleucel cell expansion, activation and tumour cell killing. The median duration of CRS was 8.0 days (range: 1-36 days). Grade 3/4 events occurred at a median of 6.0 days (range: 2-33 days) post-infusion. All events of CRS occurred exclusively within the first 8 weeks post-infusion. CRS was reversible in most cases and was managed with supportive care and anti-cytokine therapy as needed. Treatment with tocilizumab was required for 41.7% of the patients, 6% received siltuximab and 23% had treatment with corticosteroids in addition to other anti-cytokine drugs (Table 12). Additionally, approximately half of the patients with CRS (56.0%) required intensive care unit level care at a median of 6 days (range: 1-24 days) after the infusion, and remained for a median duration of 7 days (range: 1-34 days).

Table 12 Anti-cytokine therapy during CRS (Safety analysis set – Patients with CRS)

	Study B2202 N=58	Study B2205J N=26	All patients N=84
Systemic anti-cytokine therapy given - n (%)	28 (48.3)	7 (26.9)	35 (41.7)
Tocilizumab	28 (48.3)	7 (26.9)	35 (41.7)
1 dose	17 (29.3)	2 (7.7)	19 (22.6)
2 doses	8 (13.8)	2 (7.7)	10 (11.9)
3 doses	3 (5.2)	3 (11.5)	6 (7.1)
4 doses	0	0	0
>4 doses	0	0	0
Siltuximab	5 (8.6)	0	5 (6.0)
Corticosteroids	14 (24.1)	5 (19.2)	19 (22.6)
Other	2 (3.4)	5 (19.2)	7 (8.3)

Source: [SCS Appendix 1-Table 3-14.1]

Both cardiac dysfunction and renal failure can be potentially life-threatening complications of CRS. Overall, 47.1% of the patients experienced cardiac events (Grade 3: 13.5%; Grade 4: 7.7%) during the study. Most patients with grade 3/4 cardiac events experienced these concurrently with CRS. The occurrence were declining over time. Furthermore, seven patients in ELIANA and 4 patients in ENSIGN underwent renal dialysis for fluid overload and/or renal failure; all events occurred during CRS and were attributable to tisagenlecleucel.

Data show that CRS is observed regardless of response status. However, the proportion of patients with CRS and associated side effects was greater among patients with high baseline tumour burden compared to those with low tumour burden. Peak serum cytokine levels correlated with CRS severity.

Neurological AEs were observed in 37.5% (Grade 3: 9.6%; Grade 4: 1%) of the paediatric ALL patients. These events were often seen as part of the CRS, in particular with high fever, and occurred within few days post-infusion. The majority of neurologic events occurred first 30 days post-infusion. Predominantly, nervous system disorders were observed in 57.7% of the infused patents and psychiatric reactions in 44.2%. Headache and encephalopathy were the most frequent nervous system disorders, whereas

confusional state and delirium were the most frequent psychiatric disorders. The majority of neurological events resolved completely, however, 7% of the patients with neurological events were not recovered at the time of data cut-off. Prior history of other CNS diagnoses is considered a risk factor.

Due to the time sequence and frequency of severe CRS and (early) neurological events > Grade 3, patients should according to the SmPC be monitored daily for signs and symptoms of potential CRS, neurological events and other toxicities for the first 10 days following infusion. Physicians should also consider hospitalisation in this time period or at the first signs/symptoms of CRS and/or neurological events. Additionally, patients should be instructed to remain within proximity of a qualified clinical facility for at least 4 weeks following tisagenlecleucel infusion.

B-cell aplasia is an on-target effect of tisagenlecleucel and treated patients may therefore experience hypo- or agammaglobulinemia as long as tisagenlecleucel persists in the patients. Since tisagenlecleucel is a cellular immunotherapy derived from a mixed population of CD4+ and CD8+ T cells at various stages of cell differentiation, the CAR-T cells of this medicinal product are expected to follow the normal fate of T cells with different phenotypes. Notably, memory T cells can live for up to six months (25), whereas naive T cells can live up to nine years in healthy humans (26).

Available data from the ELIANA and ENSIGN trials demonstrated that the tisagenlecleucel transgene can persist for up to 25 months in the peripheral blood of responding paediatric and young adult patients with ALL. Further, the CD3+CAR+ cells showed a half-life (geometric mean) of approximately 21.7 days, but were detectable for up to a year in the bone marrow of responding patients. Importantly, the observed persistence of tisagenlecleucel is expected to increase as the data available matures. In view of that, tisagenlecleucel may potentially be detectable in treated patients for an extended period of time and depletion of normal B-cells/agammaglobulinemi within this timespan constitute a high risk of the treatment. Consequently, successful treatment with tisagenlecleucel resulted in acquired hypogammaglobulinemia due to the loss of normal B cells. Hypogammaglobulinaemia regardless of relationship was seen in 36.5% (Grade 3: 4.8%) of the patients, whereas those AEs suspected to be related to the study drug was reported in 32.7%. As occurrence of hypo- or agammaglobulinemia might rendering the patients more susceptible to infections, patients with hypogammaglobulinemi need to be maintained on supplemental treatment with intravenous gamma globulins (IVIG). In the pooled studies, immunoglobuline replacement therapy was given to 47.1% of the patients post-tisagenlecleucel infusion.

Infectious risk in this ALL group is significantly elevated due to disease- and chemotherapy-induced neutropenia, and prior infectious exposures. Subsequently, the on-target toxicity of tisagenlecleucel therapy results in B-cell aplasia and can make patients more susceptible to infections due to hypogammaglobulinemia. Infections were seen in 67% of the paediatric ALL patients, and 44.2% (All grades; Grade 3: 17.3%; Grade 4: 2.9%) got infections within 8 weeks post-infusion.

Febrile neutropenia experienced by 36% of the paediatric ALL patients was managed with standard practice of hospital admission, culture surveillance, broad spectrum antibiotics, fluids and other supportive care. Febrile neutropenia may be associated with both LD therapy and tisagenlecleucel, and may be concurrent with CRS. The occurrence of febrile neutropenia was mostly seen within the first eight

weeks post-infusion (All grades: 34.6%; Grade 3: 32.7%; Grade 4: 1.9%), and the proportion of patients reduced substantially >8 weeks to 1 year post-infusion.

Hematopoietic cytopenias were seen in 36% (All grades; Grade 3: 14.4%; Grade 4: 15.4%) of the paediatric ALL patients and was observed both within 28 days as well as several months post-infusion. The aetiology of the cytopenias may be the CAR T-cell therapy itself, the underlying ALL, and prior ALL and LD therapies administered prior to the tisagenlecleucel infusion. Management of hematopoietic cytopenias was blood product support, growth factors and/or antibiotics as indicated. Myeloid growth factors is not recommended until CRS has been resolved and typically not before 28 days have elapsed following tisagenlecleucel-infusion.

Submitted health economic analyses

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

AE costs are described and assessed in section 4.1.2. In summary, AE costs were calculated based on rates of AEs and unit costs per AE. The AE rates inputs were obtained from the ELIANA trial data (data cut-off: 25 Apr 2017) for tisagenlecleucel, and Hijiya et al. 2011 for CEC. Only grade 3 or 4 AEs with greater than 5% rates in any of the treatment arms were considered. Both CRS and B-cell aplasia could be associated with substantial resource use, and were included specifically to the tisagenlecleucel arm.

Treatment and AEs disutilities are described and assessed in section 3.4.4. Treatment disutilities for tisagenlecleucel (for the duration of hospitalisation after the infusion), chemotherapies and subsequent alloSCT were considered. Additional treatment disutilities associated with CRS were added separately.

NoMA´s assessment

Current treatment options for paediatric and young adult patients with relapsed/refractory B-cell ALL are intensive therapies associated with significant toxicity, treatment related mortality and a poor quality of life.

Tisagenlecleucel carries considerable known risk to the recipient, most notably in the first 8 weeks after exposure. However, long-term safety data is limited due to short follow-up time and limited number of patients included in the clinical studies. Therefore, there may be unknown risks associated with tisagenlecleucel which only become apparent after long-term follow-up. Some important safety issues in the long-term are the risk of delayed neurological reactions and an expected acquisition of opportunistic infections due to B-cell aplasia.

3.4.4 Health related quality of life

Submitted documentation

ELIANA trial

Health-related quality-of-life (HRQoL) was evaluated by the Pediatric QoL Inventory (PedsQL) and EQ-5D questionnaires completed by patients aged 8 years and above (n = 58) in the ELIANA trial. The PedsQL

items are linearly transformed to a 0-100 scale, so that higher scores indicate better HRQOL (Health-Related Quality of Life) (27).

The majority of patients who failed to respond to treatment and those who relapsed, dropped out from the study, and as a result their patient-reported outcome data were unavailable. Consequently, the results only correspond to patients who were responding to treatment.

Among patients responding, improvements in HRQoL were observed post tisagenlecleucel infusion:

- The mean change from baseline in the PedsQL total score was 13.5 at Month 3 (n=35), and 16.9 at Month 6 (n=30).
- The mean change from baseline in the EQ VAS was 16.5 at Month 3 (n=33) and 15.9 at Month 6 (n=27).

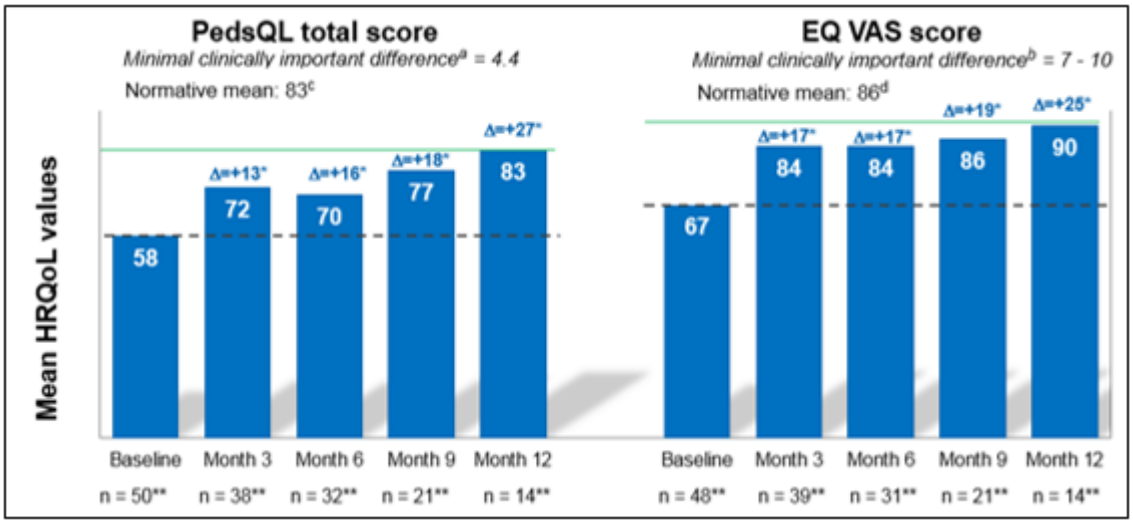


Figure 8 HRQoL baseline and post-baseline scores in the ELIANA trial

Two different versions of EQ-5D were used in the ELIANA trial. EQ-5D-Y was used for patients aged between 8 and 12 years at the study entry, and general EQ-5D was used for patients aged 13 years and above. Because the value sets for converting EQ-5D-Y to a utility score is still under development, the utility scores were derived based on the EQ-5D data only, that is, only for responding patients aged 13 years or more.

Descriptive statistics on the EQ-5D values generated using patient-level EQ-5D data from the ELIANA trial (data cut-off 31 Dec 2017) were calculated by categories corresponding to the model health states EFS and Progressive Disease (PD). To inform the utility value for the PD state in the model, EQ-5D estimates from both *relapsed state* before treatment and *post-EFS* were pooled.

EQ-5D utility scores were calculated based on individual dimension scores and using UK preference-weights (28).

Table 13 Descriptive statistics on EQ-5D utility values in the ELIANA trial

Health state	Patients (N)	Assessments (N)	Utility value (mean)	SD
EFS	29	104	**0.80**	0.23
PD	31	46	**0.63**	0.36
- Relapsed state before treatment	31	31	0.59	0.36
- Post EFS	10	15	0.71	0.34

Published HRQoL studies

Novartis conducted a systematic literature review of utilities, costs and cost-effectiveness. The authors of the review found no studies reporting utility values for paediatric and young adult patients with relapsed/refractory ALL. An additional hand search identified three publications reporting utility values for patient populations that could be considered as proxy for relapsed/refractory paediatric ALL:

- Aristides et al 2015 (29) that reported utility values for health states in adults with relapsed or refractory B-precursor ALL in the UK.
- ICER CAR-T Evidence Report (30)
- UK NICE CAR-T mock appraisal (11)

Both the ICER report and the NICE mock appraisal derived health state utilities from a publication of Kelly et al 2015 (31) and disutility associated with treatment from a publication of Sung et al 2003 (32).

Kelly et al. (31) undertook a decision analysis of cranial radiation therapy for paediatric T-cell ALL patients, including a systematic review of utility studies to inform this. While the study focused on T-cell ALL, the review of utilities did not stipulate type of ALL and hence included all forms of ALL. The study used existing mapping functions to convert generic HRQoL measures (SF-36 and CHRIs) to preference based utility estimates (HUI2 and EQ-5D). The study reported the following health states and corresponding utilities:

- 'In the state of relapse': 0.75 (0.44–1) (mapped value from CHRIs to EQ5D)
- 'Cured after relapse – all relapsed patients treated with CRT': 0.91 (0.87–0.95) (mapped value from SF-36 to HUI2, need to assume no long terms disutility AEs from CRT)

For the 'Cured after relapse' state, the utility values were based on the SF-36 scores from a study by Essig et al 2012 (33). Essig et al measured HRQoL of ALL survivors (n=457) as part of the Swiss Childhood Cancer Survivor Study (SCCSS). A SF-36 questionnaire was sent to all ALL survivors in Switzerland who had been diagnosed between 1976–2003 at age <16 years, survived ≥5 years, and who were currently aged ≥16 years. Kelly et al extracted adjusted SF-36 scores from the Essig et al study and converted them to HUI2 scores, using established algorithms (34).

Utilities for those in the relapse state were generated from HRQoL scores from a study by Rodday et al (35) of peadiatric patients undergoing myeloablative hematopoietic SCT, regardless of causal diagnosis

(76% causal malignancy). Rodday et al collected HRQoL as part of two longitudinal SCT studies, on 312 parent–child pairs using the Child Health Ratings Inventories (CHRIs). Parents of children aged 5–18 completed the pediatric global HRQL scale about their child and 117 adolescents completed the scale themselves. Kelly et al used an algorithm established by Revicki et al (36) to map HRQoL data from CHRIs to EQ-5D using US population for preference scoring.

The study by Sung et al. (32) considers physician-elicited estimates of utility for acute myeloid leukaemia patients who have survived without recurrent disease post transplantation. Sung et al. additionally present estimates of disutility associated with treatment with chemotherapy and transplantation, estimated as 0.42 (plausible range 0.16–0.83) and 0.57 (plausible range 0.31–0.87), respectively. No estimates of the duration of these disutilities are presented.

Submitted health economic analyses

Health states utilities

Utility values in the model were assumed dependent on a health state and independent on a treatment arm. Because a trial-based utility score was only available for 33 patients aged 13 years and above in the ELIANA, the base-case utility inputs were based on Kelly et al 2015 (31). ELIANA-based utility inputs were used in a sensitivity analysis.

Based on Kelly et al, EFS utility was assumed to be the same as the *cured after relapse* state value (0.91) and the PD utility was assumed to be the same as *in the state of relapse* value (0.75). The same input and assumptions were considered by the NICE mock appraisal.

Table 14 Health states utilies used in submitted health economic analyses

Health state	Utility	
	Source: Kelly et al (base case)	Source: ELIANA (sensitivity analysis)
Progressive disease	0.75	0.63
EFS	0.91	0.80

Age adjustment of health state utility values

The model considered age-related decrements as the modelled population became older over the modelled time horizon. The decrements were calculated based on Janssen et al. (2014) (37), which described the health utilities of healthy populations by different age groups using the EQ-5D index population norms based on the UK time-trade-off value sets.

Disutilities from adverse events

Novartis based the estimates for the short-term impact of chemotherapy and alloSCT on health-related quality of life on the study by Sung et al. (38). In this study, health utilities were derived from physician elicitated VAS scores. A decrement in utility of 0.57 for alloSCT and 0.42 for all forms of chemotherapy was assumed. Sung et al. did not report the duration for these utility estimates. Novartis therefore assumed the disutility for alloSCT lasts for one year, while the duration of disutility for chemotherapy

equals the treatment duration. Novartis assumed the HRQoL for grade 3/4 CRS was 0 for a week's duration, based on the ELIANA trial.

NoMA´s assessment

Health state utilities

NoMA has several comments on the health states utilities based on Kelly et al:

- There is no information in the Kelly et al publication if the studies used for the utility inputs were found based on a systematic literature review. Novartis refers to the NICE mock appraisal where the Kelly et al study was used. However, the sources for utilities were not identified from a systematic litterature review in the NICE mock appraisal: "A pragmatic approach was taken to identify potentially relevant sources for health utilities. Google and Google Scholar were used to search for publicly available utility estimates, alongside a search of known economic evaluations and HTA appraisals in ALL".
- The populations and the health states in the Essig et al (33) and Rodday et al (35) studies are also differerent from the population in the ELIANA trial and the EFS and PD health states in the economic model. The utilities from Kelly et al may therefore not be representative for the population and the health states in the STA. Rodday et al examines the HRQoL outcome of patients undergoing a HSCT. Their prospects of survival may be greater than the prognosis for patients relapsing from CAR T or salvage therapy.
- The HRQL scores used to calculate the health state utilities in Kelly et al was based on different studies using different HRQoL instruments (SF-36 vs CHRIs). The HRQoL data for the different health states may therefore not be comparable.
- Within the same analysis, Kelly et al used different preference-based instruments (EQ-5D and HUI2) to measure utilities. The utilities may then not be comparable as these instruments differ in the dimensions of health they cover, in the number of levels defined on each dimension, in the description of these levels and in the severity of the most severe level (39). NoMA guidelines recommend EQ-5D in order to make comparisons between different STAs feasible.
- The tariffs used for setting values for HRQoL were based on the US population (EQ-5D) and on the population from parents of schoolchildren in the city of Hamilton, Canada (HUI2) (39). For consistency, NoMA guidelines recommend that the UK population-based tariff should be used for STAs in Norway until a more relevant and applicable tariff is available. As a standard for STAs the use of EQ-5D with UK tariffs is recommended (6).
- Kelly et al use an algorithm established by Revicki et al (36) to map HRQoL data from CHRIs to EQ-5D. The Revicki-study predicted EQ-5D index scores from patient-reported outcomes measurement information system (PROMIS) global items and domain item banks. Either Kelly et al (31) or the Revicki-study explain the link between CHRIs and the PROMIS-databank. Hence, NoMA can not validate this mapping exercise.

Novartis used ELIANA-based utility inputs in a sensitivity analysis. Patient-level EQ-5D data from the ELIANA study and UK population-based tariff were used to calculate health state utilities for EFS and PD.

The use of EQ-5D with UK tariffs is recommended in the NoMA guidelines. The use of patient-level EQ-5D data collected from the exact population of interest within a trial is generally considered to be a strength.

However, the collection of patient reported outcomes in the ELIANA trial raises some issues. Utility scores were only available for 33 patients aged 13 years and above in the ELIANA trial, and corresponded to patients who were responding to treatment. Furthermore, patient-reported outcomes may be biased in an open label trial design. The ELIANA trial also has short median follow-up time (20.8 months at cutoff date 31 Dec 2017). During the follow-up, improvements over time in HRQoL were observed post tisagenlecleucel infusion among the responders.

Both the Kelly et al study and the ELIANA study have shortcomings in estimating health state utilities. In NoMA's opinion it is challenging to validate the utility values from Kelly et al (31) as the patient populations differs, the HRQoL- and preference based instruments differs, and the tariffs are not consistent with NoMA guidelines. In addition we struggle to interpret the mapping exercise used in Kelly et al. An important shortcoming of the utility values from the ELIANA trial, is that a health state utility for the EFS state (0.80) based on the short follow-up in the trial may be conservative for estimating the HRQoL of long term survivors. Essig et al 2012 (33) found that ALL survivors reported similar or higher HRQoL scores on all scales compared to the general population. The utility value from Kelly et al for the EFS state (0.91) was based on the study by Essig et al.

In the model, all patients alive at year 5 are assumed to have long-term survival. NoMA uses health states utilities based on the ELIANA trial for the first 5 years in the base case, and from the Kelly et al study after 5 years to better reflect the potential long-term survival of patients treated with tisagenlecleucel. NoMA acknowledges that this may be an optimistic estimate for the HRQoL of long term survivors, as excess mortality in paediatric ALL patients compared to the general population has been observed beyond 5 years (14-17). The long-term outcomes of CAR-T therapy – both in terms of efficacy and safety – are not known. For example, the risk of infections due to B-cell aplasia may persist for years.

Long term survival

Novartis has assumed that HRQoL and costs in long-term survivors is linked to the respective health states. All patients alive at year 5 are assumed by Novartis to have long-term survival. A proportion of patients however remains in the progressed health state after 5 years in the model. This means that a proportion of the patients that are assumed to be long-term survivors continues to experience reduced quality of life and costs associated with progressed disease up untill year 45. To improve consistency between the assumptions for long-term survival, quality of life and costs after 5 years, NoMA has assumed that all patients alive after 5 years have the HRQoL and costs associated with the EFS health state.

Age adjustment of health state utility values

Health state utility values are adjusted for age based on a study from Janssen et al (2014) (37) in the submitted analyses from Novartis. NoMA guidelines refer to health state utility values from two Swedish studies, Sun et al 2012 (40) and Burstrøm et al 2001 (41). In these studies, Swedish age-specific quality of

life data is combined with UK population-based EQ-5D value-setting tariffs. See Appendix 1 Severity and shortfall for more information.

Disutility from adverse events

There appears to be a lack of literature on the short-term impact of AEs on HRQoL for tisagenlecleucel, chemotherapy (40) and alloSCT in paediatric ALL (42, 43). The disutility estimates of 0.57 for alloSCT and 0.42 for chemotherapy from Sung et al. (32) are surrounded by considerable uncertainty, as they are based on physician-elicitated VAS scores and no duration was reported. Novartis assumed a 1-year duration of disutility for alloSCT and a 46 day-duration of disutility for chemotherapy (equal to the average treatment duration). This approach implies that the HRQoL in patients who receive alloSCT will be 0.23 for patients that are event free for one year when using this estimate together with the utility estimates from ELIANIA for EFS. NoMA has not received any evidence that supports this assumption, and considers the approach taken by Novartis to result in an overly conservative estimate of HRQoL for patients that received alloSCT. NoMA prefers an approach that is consistent with the assumed disutility for chemotherapy where the disutility is applied during the treatment phase and assumed to capture all treatment-related disutility. Although some patients may experience longer-term AEs after alloSCT, including graft versus host disease, NoMA assumes this is captured in the disutility estimate. The American Cancer Society describes that conditioning treatment and the recovery process for stem cell transplants takes about 4 – 8 weeks(44). NoMA has therefore adjusted the duration of disutility for alloSCT to 2 months in the model. Furthermore, NoMA has incorporated the same utility decrement for the proportion of patients in the tisagenlecleucel arm that received bridging chemotherapy as part of the ITT analysis.

NoMA has explored the impact of AEs on model outcomes in a scenario analyses.

4 HEALTH ECONOMIC ANALYSES

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

4.1 MODEL, METHOD AND ASSUMPTIONS

Novartis used a three-state partitioned survival (PartSA) model to assess the cost-effectiveness of tisagenleucel compared with CEC, blinatumomab, salvage chemotherapy, and clofarabine monotherapy. A simplified representation of the model structure is shown in Figure 9. The three states include event-free survival (EFS), progressive/relapsed disease (PD/RL), and death. At any time point, the proportion of patients under the EFS curve is in the EFS health state. The proportion of patients over the overall survival (OS) curve is in the state of death. The remaining patients are in the PD/RL health state. Survival curves in the PartSA approach are based on independent analyses of OS and EFS endpoints, and a correlation structure between OS and EFS is therefore not explicitly modelled.

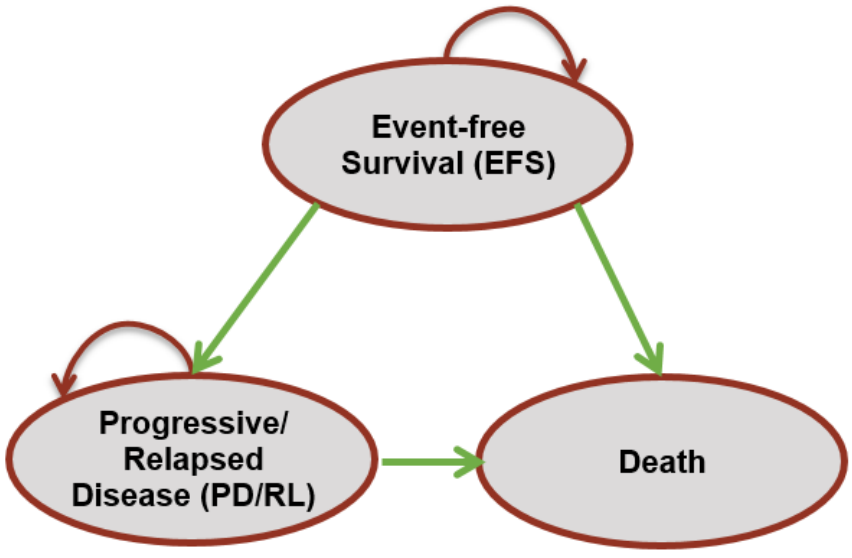


Figure 9: Model structure (source: submission by Novartis)

Patients enter the model in the EFS health state at study enrollment in the ITT analysis and at infusion in the mITT analysis. At the end of each month (cycle length in the model), patients can either remain at this health state or move to the PD/RL health state or to death. Costs and health effects (utility weights) are

calculated separately for each health state. Costs and benefits are summarized per treatment arm for the specified time horizon.

NoMA´s assessment
As described in chapter 1.4.3 and 3.3, NoMA consider CEC therapy to be the most relevant comparator in the analysis. The model is well described in the submission by Novartis, and the implementation of the model in Excel is relatively transparent, and important parameters and assumptions are easy to change. The PartSA model is a common approach in oncology to estimate the effect of treatment based on data from clinical trials. The model takes into account the effect of treatment on survival, disease-related symptoms and treatment-related side effects. PartSA models are described in detail in the literature (45). Strengths include the direct relationship between reported study endpoints and survival functions used in the PartSA model to estimate the proportions of patients in the alternative health states in the model. This makes development and communication of the model relatively easy. An important limitation of PartSA models is that the survival functions are modelled independently, which can be problematic since events are often structurally dependent and prognostic (such as progression and survival). This may imply that extrapolation of trends beyond the study period is not always appropriate, especially when study data is immature (e.g., median OS or EFS is not reached). Since transition probabilities (e.g. survival for progressive patients) are not explicitly modelled in PartSA models, the possibility of evaluating the plausibility of the extrapolation is limited. Alternative approaches such as state-transition models may include explicit transitions, but it may be challenging to find sufficient data to estimate all relevant transition probabilities.

As described in chapter 3.4.2, EFS data for the CEC comparator was not available. Novartis therefore derived the EFS curve for CEC from the OS data, by applying a proportional relationship between OS and EFS as estimated in a UK study on the effect of mitoxantrone in paediatric ALL patients (median follow-up of 41 months). Novartis assumes that all patients that are alive after 5 years are long-term survivors. The cumulative survival probabilities of EFS were assumed by Novartis to flatten up after 5 years until they reached OS.

NoMA notes that approximately 5% and 30% of the surviving patients at year 5 in the tisagenlecleucel arm and CEC arm respectively is in the progressive/relapsed disease state in the model. For the tisagenlecleucel arm, the EFS and OS curves cross at approximately 21 years (8 years for the mITT population), while for the CEC arm the curves cross after 45 years. This means that a proportion of patients that survived after 5 years is assumed to continue experiencing a reduced HRQoL and costs associated with progressive/relapsed disease for many years. NoMA considers this to be inconsistent with the assumption that all surviving patients after 5 years have a long-term survival and the risk of disease recurrence is limited. NoMA therefore has assumed that all patients alive after 5 years have the quality of life and costs associated with the EFS health state.

4.1.1 Analysis perspective

The main analysis by Novartis is performed from a Norwegian healthcare perspective and does not include indirect costs. Health outcomes include patients' life-years and health-related quality of life.

Discounting of costs and effect is set to 4%.

The model uses a monthly cycle length, and a lifetime horizon of 88 years.

NoMA´s assesment

The healthcare perspective and the discount rate are in accordance with the Norwegian guidelines (6). The monthly cycle length is sufficient for reflecting short-term changes in costs and health states. The lifetime horizon is appropriate for capturing the curative potential of tisagenleucel.

4.1.2 Resource use and costs

Submitted documentation

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

Pre-treatment cost

Novartis has calculated costs of leukapheresis, cell freezing and shipment, and the costs of administration of leukapheresis product with reference to Rigshospitalet in Denmark. The unit costs are summarised in Table 15. Exchange rate for September 2018 was used to convert from DKK to NOK.

Table 15 Unit costs for leukapheresis from Rigshospitalet in NOK

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

Patients treated with tisagenlecleucel receive lymphodepleting chemotherapy before infusion. Drug costs for lymphodepleting regimens were calculated as a function of unit drug costs, dosing, and proportion of patients receiving each regimen, see section 3.2. Cost of lymphodepleting therapy is based on two regimens: Regimen 1, including fludarabine and cyclophosphamide, and Regimen 2, including etoposide and cytarabine. The distribution of patients to each regimen is obtained from the ELIANA trial, in which 94.67% of patients received Regimen 1. Vial sharing was not considered when estimating the drug cost in the base case.

Treatment costs

Treatment costs consisted of drug/procedure acquisition costs, outpatient administration costs, and hospitalisation and ICU costs. Vial sharing was not considered when estimating the drug cost in the base-case. Table 16 shows a summary of treatment costs for intervention and comparator. The table includes only direct treatment costs of drug price and hospitalisation, and does not include potential downstream follow-up and end-of life costs.

Table 16: Summary of treatment costs for intervention and comparator strategies*

Treatment strategy	Total treatment cost (NOK)
Tisagenlecleucel	3 610 211
CEC	760 195
Allogenic SCT	2 913 410 (includes follow-up costs)

*The table includes only direct treatment costs and does not include potential downstream follow-up and end-of life costs. NoMA has only included comparators for a potential Norwegian setting, see sections 1.4.3 and 3.3.

Tisagenlecleucel

Novartis used a unit price of tisagenlecleucel in the model of NOK 3 082 800. Novartis assume that all paediatric patients are hospitalised for the infusion of CAR-T-cells. The estimated total hospitalisation for CAR-T-cell infusion was NOK 527 411, based on a daily cost per hospitalisation of NOK 17 933 based on average cost from SAMDATA 2015, adjusted for inflation (46). Hospitalisation length of stay is 25.67 days based on data from the ELIANA trial. On average, tisagenlecleucel patients were hospitalised at the intensive care unit for 1.8 days for reasons other than CRS, based on ELIANA trial. Novartis assumed that the cost of ICU was NOK 35 866 per day (twice the cost of general ward), based on expert opinon.

CEC

Drug acquisition costs were calculated as a function of unit drug costs, dosing, and treatment duration. The dosing schedule and treatment duration of CEC was based on the treatment regimens evaluated in Hijiya et al. (2011) (9), one of the publications used for the survival estimate input. As information on hospitalisation length of stay was not reported in CEC publications, this was assumed to be 28 days, based on the mean duration of hospitalisation for salvage chemotherapy reported in Gaynon et al. (2006)(47). Patients were assumed to receive the treatment with CEC in an inpatient setting. The cost per inpatient day of CEC administration was assumed the same as for tisagenlecleucel.

Based on these assumptions, Novartis estimated a total hospitalisation cost of NOK 502 125 and a total drug/procedure cost of NOK 258 070, which amounted to a total treatment cost of NOK 760 195 for CEC.

Allogenic SCT

The cost of alloSCT was based on expert opinion and various DRG costs (DRG price list for 2018). Specifically, alloSCT cost was considered in three parts: pre-treatment and stem cell harvesting, the cost

of the procedure, and the cost of long-term follow-up (Table 17). The stem cell harvesting cost were based on procedures HIA, HC1, HC2 and HC3 (each of them associated with DRG405 with weight = 2,607), which accumulated to a total cost of NOK 452 867. The cost associated with the alloSCT procedure was based on DRG481C (weight = 33,195), resulting in a cost of NOK 1 441 492. In the first year after treatment, follow-up was assumed to involve 6 bone marrow aspiration in general anaesthesia at months 1, 2, 3, 6, 9 and 12, with a total cost of NOK 679 301 (6*DRG405 with weight = 2,607). The second-year follow-up costs involved 3 bone marrow aspiration in general anaesthesia at months 16, 20 and 24 (after treatment), with a total cost of NOK 339 650 (3*DRG405 with weight = 2,607). The follow-up cost input was weighted by the proportion of patients who remained alive at different time periods (i.e. 6 months, 12 months, and 24 months) post the alloSCT procedure.

Table 17: Cost of allogenic stem cell transplantation including pre-treatment

	Procedure	DRG code	DRG weight	Estimated cost
Pre-treatment costs				
	HIA	DRG405	2,607	113 217
	HC1	DRG405	2,607	113 217
	HC2	DRG405	2,607	113 217
	HC3	DRG405	2,607	113 217
Treatment cost (initial SCT procedure)				
	AlloSCT	DRG481C	33,195	1 441 592
First-year follow-up costs: 6 bone marrow aspiration in general anesthesia				
	Month1	DRG405	2,607	113 217
	Month 2	DRG405	2,607	113 217
	Month 3	DRG405	2,607	113 217
	Month 6	DRG405	2,607	113 217
	Month 9	DRG405	2,607	113 217
	Month12	DRG405	2,607	113 217
Total cost of allogenic SCT including first-year follow-up costs				**2 573 760**
Second-year follow-up costs				
	Month16	DRG405	2,607	113 217
	Month 20	DRG405	2,607	113 217
	Month 24	DRG405	2,607	113 217
Total second-year follow-up costs				**339 650**

The model implies that patients can receive subsequent alloSCT after initial chemotherapy. The cost and disutility of subsequent SCT were added separately for the proportion of patients who received subsequent SCT for each arm. The rates of subsequent SCT were obtained from the same clinical trial study used for the efficacy estimation. The latest data cut-off was used to estimate the subsequent

alloSCT rate for tisagenlecleucel: ELIANA (31 Dec 2017), ENSIGN (06 Oct 2017) and B2101J (30 Jan 2017) trials.

Subsequent alloSCT rates for tisagenlecleucel and CEC therapy are obtained from the same sources used for efficacy input.

Table 18: Subsequent SCT rates used in the model

	Subsequent alloSCT rate (%)	Subsequent alloSCT cost	References for subsequent alloSCT rate inputs
Tisagenlecleucel	16.58%	NOK 370 422	Pooled data based on ELIANA, ENSIGN, and B2101J
Clofarabine combination (CEC)	37.84%	NOK 845 339	Hijiya 2011, Miano 2012 and Locatelli 2009

Follow-up costs

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

For patients that received CEC and remained in the EFS state, the frequency of follow-up was obtained from the UK Leukaemia and Lymphoma research guideline (48). Because the specific laboratory tests and procedures were not specified in UK Leukaemia and Lymphoma research guideline, these items were obtained from the National Comprehensive Cancer Network (NCCN) guideline (49). For patients that received tisagenlecleucel and remained in the EFS state, the frequency of follow-up was derived from the ELIANA trial protocol.

The frequency of follow-up was assumed to be the same for the PD state across all comparator arms and was assumed to be the same as the EFS state of chemotherapies during year 1. Unit costs per provider visit and per test/procedure were collected from Norwegian fee schedules and the NHS Reference costs 2015–2016 (NHS, 2017).

Table 19: Unit costs for follow-up procedures

Description	Input (NOK)	Code (if available)	Year of cost	Source
Consultant visit	2 301	DRG 917O	2018	DRG price list 2018
Hematology panel	60	707a	2018	Lovdata poliklinikk-takster
Urinalysis	N/A	N/A	N/A	
Coagulation panel	270	707c	2018	Lovdata poliklinikk-takster
Chemistry panel	100	707a	2018	Lovdata poliklinikk-takster
Chemistry panel (including liver function test)	N/A	N/A	N/A	
Cerebrospinal fluid (CSF)	2 378	917A	2018	DRG price list 2018
Serum test	308		2018	
B cell and T cell test	17,49	DAPS03	2015-2016	NHS National schedule of reference costs 2015-2016
Electrocardiogram (ECG)	120	707 (taking og tyding av EKG)	2018	Normaltariffen 2017-18
Bone marrow aspirate	2 343	817S	2018	DRG price list 2018
Bone marrow biopsy	2 343	405	2018	DRG price list 2018
Echocardiogram	1 954	905A	2018	DRG price list 2018
Liver function test	40	707a	2018	Lovdata poliklinikk-takster

Adverse event costs

AE costs were calculated for tisagenlecleucel, CEC, and alloSCT based on rates of AEs and their unit costs. The AE costs were estimated based on the literature or assumed to be the same as AEs within the same category mostly using NHS reference costs 2015-2016.

CRS is an AE that is specific to treatment with tisagenlecleucel, and could be associated with substantial resource use. CRS event costs were calculated as the sum of the ICU admission cost and tocilizumab drug and administration costs. Length of stay for ICU and the dosing of tocilizumab related to CRS were obtained from the ELIANA trial data.

The model also considered B-cell aplasia specific to the tisagenlecleucel arm. The model considered 73% patients with tisagenlecleucel infusion would receive IVIG based on the ELIANA trial data, and the median time to B-cell recovery was assumed the median treatment duration (11.4 months). The total monthly drug cost was calculated based on a dosing schedule obtained from the NICE mock appraisal (11). The respective unit costs were based on the price of Octagam with a dose of 220 ml 100 mg/ml. Corresponding monthly administration cost was calculated from NHS reference costs 2015-2016 using outpatient cost. The total IVIG cost was calculated to be NOK 11 053 each month.

Terminal care costs

All patients who transition to death were assumed to incur one-time terminal care costs. The terminal care cost inputs were assumed to be NOK 86 141, based on the entire hospitalisation episode cost reported for non-elective long stay paediatric ALL services in the NHS reference costs 2015-2016. The same assumption was considered in the NICE mock appraisal (11).

NoMA´s assessment

NoMA prefers the use of Norwegian cost estimates. Novartis has based several cost estimates on NHS reference costs 2015-2016, and it is unclear to what extent these unit costs are generalisable to the Norwegian healthcare system. NoMA noted that these unit costs have been converted to NOK without an adjustment for purchasing power parities (PPP) or inflation to the current year. NoMA has adjusted for this.

Hospitalisation cost

Input data for hospitalisation costs are used to calculate treatment costs for both tisagenlecleucel and comparators, and subsequent AE costs. For input data Novartis used a mean cost of 17 933 per bed day sourced from SAMDATA. The NoMA guidelines mention SAMDATA as a source if DRG or other more reliable sources are not suffiecient. For treatments at the ICU Novartis assumed the costs to be twice as high as the SAMDATA estimate, hence NOK 35 866.

The SAMDATA average of resource use per day at hospitals includes a range of procedures with different complexity. The data from SAMDATA shows that Oslo University Hospital (OUS) has a higher average resource use per day than other hospitals in Norway. Clinical experts expect CAR-T treatment of paediatric ALL to be administered at OUS.

The greater complexity in treating children with ALL may suggest higher than average unit costs for hospitalisation. It is unclear whether the SAMDATA estimate reflects this, as it consists of an average of all procedures, both complex and simple.

A recent study by Lindemark et al (2017) assessed the cost effectiveness of the Norwegian ICU compared with the general ward (50). In this study they calculated a mean cost of general ward and ICU stay in Norway. The mean cost used in this study of general ward was NOK 8 000 (4 000-12 000) per bed day and NOK 50 000 (30 000-70 000) per bed day at ICU (51). The data are based on personal interviews with four hospital trusts in Norway.

Lindemark et al chose the mean cost of an ICU and general ward based on the following assumptions:

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

The reported costs in the Lindemark-study show great variations. Lindemark et al explains that the variation in cost estimates between hospitals can partly be explained by local adaptation of the national cost per patient specification.

The data in the Lindemark study do not distinguish unit costs for paediatric and adult care. Literature suggests that paediatric care and hematology-oncology can be more expensive than average care (52). Several Norwegian DRG tariffs are higher for paediatric care than for adults for the same procedure (ie.

DRG codes 25 and 26 for cramp and headaches, DRG-codes 96,97 and 98 (a,b) for bronchitis and asthma, and DRG-codes 481 (b,c) for alloSCT) (53). Similar trend can be seen in the NHS reference costs database. NoMA therefore considers the higher bound for the cost per bedday at the general ward (12 000 NOK) from the study by Lindemark to be most relevant for this analysis.

Lindemark et al assumes that the cost per day in the ICU is highest in the first 24 hours and then falls substantially, with reference to Kahn et al (54) and Dasta et al (55). Normalised to the average cost of an ICU bed day, Lindemark modelled ICU daily costs such that ICU days 1 and 2 were 3- and 1.5-times more costly, respectively, than ICU day 3 onwards. The average days of ICU in Lindemark was 5 days.

NoMA acknowledges that patients experiencing grade 3 and 4 CRS are hospitalised at the ICU for a longer time than the average in the Lindemark study. This may suggest a lower mean cost of ICU stay per day on average. ICU treatment for this patient population is assumed to be critical and complex.

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

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

For the ICU bed days subsequent to tisagenlecleucel treatment (1.8 days) this approach results in a mean ICU cost of NOK 49 000. For ICU bed days in relation to CRS (11 days) the estimated mean cost is NOK 28 636.

Pre-treatment costs

The pre-treatment costs consist of three main cost components: leukapheresis, lymphodepleting chemotherapy and hospitalisation.

For leukapheresis costs, Novartis has used cost estimates from the Danish Rigshospitalet. NoMA has received an overview of the costs for leukapheresis from the Section of cell laboratory at the OUS (56). These costs represent the average unit costs from the clinical trials of this CAR-T cell therapy at OUS. The costs ascribed to leukapheresis and monotoring from both OUS and Rigshospitalet is summarised in Table 20 (compared by NoMA).

Table 20 Unit costs for leukapheresis product at OUS and Rigshospitalet

	OUS (NOK)	Rigshospitalet (NOK)
1. Production and shipment of frozen cells:		
Procedure/task		
Material and reagents	23 566	16 124 (Apheresis, incl. Analysis)
Working hours for leukapheresis and freezing teams (4 hrs doctor, 18 hrs bio technician)	11 332	8 384 (Cell Freezing)
Facilities (Cleanroom, liquid nitrogen storage, QC-lab)	38 889	

Batch documentation, QC and release	11 111	
Shipment, including documentation (3 hrs bio technician)	1 308	6 450 (Shipment)
Total price per production (per patient)	**86 206**	**30 958**
2. Receiving and intermediate storage of cells and documentation		
Storage in liquid nitrogen	2 222	
Work in relation to receiving, intermediate storage and documentation (3 hrs bio technician)	1 308	
Total price for receiving, intermediate storage and documentation per patient	**3 530**	**13 544** (Receiving, containing, transport and defrosting)
3. Thawing of cells bedside:		
Preparation of dry shipper, transfer of cells and documentation (1 hr doctor, 3 hrs bio technician)	2 179	
Working hours for thawing, documentation and transportation (1 hr doctor, 3 hrs bio technician)	2 179	
Total price for thawing bedside (per patient)	**4 358**	
Timepris lege 871,-		
Timepris sykepleier/bioing/tekniker 436,-		
Total price:	**94 094**	**44 502**

Table 20 shows that the total unit costs for performing leukepheresis as estimated by OUS and Rigshospitalet differs. The OUS unit costs are more detailed. Hourly wage used in the OUS input data is equal the unit costs of hourly wage in the NoMA unit costs database.

In NoMA's opinion, the main difference between the two input sources is the inclusion of *Facilities* and *Batch documentation* in the OUS data. The facility costs are estimated as the average cost for operating expense of using the clean room. The operating expenses of the clean room specified by the OUS include conduction of quality controls, environmental control, services, maintenance and expenses of cleaning clothes. The cost specified for batch documentation includes all documentation activities in connection to the production of the cells according to regulated quality standards, in addition to the standards requested by Novartis. According to OUS, the work load is expected to be similar in a commercial setting as in a clinical study setting.

NoMA considers the average costs of operating expenses to be relevant for the analyses, and uses the unit costs provided by OUS in the analyses. These costs are covered by the hospital where patients treated with CAR-T cell treatment are assumed to be treated in Norway. Furthermore, these cost estimates are more detailed than the calculations from Rigshospitalet in Denmark.

Novartis has assumed that the length of stay in hospitals for lymphodepleting therapy is 14 days, and that about 65% of patients will be hospitalised based on the ELIANA trial. The clinical study report of the ELIANA trial, however, suggest that 94,7% of the patients stay at hospital for 41,5 days from lymphodepleting therapy. This measure accounts for all hospitalisation, both lymphodepleting regimen, infusion and complications experienced due to AEs.

Norwegian clinical experts have estimated that it is relevant for Norwegian patients to be hospitalised for 5-7 days for lymphodepleting therapy. They suggest that the length of stay for a standard patient in Norwegian clinical practice may be shorter than reported in the ELIANA trial. The ELIANA trial includes the average length of stay, and represents a broader spectre of patients and thereby represent a larger variation in hospitalisation length of stay. NoMA has accepted Novartis input from the ELIANA trial. In scenario analysis we have used the assumption by Norwegian clinicians.

Treatment costs

Tisagenlecleucel

The price of tisagenlecleucel in the submitted model was NOK 3 082 800. This price did not reflect the pharmacy markup, as Novartis assumed that tisagenlecleucel could be delivered directly to hospitals. However, according to Norwegian pharmacy legislation, tisagenlecleucel must be delievered to and distributed to the hospital from a pharmacy. The total price to be used in the model including pharmacy mark up will be NOK 3 167 606. This equals the list price of tisagenlecleucel excl. VAT. In scenario analyses, NoMA has explored the effect of pharmacy markup on the ICER.

The length of stay at hospitals was based on data from the ELIANA trial. Norwegian clinical experts agree that the data fits the Norwegian experience from the trials. However, clinical advice is that patients that live close to the hospital may be able to stay home after 14 days. NoMA accepts Novartis input for length of stay, and in hospital for treatment of tisagenlecleucel. In scenario analysis NoMA has calculated that patients stay in hospital for 14 days, and then stay in patient hotel or at home, for up to 28 days as recommended in the SmPC.

In the ITT population 81% of the patients were infused with tisagenlecleucel in the ELIANA trial, and the tisagenlecleucel costs are included only for the infused patients in the ITT model. The remaining non-infused patients received treatment with CEC.

Bridging therapy should be included for treatment with tisagenlecleucel. The proportion of patients who recieved bridging chemotherapy is derived from the pooled trial data of ELIANA, ENSIGN and B2101J, and set to 71.3%. The cost of bridging chemotherapy is assumed to be equal to the total drug and administration cost of salvage chemotherapy, and includes fludarabine 5 doses, cytarabine 5 doses, and idarubicin 3 doses. However, Novartis has not included the hospitalisation cost of bridging therapy. NoMA has included hospitalisation cost of 21 days in hospital for bridging therapy, as estimated by Novartis for salvage chemotherapy treatment.

CEC

Costs of CEC consists of two cost components: drug costs and hospital costs. The drug costs are based on the schedule and dosing treatment duration from Hijiya et al (2011)(9). NoMA accepts the total drug costs calculated with reference to Hijiya et al (2011).

The hospitalisation length of stay is assumed to be 28 days, with reference to Gaynon et al (2006) (47). The Gaynon study report a mean duration of hospitalisation for salvage chemotherapy for patients in US collected between 1995 and 1998. The average of hospital stay for the induction phase was 28 days.

NoMA considers that data from the Gaynon-study has important weaknesses. Firstly, the patients were recruited for participation in the study for more than twenty years ago. The delivery and effectiveness of care for these patients has changed since then. Secondly, the study was conducted at US hospitals where treatments are reimbursed by insurance companies as opposed to a single payer in Norway. Thirdly, the patients are treated from first relapse which deviates from the patient population in this analysis.

Novartis provided two additional sources for length of stay with CEC treatment. The Lawson study (57) reports the UK experience in treating relapsed childhood acute lymphoblastic leukaemia with salvage chemotherapy. It collected data for 256 patients between 1991 and 1995 with follow up up to 1998. The length of stay in the Lawson study was 16 days for the induction phase and 7 days for consolidation phases. Dombret and colleagues (2016) (58) conducted a study in France of adult patients that are multiple relapsed or refractory and treated with salvage chemotherapy. Thirty-three patients were included from 2003 to 2014, with a mean age of 49 years. The length of stay in the Dombret study was 16.8 days.

According to a Norwegian clinician that NoMA consulted, the CEC treatment lasts 7 days each cycle. The patients continue to be hospitalised due to a risk of infections. According to the clinical advice the Dombret estimate of 16.8 days for each treatment cycle best reflects Norwegian practice. The model includes three treatment cycles, where 32% of the patients are treated in the second cycle and 8% of the patients in the third cycle. Hence, NoMA estimates the total days of in-hospital care for all three cycles to be 23.5 days.

Subsequent allogenic SCT

The cost of alloSCT was based on information from an expert clinician contacted by Novartis and various DRG costs (DRG price list for 2018). Clinicians NoMA has been in contact with explained that there are different procedures for collecting stem cells, whether or not the donor is a sibling, a family member or not related. The DRG-codes used for cost estimates are accepted.

Novartis has not included the number of follow up visits in the follow-up costs for the first year in the model. This underestimates the total costs of alloSCT. NoMA has therefore adjusted the total costs of alloSCT to include 24 months of follow up.

The proportion of patients receiving alloSCT is sourced from the same studies that are used for the efficacy estimation. Hijiya et al (9) reports that 60% of the patients who were treatet with alloSCT were alive and in remission at last follow up (about 1 year). This suggest that only 60% of the costs should be included in the second year follow up reducing the second year costs from 339 650 NOK to 203 790 NOK.

Follow up costs

Unit costs per provider visit and per test/procedure were collected from Norwegian tariffs and the NHS Reference costs 2015–2016 (NHS, 2017). These costs has not been validated by NoMA as these costs have little impact on the model outcomes.

Adverse event costs

Novartis based the cost estimates for AEs on the average cost of relevant day cases from the NHS reference costs 2015-2016, without adjustment for PPP or inflation to the current year. NoMA has adjusted these estimates for PPP and inflation in base case analyses.

Cost of CRS

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

Accoring to the clinical study report 94,7% of the patients were hospitalised for a total mean duration of 41,5 days. During hospitalisation, some patients were admitted to the ICU for 12 days. This suggest that only the incremental costs for ICU admittance compared to the general ward should be added. By adding the total costs of the ICU stay, Novartis has double counted the costs of hospitalisation for patients admitted to the ICU.

NoMA has adjusted for this by only adding the incremental costs for ICU admittance in the analysis.

B-cell aplasia

Novartis has calculated costs of IVIG treatment in patients with B-cell aplasia in the tisagenleucel arm. Novartis used the costs for Octagam in their estimation. According to the Hospital Procurement trust Panzyga is the preferred pharmaceutical since September 2017 (59). This is also confirmed by Norwegian clinical experts. The price of Panzyga is higher than Octagam.

Novartis has used a dose of 220 ml of 100 mg/ml. NoMA considers this dose to be an overestimation. The dose of Octagam and Panzyga is 0.2 – 0.4 g per kg every 3-4 weeks. The average weight for patients in the ELIANA trial was 42 kg. The cycle dose can therefore be expected to be lower than estimated by Novartis.

NoMA has assumed an average dose of 0.3 g per kg every 3-4 weeks. This corresponds to 15 g every montly cycle. This dose require the following packages:

Brand	Package	Price ex VAT in NOK
Panzyga	100 mg/ml 100 ml	5 354
Panzyga	100 mg/ml 50 ml	2 691

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

and administration costs of Panzyga for the entire period of IVIG treatment. The total costs used in NoMA's analysis is NOK 10 431.

Novartis assumed 73% patients with tisagenlecleucel infusion would receive IVIG based on the ELIANA trial data, and the median time to B-cell recovery was assumed the median treatment duration (11.4 months). NoMA considers it likely that the proportion of all infused patients that would receive IVIG treatment (73%) is overestimated by Novartis, as only 47.1% out of the infused patients received IVIG treatment in the clinical trials. NoMA noted that approximately 69% of patients with B-cell aplasia had not recovered by the end of the 24 month follow-up (Figure 10). As this data suggests many patients may suffer prolonged B-cell aplasia, the use of the median duration is likely to underestimate the long-term duration of B-cell aplasia.

NoMA would have preferred an analysis of patient level data on all-cause time to IVIG treatment discontinuation. Since this data was not available, NoMA has instead explored an alternative scenario for estimating long-term costs of treating B-cell aplasia. NoMA used Webplotdigiziter and the algorithm developed by Guyot and colleagues (10) to replicate the patient level data for time to B-cell recovery from Figure 10. NoMA fitted standard and flexible parametric survival models to this data in order to obtain an estimate of mean time to B-cell recovery (Figure 11). Although the generalised gamma and spline models provided a better fit to the data based on the AIC statistic, they did not converge to 0. NoMA therefore selected the lognormal function as it converged to 0 and provided the best visual and stasticial fit to the data out of the standard parametric models. The Kaplan Meier curve for time to B-cell recovery does not account for the competing risk of death. NoMA therefore made an adjustment for overall survival as estimated in the economic model. Finally, NoMA assumed 47.1% of the estimated number of patients with B-cell aplasia would receive IVIG treatment, as observed in the ELIANA trial. The estimated proportion of patients with B-cell aplasia and on IVIG treatment over time is presented in Figure 12. Using these estimates resulted in a discounted total lifetime cost of NOK 150 614 for treating B-cell aplasia in the mITT population, compared to a cost of NOK 92 404 in the updated base case by Novartis. Some important limitations to NoMAs approach include the immature data on B-cell recovery resulting in large uncertainty surrounding the extrapolation and long-term predictions, the presence of competing risks in the Kaplan-Meier data, the assumption that overall survival and time to B-cell recovery are independent, and the constant proportion (47.1%) of patients with B-cell aplasia that is assumed to receive IVIG treatment (which may be dynamic over time). The direction and impact of these uncertainties on the estimated cost is unclear. NoMA evaluated the impact of AEs on model outcomes in scenario analyses.

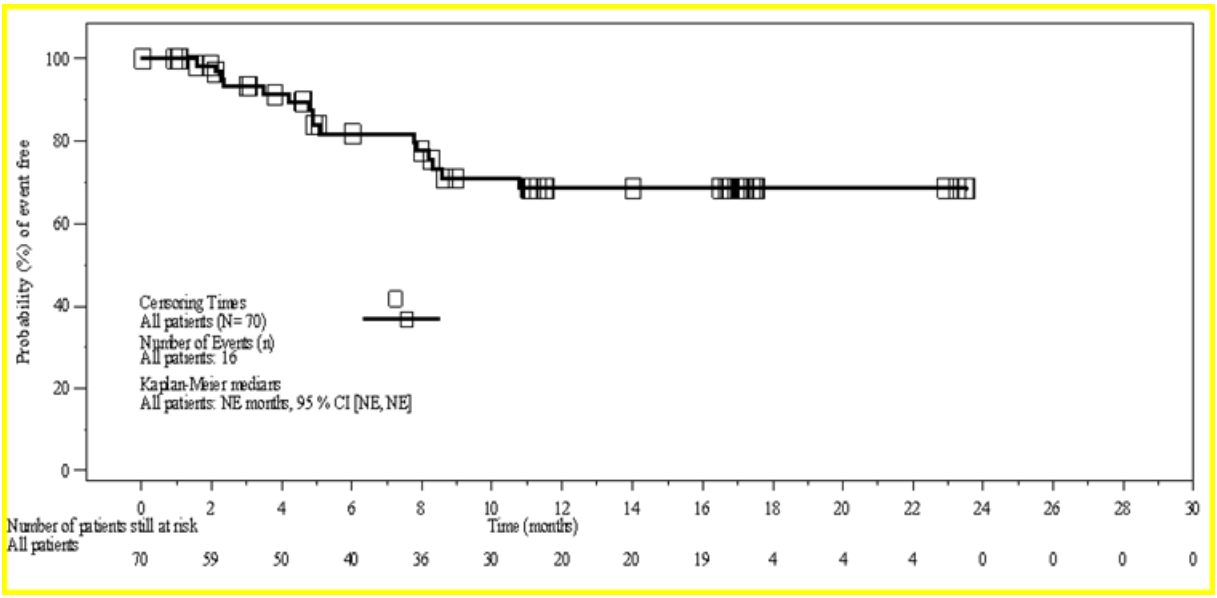


Figure 10 Kaplan-Meier curve for time to B-cell recovery in ELIANA (source: Novartis)

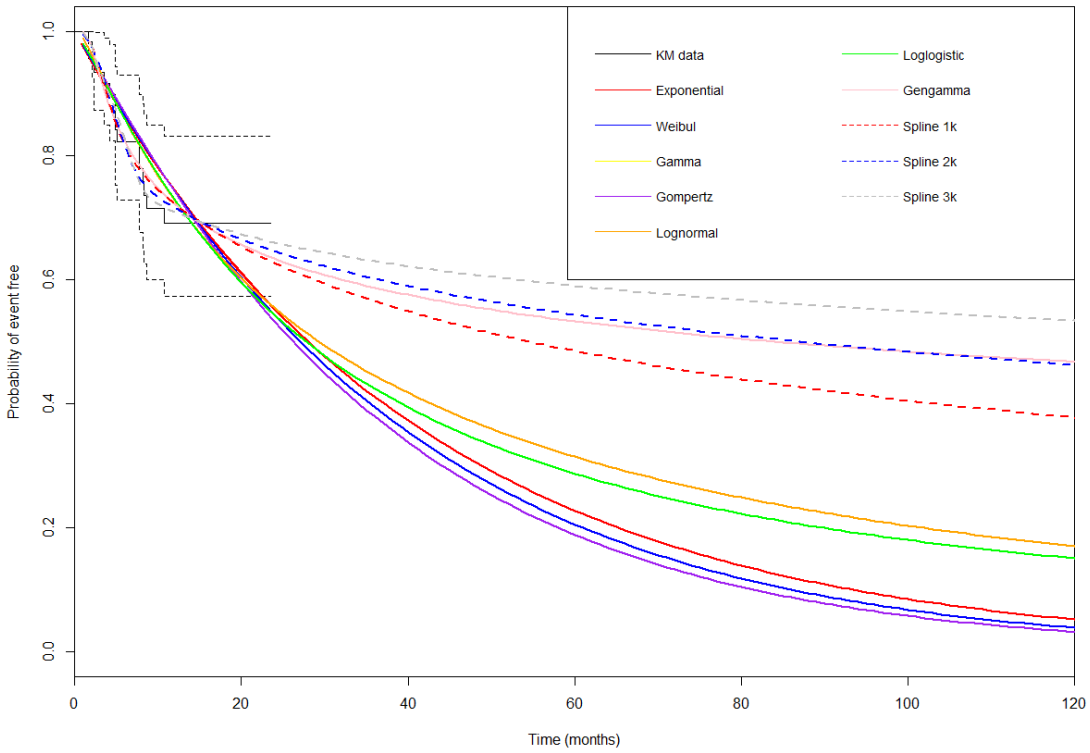


Figure 11. Parametric survival models for time to B-cell recovery

Survival function	**AIC**
Exponential	152.4328
Weibul	154.3955
Gamma	154.2630
Gompertz	154.2630
Lognormal	150.8989
Loglogistic	153.0462
Gengamma	147.6651
Spline 1k	149.4548
Spline 2k	151.0165
Spline 3k	151.8719

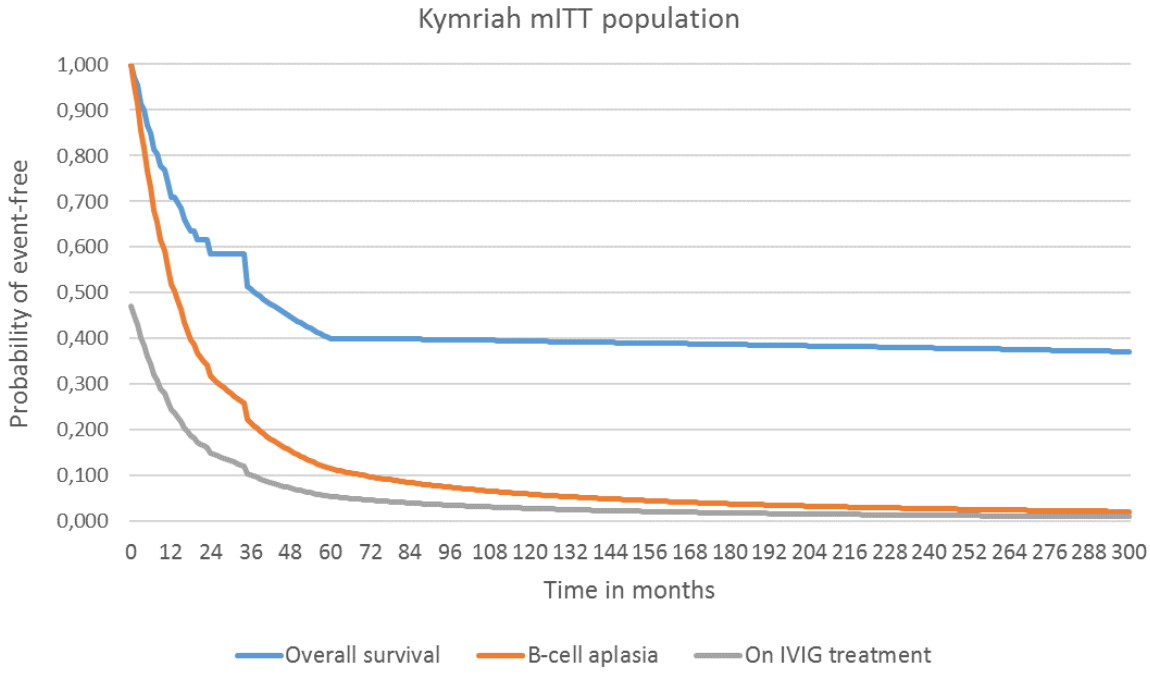


Figure 12.Base case analysis by NoMA of B-cell aplasia and IVIG treatment duration for the mITT population in the tisagenleucel arm.

Terminal care costs

The terminal care cost inputs were assumed to be NOK 86 141, based on the entire hospitalisation episode cost reported for non-elective long stay paediatric ALL services in the NHS reference costs 2015-2016. These costs has not been validated by NoMA as these costs have little impact on the model outcomes. NoMA accepts the terminal care costs.

4.2 RESULTS

4.2.1 Novartis' main analysis

Base case results for tisagenlecleucel versus CEC chemotherapy from Novartis' main analysis are presented in Table 21.

Table 21 Results from Novartis's base case. mITT population (infused patients)

	Tisagenlecleucel	CEC followed by subsequent SCT	Difference
Total costs	NOK 4 548 429	NOK 1 721 989	NOK 2 826 440
Total QALYs	8.28	1.33	6.95
Total life years	9.73	1.87	7.86
Incremental cost per QALY gained			**NOK 406 605**
Incremental cost per life year gained			NOK 359 726

4.2.2 NoMA´s base case analyses

NoMA has estimated a cost-effectiveness ratio for tisagenlecleucel compared to CEC. Multiple important limitations and uncertainties in the analyses were identified and remained, and NoMA therefore considers the cost-effectiveness estimates to be highly uncertain. Results from NoMA's base case analyses are presented in Table 22 and Table 23 for ITT population and mITT population respectively.

Table 22 Results from NoMA´s base case analysis: ITT population

	Tisagenlecleucel	CEC followed by subsequent SCT	Difference
Total costs	NOK 4 097 982	NOK 1 706 135	NOK 2 391 847
Total QALYs	7.12	3.44	3.67
Total life years	8.48	4.15	4.33
Incremental cost per QALY gained			**NOK 651 101**
Incremental cost per life year gained			NOK 552 010

Table 23 Results from NoMA´s base case analysis: mITT population

	Tisagenlecleucel	CEC followed by subsequent SCT	Difference
Total costs	NOK 4 699 699	NOK 1 706 135	NOK 2 993 564
Total QALYs	8.06	3.14	4.62
Total life years	9.55	4.15	5.40
Incremental cost per QALY gained			**NOK 648 088**
Incremental cost per life year gained			NOK 554 144

Table 25 summarizes the changes made in NoMA's basecase analyses:

Table 24 NoMA's changes from Novartis' basecase

Parameter	**Novartis base case**	**NoMA's base case**
Efficacy		
Source of OS and EFS data for tisagenlecleucel	ELIANA + ENSIGN + B2101J	ELIANA + ENSIGN due to similar study design
OS extrapolation	Weighted AIC curves	ITT OS: Log-normal for tisagenlecleucel. mITT OS: Log-normal for tisagenlecleucel, spline model with two knots for CEC.
EFS extrapolation	Weighted AIC curves	ITT EFS: Log-normal for tisagenlecleucel. mITT EFS: Log-normal for tisagenlecleudel Derived from the OS curve using an EFS:OS ratio for CEC
Quality of life and costs in long-term survivors	All patients alive at year 5 are assumed to have long-term survival, but a proportion of these long-term survivors continues to experience reduced quality of life and costs associated with progressed disease up untill year 45.	Consistency between the assumptions for long-term survival, quality of life and costs after 5 years: all patients alive beyond 5 years are assumed to have the quality of life and costs associated with the EFS health state.

Health related quality of life		
Utilities - Health states	EFS: 0.91 PD: 0.75 Source: Kelly et al	First 5 years: EFS: 0.80 PD:0.63 Survival beyond 5 years: PD and EFS: 0.91 Source: ELIANA trial, Kelly et al
Disutility adverse events	1 year of disutility of 0.57 in all patients that received alloSCT Source: assumption	Disutility for alloSCT is assumed to last for the duration of the procedure + recovery (2 months), in line with the approach for disutility due to chemotherapy. Source: American Cancer Society
Disutility from bridging therapy	Not included	Included
Age adjusted utility	Source: Jannsen et al	Source: Sun et al 2012 and Burstrøm et al 2001, according to NoMA guidelines.
Resource use		
NHS cost reference database	Not adjusted for inflation and PPP	Adjusted for inflation and PPP
Lymphodepleting therapy: Hospitalisation – Length of stay	14 days for 65.5% of the population Source: ELIANA trial	14 days for 94.7% of the population Source: Clinical Study report
Leukapheresis costs	44 000 NOK Source: Rigshospitalet in Denmark	94 000 NOK Source: Section of cell laboratory at OUS.
CEC: Hospitalisation – Length of stay	28 days Source: Gaynon et al. 2006	16.8 days in each cycle Source: Dombret et al. 2016, clinical expert opinion
Tisagenlecleucel price	NOK 3 082 800 No pharmacy markup	NOK 3 167 606 Pharmacy markup included
Hospitalisation and ICU costs	NOK 35 866 Input data double counted costs of hospital stay.	Cost per bed day: NOK 12 000 Cost per ICU bed day: Day 1: NOK 70 000 Day 2: NOK 35 000 Day 3 onwards: NOK 23 333 Source: Lindemark et al, assumtions Input data only represent incremental costs of hospital stay at ICU.
Bridging therapy	NOK 8 586 Hospital costs not included	NOK 304 988 Hospital costs included for 21 days
alloSTC:	Not included	Included

Costs of follow up year one	(in ICER calculation)	
alloSTC: Costs of follow up year two	Included for 100% of patients. Source: Assumption	Adjusted for the proportion of patients surviving the first year (60%). Source: Hijiya et al.
Adverse events – B cell aplasia: IVIG treatment unit costs	Unit costs of treatment each month NOK 11 053 Source: SmPC Octagam	Dosing adjusted downwards. Unit Costs of treatment each month NOK 10463. Source: SmPC Panzyga
Adverse events – B cell aplasia: IVIG treatment total costs	NOK 92 404 Treatment duration of 11,4 months for 73% of the patients. Source: Assumption	NOK 150 614 Treatment duration based on a parametric extrapolation of KM data on time until B-cell recovery, adjusted for OS and the proportion of patients who received IVIG in the ELIANA trial (47.1%). Source: ELIANA trial data

Red coulor: ICER increase from Novartis' scenario
Green colour: ICER decrease from Novartis' scenario
Yellow colour: minor changes in ICER

4.2.3 Sensitivity and scenario analyses

Novartis has performed one way sensitivity analysis and a probabalistic sensitivity analysis. The key drivers that affect the ICER in Novartis' sensitivity analysis are the price of tisagenlecleucel, extrapolation of OS-curve, discount rate, IVIG costs and time horizon. This is presented by a tornado diagram.

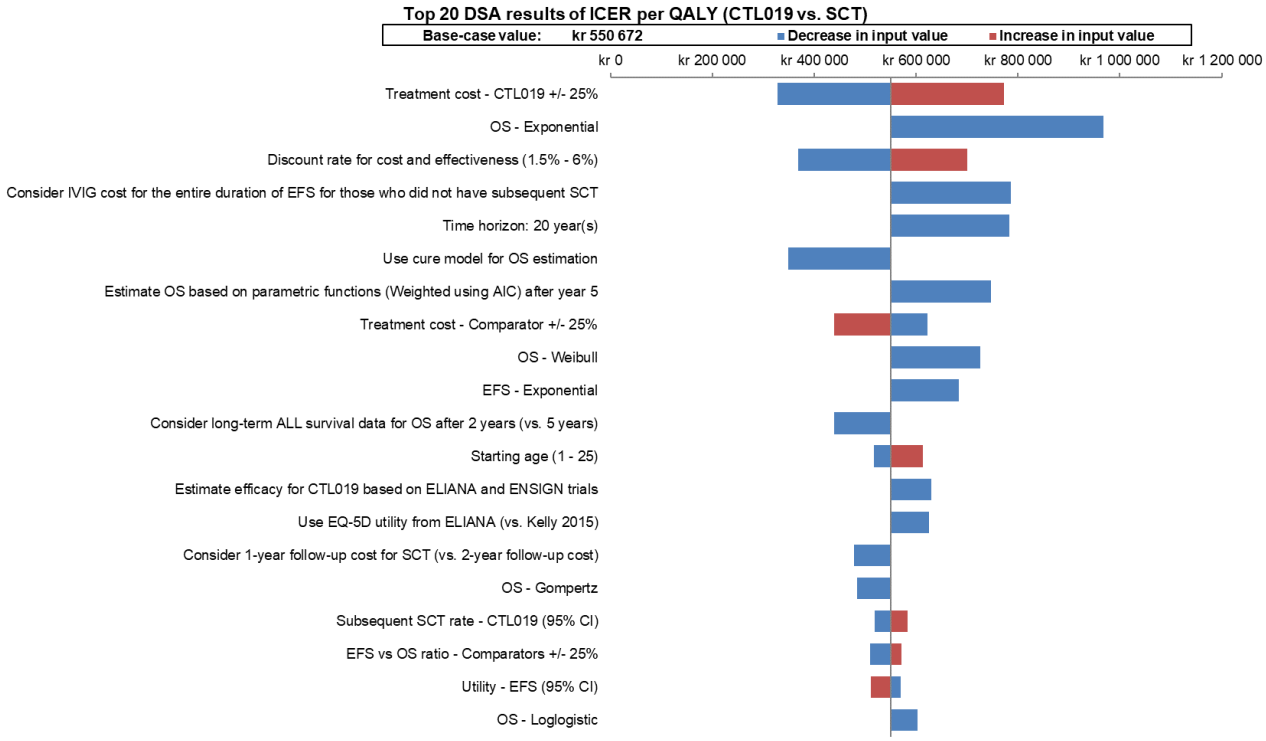


Figure 13 Tornado analysis of the cost per QALY of tisagenlecleucel against allogenic stem cell transplantation (top 20 scenarios) – naïve comparisons, by Novartis

NoMA has performed the following scenario analyses based on the ITT population.

Table 25 NoMA's scenario analyses

	Parameter	NoMA's base case	Scenario analyses	ICER in scenario analyses (NOK)
	Basecase analysis (ITT population)	**See 4.2.2 for all changes**	**-**	**651 101**
1	OS extrapolation	Spline model with two knots for CEC; Log-normal for tisagenlecleucel	Gompertz for CEC and tisagenlecleucel	523 453
2	Cure model	Standard parametric functions	Mixture cure models	483 622
3	Utilities - Health states	First 5 years: EFS: 0.80 PD: 0.63 Survival beyond 5 years: PD and EFS: 0.91 Source: ELIANA trial, Kelly et al	First 5 years: EFS: 0.91 PD: 0.75 Survival beyond 5 years: PD and EFS: 0.91 Source: Kelly et al	627 512
4	Hospitalisation – Length of stay – Lymphodepleting chemotherapy	14 days Source: ELIANA trial	6 days Source: clinical expert opinion	631 157
5	Hospitalisation – Length of stay – tisagenlecleucel infusion	26 days Source: ELIANA	From day 14 to 28, patients stay at a patient hotel or at home. Price pr night for patient hotel is NOK 565. Source: Clinical expert opinion, SPC, Regulations of patient travel.	619 545
6	Adverse events IVIG treatment costs	NOK 150 614 Treatment duration based on a parametric extrapolation of KM data on time until B cell recovery, adjusted for OS and the proportion of patients who received IVIG in the ELIANA trial (47.1%). Source: ELIANA trial data	NOK 319 776 Treatment duration based on a parametric extrapolation of KM data on time until B cell recovery, adjusted for OS. All patients that have not recovered from B cell aplasia receive IVIG treatment. Source: Assumption	688 211
7	Pharmacy markup	Included Price of tisagenlecleucel: NOK 3 167 606	Not included Price of tisagenlecleucel: NOK 3 082 800	632 496

1. **OS extrapolation**: The Gompertz function is tested because of the good mathematical and visual fit to the tisagenlecleucel and CEC data.
2. **Cure model**: NoMA also considered the selection of a mixture cure model given the curative potential of tisagenlecleucel. The cure model was not used, however, as the preferred option in the analyses due to immature and heavily censored data. The cure models offering the best mathematical fit are used in the scenario analysis. The OS cure fraction is 49% for tisagenlecleucel and 23% for CEC.
3. **Health related quality of life**: Both methods of estimating health state utilities have shortcomings. The Essig et al (33) study conclude that ALL survivors reported similar or higher HRQoL scores compared to the general population. Using the utility estimates from Kelly et al (31) increase the benefit of remission and thereby decreases the ICER.
4. **Hospitalisation – Lymphodepleting therapy:** According to clinical experts, the standard patient in Norway would be hospitalised for 6 days for lymphodepleting therapy. A shorter time spent in hospital decrease the costs of lymphodepleting therapy. This reduce the ICER.
5. **Hospitalisation – Length of stay – infusion:** According to a clinical expert, the patients should stay at the hospital for the first 14 days. After this they may stay at home or in patient hotel. The SmPC states that all patients should be near the qualified hospital for up to 4 weeks (28 days). We have assumed that 14% of the patients may stay at home from day 14 to 28. The reimbursement tariff for staying at a hotel is NOK 565 (60). We have used this as a proxy for the cost of hotel. With fewer days at the hospital the need of hospital resources are reduced.
6. **Adverse events IVIG treatment costs**: Both the proportion of patients on IVIG treatment and the duration of treatment is uncertain. In a scenario analysis we have explored a prolonged duration of IVIG treatment to capture the potential long-term consquences B cell aplasia. Different assumptions for the proportion of patients treated with IVIG and the treatment duration impact the ICER substantially.

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

NoMA has estimated a cost-effectiveness ratio for tisagenlecleucel compared to CEC. The outcomes of alternative scenario analyses are generally within the range of what can be considered a cost-effective use of healthcare resources, but multiple important limitations and uncertainties in the analysis were identified and remained. NoMA therefore considers the cost-effectiveness estimates to be highly uncertain.

In NoMA's base case analyses, the additional costs for tisagenlecleucel compared to CEC followed by subsequent alloSCT, with public list prices for medicines, are:

- 651 000 NOK per QALY gained in the ITT population (enrolled patients)
- 648 000 NOK per QALY gained in the mITT population (infused patients)

5 BUDGET IMPACT ANALYSIS

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

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

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

5.1 ESTIMATION OF THE NUMBER OF PATIENTS POTENTIALLY ELIGIBLE FOR TREATMENT

Clinical experts recruited by the regional health authorities have estimated that around 5 paediatric and young adult patients with relapsed/refractory B-cell ALL 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 26. The number of patients expected to be treated if Kymriah is not recommended is presented in Table 27.

Table 26 The number of patients expected to be treated with Kymriah (tisagenlecleucel) in the next 5 years – scenario where Kyrmiah (tisagenleucel) is recommend

	År 1	År 2	År 3	År 4	År 5
Kymriah (tisagenlecleucel)	5	5	5	5	5
CEC	0	0	0	0	0
Total	5	5	5	5	5

Table 27 The number of patients expected to be treated with Kymriah (tisagenlecleucel) in the next 5 years – scenario where Kyrmiah (tisagenleucel) is not recommend

	År 1	År 2	År 3	År 4	År 5
Kymriah (tisagenlecleucel)	0	0	0	0	0
CEC	5	5	5	5	5
Total	5	5	5	5	5

5.2 COST ESTIMATES

NoMA has calculated the budget impact for two scenarios:

1. Drug costs for bridging chemotherapy, pre-treatment, Kymriah, and CEC. 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 population and all changes by NoMA as described in chapter 4.2.2 are incorporated.

Drug costs in NOK per patient per year after treatment initiation according to scenario 1 are presented in Table 28.

Table 28 Drug costs per patient per year after treatment initiation. List price, including VAT and undiscounted.

	Year 1	Year 2	Year 3	Year 4	Year 5
Kymriah (tisagenlecleucel)	3 492 957	0	0	0	0
Clofarabine combination (CEC)	322 587	0	0	0	0

Healthcare costs in NOK per patient per year after treatment initiation according to scenario 2 are presented in Table 29.

Table 29 Healthcare costs per patient per year after treatment initiation. List price, including VAT and undiscounted.

	Year 1	Year 2	Year 3	Year 4	Year 5
Kymriah (tisagenlecleucel)	4 652 487	16 804	9 105	9 670	5 723
Clofarabine combination (CEC)	1 748 214	4 229	2 062	5 363	3 038

5.3 BUDGET IMPACT

The estimated budget impact in NOK as a result of drug costs only (scenario 1) for the eligible patient population is presented in Table 30.

Table 30 Estimated budget impact of drug costs for the eligible patient population. List price, including VAT and undiscounted.

	Year 1	Year 2	Year 3	Year 4	Year 5
Kymriah (tisagenlecleucel) recommended for use	17 464 786	17 464 786	17 464 786	17 464 786	17 464 786
Kymriah (tisagenlecleucel) not recommended for use	1 612 937	1 612 937	1 612 937	1 612 937	1 612 937
Budget impact of recommendation	15 851 849	15 851 849	15 851 849	15 851 849	15 851 849

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 31.

Table 31 Estimated budget impact of healthcare costs for the eligible patient population. List price, including VAT and undiscounted.

	Year 1	Year 2	Year 3	Year 4	Year 5
Kymriah (tisagenlecleucel) recommended for use	23 262 433	23 346 454	23 391 977	23 440 329	23 468 946
Kymriah (tisagenlecleucel) not recommended for use	8 741 071	8 762 216	8 772 527	8 799 344	8 814 536
Budget impact of recommendation	14 521 363	14 584 237	14 619 449	14 640 985	14 654 410

The budget impact of a positive recommendation for Kymriah for the eligible patient population as described in this STA is estimated to be around 15 million NOK including VAT in the fifth year after introduction. The calculations are uncertain and based on simplifications.

6 SUMMARY AND CONCLUSION

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

NoMA's assessment of the benefit criterion:

The clinical efficacy and safety of tisagencelcelucel was demonstrated in one main study (ELIANA) and two supportive studies (ENSIGN and B2101J) in about 190 paediatric and young adult patients with relapsed/refractory B-cell ALL. Results of the trials demonstrated high remission rates following a single infusion of tisagenlecleucel. The overall remission rate within 3 months was 82% among the patients who received a tisagenlecleucel infusion in the ELIANA trial. The rate of EFS and OS at 12 months were 46% and 70%, respectively, in the ITT population. The survival data are immature.

The tisagenlecleucel clinical trials all had single arm study designs, and Novartis has conducted a MAIC with CEC as comparator to document the relative efficacy. The results of the MAIC are very uncertain due to the small sample size and heterogeneity of the CEC comparator, and too few matching variables to adjust for differences between the patient populations in the comparison. Consequently, although the superior efficacy of tisagenlecleucel over CEC seems clear, the relative effect of tisagenlecleucel vs CEC cannot be reliably established.

In NoMAs base case analyses, the mean incremental effect of tisagenlecleucel treatment compared to CEC treatment was 3.7 QALYs per patient in the ITT population. NoMA considers this estimate to be highly uncertain due to the important limitations described in this assessment.

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 acquisation, and procedure costs for tisagenlecleucel and comparator, drug administration costs, hospitalisation and ICU costs, adverse event costs, subsequent alloSCT costs, follow-up and monitoring costs, and terminal care costs.

The list price for tisagenlecleucel is NOK 3 167 606 excluding VAT. The mean total healthcare cost was approximately 4.1 million NOK per patient for tisagenleucel and 1.7 million NOK per patient for CEC treatment in NoMAs base case analysis, resulting in a mean incremental healthcare cost of 2.4 million per patient, in the ITT population. The costs for pre-treatment and AEs are higher for tisagenlecleucel compared to CEC, and the cost for subsequent alloSCT are lower.

NoMA's assessment of the severity criterion:

Paediatric and young adult ALL-patients that are refractory, in relapse post-transplant or in second or later relapse have a very poor prognosis. NoMA estimated an absolute shortfall (AS) of approximately 51 QALYs.

NoMA's assessment of budget impact:

NoMA estimated the budget impact for the specialist health services to be around 15 million NOK including VAT in the fifth year after introduction, if tisagenlecleucel is introduced for the treatment of paediatric and young adult patients with relapsed/refractory B-cell ALL.

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

The studies of tisagenlecleucel are considered to have considerable shortcomings to inform a STA. The studies have single arm designs, are small, and have short median follow-up time.

The studies lack a contoll arm, and it is therefore not possible to compare outcomes from these trials with outcomes from the comparator trials without a high degree of uncertainty.

Long-term outcomes, both in terms of efficacy and safety, are currently not known. Since CAR-T cell therapy is a new treatment principle, which involves genetic modification of the patient's own T cells, there is a particular uncertainty about long-term effects. Thus far, none of the trials for CAR-T therapy have followed patients long enough to ascertain whether children with ongoing remission could be considered cured. An additional uncertainty is the duration of B cell aplasia. Patients with hypogammaglobulinemia due to B cell aplasia are at risk for infections and may need prolonged supplemental treatment with IVIG. The proportion of patients that require IVIG treatment and the duration of treatment is unclear, and the model outcomes are sensitive to different assumptions.

Tisagenlecleucel is targeted towards a small patient group with a severe condition in which it is difficult to conduct randomised controlled studies. Therefore, a less stringent requirement for documentation is considered acceptable (61).

Arrangement of pharmaceuticals for very small patient groups with extremely severe conditions

When assessing interventions targeted towards very small patient groups with an extremely severe condition, higher resource use than for other interventions may be acceptable (61).

The three guiding criteria for deciding whether a medicine is for treating a very small patient group with an extremely severe condition are as follows (61):

1. Very small patient group:
   a) Fewer than 1 patient per 100 000 inhabitants on a global basis per medicine (prevalence on a global basis).
   b) Fewer than 50 patients in Norway per medicine (steady state prevalence in Norway).
2. Extremely severe condition: AS corresponding to at least 30 lost QALYs.

3. Considerable expected benefit from the medicine: a minimum of two gained QALYs compared to standard treatment.

Relapsed/refractory paediatric ALL is an extremely severe condition (AS 51 QALYs), the expected benefit from the tisagenlecleucel treatment is considerable (3.7 QALYs gained), and the patient group is very small (5 patients annually in Norway).

However, NoMA believes that the total number of patients that is eligible for tisagenlecleucel treatment, on a global basis and in Norway, eventually will exceed the indicative criteria applied for *very small patient groups with extremely severe conditions.* Tisagenlecleucel is also licensed for the treatment of adult patients with relapsed or refractory DLBCL after two or more lines of systemic therapy, and about 30 – 50 DLBCL patients may be candidates for treatment with tisagenlecleucel each year in Norway according to clinical experts. Planned studies of tisagenlecleucel in earlier treatment lines for both ALL (the CASSIOPEIA trial) and DLBCL (the BELINDA trial) may eventually increase the number of patients treated with tisagenlecleucel. In addition, research programs are underway for tisagenlecleucel targeting other hematologic malignancies.

NoMA´s overall evaluation

NoMA identified multiple important limitations and uncertainties in the analyses that remained. NoMA considers the estimated gain in overall and quality adjusted survival for tisagenlecleucel compared to CEC followed by subsequent alloSCT to be highly uncertain. The outcomes of alternative scenario analyses are generally within the range of what can be considered a cost-effective use of healthcare resources. Although this does not take away the limitations and uncertainty in the analysis, NoMA considers there may be plausible potential for tisagenlecleucel to be a cost-effective treatment option for relapsed/refractory paediatric and young adult ALL patients, given the degree of severity for the patient group.

Norwegian Medicines Agency, 08-11-2018

Elisabeth Bryn (e.f.)

Mathyn Vervaart

Ania Urbaniak

Maria Elisabeth Kalland

Kirsti Hjelme

Einar Andreassen

APPENDIX 1 SEVERITY AND SHORTFALL

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

The calculation of absolute shortfall is done in stages:

1) The mean age at start of treatment for the relevant Norwegian patient group which is being considered for the new treatment is defined. We refer to the age as A. We have used the average age of patients enrolled in the ELIANA and ENSIGN trials of 12 years as A.
2) The number of remaining QALYs (undiscounted) for an average person from the general population with the age A is estimated. We refer to this as $QALYs_A$. We use mortality data for the Norwegian population from Statistics Norway (62) in calculating expected remaining lifetime at different ages. This is combined with age-specific quality of life data to calculate quality adjusted remaining lifetime for different ages. Pending reliable Norwegian figures, we use Swedish age-specific quality of life data, with value sets based on UK general population available for EQ-5D, based on Sun et al (40) and Burstrøm et al (41). See Table 32 below.
3) The prognosis for the relevant Norwegian patient group is calculated. The prognosis is the average number of remaining QALYs (undiscounted) for the patient group with the current standard treatment. We refer to this as P_A. We calculate the prognosis from the number of QALYs the patients can expect with the comparator treatment in the health economic analysis.
4) The absolute shortfall (AS) is the difference between the estimated number of remaining QALYs for the general population at the same age (point 2) and the expected number of remaining QALYs for the patient group with the comparator treatment (point 3).
5) Absolute shortfall (AS) = $QALYs_A - P_A$

Table 32 Calculation of severity

Age	A	12
Expected $QALYs_A$ without disease (undiscounted)	$QALYs_A$	58.62
Expected number of $QALYs_A$ with disease (undiscounted)	P_A	7.46
Number of lost QALYs with disease (absolute shortfall)	AS	51.16

NoMA estimates the absolute shortfall based on current standard care to be approximately 51 QALYs

Expected remaining QALYs in the general population

Table 33 shows the expected remaining QALYs and health state utility values (HSUV) respectively, by age for the general population. Expected remaining QALYs are based on mortality data for the Norwegian population from Statistics Norway (62) and the age-specific HSUV in the right hand column.

Pending reliable Norwegian figures, the HSUV from two Swedish studies have been used (40, 41). In the studies, Swedish age-specific quality of life data is combined with British population-based EQ-5D value-setting tariffs (28).

HSUV for the age group 21-73 years are taken from Sun et al (40), which is the most recent of the two Swedish studies and has the greatest number of respondents. In this publication, HSUV for other age groups are not presented. For the age group 0-20 years, we have assumed that HSUV are somewhat higher than for the age group 20-33 years. We have set it at 0.89.

In order to obtain fairly even age ranges, we have established an age group 74-88 years based on data from Burstrøm et al (41). For this group, we have calculated a simplified weighted average which gives a HSUV of 0.76 (rounded). The calculation is based on the following: For the age group 74-79 years we assume a HSUV at 0.79 based on Burstrøm et al. For the age group 80-88 years we use a HSUV of 0.74 from Burstrøm et al.

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

Table 33 Expected remaining QALYs and HSUV in the general population

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

29	43,9	0,87	65	15,8	0,8	101	1,5	0,72
30	43,1	0,87	66	15,1	0,8	102	1,5	0,72
31	42,2	0,87	67	14,5	0,8	103	1,3	0,72
32	41,4	0,87	68	13,8	0,8	104	1,1	0,72
33	40,5	0,87	69	13,2	0,8	105	0,8	0,72
34	39,7	0,87	70	12,5	0,8			
35	38,8	0,85	71	11,9	0,8			

APPENDIX 2 MATCHING-ADJUSTED INDIRECT COMPARISON (MAIC): TISAGENLECLEUCEL VS. CEC

Due to the single arm trial design of the ELIANA, ENSIGN and B2101J trials, Novartis presented an indirect treatment comparison to a historical control using MAIC. MAIC use individual patient data from trials of one treatment to match baseline summary statistics reported from trials of another treatment. After matching, by using an approach similar to propensity score weighting, treatment outcomes are compared across balanced trial populations.

MEDLINE, Embase, and the Cochrane Central Register of Controlled Trials (CENTRAL), were searched to identify English-language studies conducted in humans published as of June 14, 2016. These searches were conducted using a combination of search terms and keywords for relapsed/refractory ALL (r/r ALL), paediatric patients, and the treatments of interest noted in the study protocol. The treatments of interest included tisagenlecleucel, as well as any approved or guideline-recommended interventions for paediatric r/r ALL including allogenic SCT, autologous SCT, and rescue chemotherapy. Search terms and strategies were adapted to the idiosyncrasies of each of these databases by using the appropriate indexing terms (e.g., Medical Subject Headings [MeSH] in MEDLINE and Emtree in Embase). Supplementary searches of "grey" literature were conducted to complement the literature database searches and provide data from recent or ongoing trials.

Patient-level data for tisagenlecleucel was from the ELIANA, ENSIGN, and B2101J studies. For B2101J, patients with non-CNS3 ALL were included in the analyses (patients with CNS3 and lymphoma patients were excluded). The data cut-off dates were 31 Dec 2017 for ELIANA; 06 Oct 2017 for ENSIGN; and 30 Jan 2017 for B2101J.

As described previously, NoMA chose CEC as the main comparator in the STA. Summary-level data for CEC was from the Miano et al. (2012) (7), Locatelli et al. (2009) (8), and Hijiya et al. (2011) (9) manuscripts. In all the studies, CEC was used as a bridge-to transplant therapy. Overall, 28 out of 74 paediatric ALL patients (38%) proceeded to SCT. The studies were all of similar design. Miano et al. (2012) and Hijiya et al. (2011) used the same dosage of CEC (clofarabine 40 mg/m2, etoposide 100 mg/m2, and cyclophosphamide 440 mg/m2). Locatelli et al. (2009) used a slightly different dose (clofarabine 40 mg/m2, etoposide 150 mg/m2, and cyclophosphamide 400 mg/m2).

The reporting of patient characteristics varied considerably among the three CEC trials. In comparison to ELIANA+ENSIGN+ B2101J, patients from the CEC trials had a similar median age (although patients from Miano et al were younger) and a similar Karnofsky status (although only reported in Hijiya et al). The tisagenlecleucel trials included only B cell patients, whereas patients in CEC trials had various immunophenotypes (32% T cell in Locatelli et al, 16% T cell or unknown in Hijiya et al, unknown in Miano et al). Although it is important to notice that only B cell patients from Locatelli were used for the OS analysis. There were also differences in the disease status (patients in the tisagenlecleucel trials had

mostly relapsed disease status as opposed to refractory in the CEC trials), the number of previous remissions/ relapses was higher for tisagenlecleucel patients, so was the number of previous lines of therapy.

The only baseline characteristics that were reported by all three trials were age, gender and prior SCT. Since age was reported as medians, it could not be pooled. In total, 20 of 74 (27.0%) CEC patients had a prior SCT which was far fewer than the 57% of tisagenlecleucel patients who had an SCT. Ultimately, gender and prior SCT were used as the only matching variables in MAIC. After consulting with clinicians and reviewing the literature, Novartis ranked the available baseline characteristics as high, medium, or low in terms of relative importance for the adjustment in the MAIC analyses. A "low" ranking indicates that adjusting for that variable is expected to have a relatively small effect on the MAIC results. Gender was given a low ranking, whereas prior SCT was given a high ranking. The resulting effective sample size (ESS) in the mITT population was 141 patients in the ELIANA+ENSIGN+ B2101J trials (73% of the original size), 106 (77%) patients in the ELIANA+ENSIGN trials, or 54 (67%) in the ELIANA trial alone. The ESS was naturally larger for the ITT population; 179 (76%), 134 (79%), 67 (70%), respectively.

The results of MAIC in terms of OS and ORR are presented separately for the mITT population (from tisagenlecleucel infusion) and for the ITT population (enrolled set from tisagenlecleucel enrolment) in Table 34 - Table 39 and Figure 14. OS from time of initiation of treatment was used for CEC.

The proportional hazard assumption was tested by means of the Schoenfeld residual tests (graphical and p-value tests) and log cumulative hazard plots. The Schoenfeld residuals test evaluates whether the slope of scaled residuals on time is zero or not. If the slope is significantly different from zero, the proportional hazard assumption is violated and hence the outcome in the form of a hazard ratio (HR) might not be appropriate. A p-value below 0.05 indicates a violation of proportionality. According to Novartis, none of the tests, in either the naïve or MAIC adjusted CEC comparisons, found evidence of strong violation of the PH assumption. In the log cumulative hazard plot the vertical distance between tisagenlecleucel and CEC curves were nearly constant over time after 2.7 months (i.e 1 month on the log scale) (Figure 14).

Table 34 Hazard ratios for OS in the mITT population.

Adjustment Scenario	Naïve Comparison		MAIC Comparison	
	Naive Comparison	p-value	MAIC Comparison	p-value
CTL019 (B2202+B2205J+B2101J) vs CEC	0.255 (0.174, 0.373)	<0.0001	0.293 (0.195, 0.439)	<0.0001
CTL019 (B2202+B2205J) vs CEC	0.268 (0.176, 0.407)	<0.0001	0.3 (0.192, 0.469)	<0.0001
CTL019 (B2202 only) vs CEC	0.216 (0.13, 0.359)	<0.0001	0.252 (0.142, 0.445)	<0.0001

Table 35 OS Six- and 12-month Survival Probabilities in the mITT population

Scenario	Months	CTL019 Unmatched % (95% CI)	CTL019 Matched % (95% CI)	Comparator % (95% CI)
CTL019 (B2202+B2205J+B2101J) vs CEC	6	85.1 (80.1, 90.5)	82.7 (76.5, 89.5)	44.6 (34.2, 58.2)
CTL019 (B2202+B2205J+B2101J) vs CEC	12	73.6 (67.3, 80.5)	70.2 (62.6, 78.8)	25.9 (17, 39.5)
CTL019 (B2202+B2205J) vs CEC	6	84.9 (78.9, 91.4)	82 (74.7, 90.1)	44.6 (34.2, 58.2)
CTL019 (B2202+B2205J) vs CEC	12	71 (63.2, 79.9)	68.5 (59.4, 79)	25.9 (17, 39.5)
CTL019 (B2202 only) vs CEC	6	88.4 (81.5, 95.8)	83.8 (74.4, 94.4)	44.6 (34.2, 58.2)
CTL019 (B2202 only) vs CEC	12	75.9 (66.8, 86.3)	74.5 (63.5, 87.5)	25.9 (17, 39.5)

Table 36 Odds ratios for ORR in the mITT population

Adjustment Scenario	Naive Comparison		MAIC Comparison	
	OR (95% CI)	p-value	OR (95% CI)	p-value
CTL019 (B2202+B2205J+B2101J) vs CEC	4.037 (2.275, 7.165)	<0.0001	3.636 (1.989, 6.647)	<0.0001
CTL019 (B2202+B2205J) vs CEC	2.853 (1.579, 5.155)	0.0005	2.538 (1.367, 4.711)	0.0032
CTL019 (B2202 only) vs CEC	4.901 (2.348, 10.228)	<0.0001	3.697 (1.678, 8.143)	0.0012

Table 37 Hazard ratios for OS in the ITT population

Adjustment Scenario	Naïve Comparison		MAIC Comparison	
	HR (95% CI)	p-value	HR (95% CI)	p-value
CTL019 (B2202+B2205J+B2101J) vs CEC	0.312 (0.218, 0.447)	<0.0001	0.352 (0.242, 0.512)	<0.0001
CTL019 (B2202+B2205J) vs CEC	0.357 (0.245, 0.522)	<0.0001	0.388 (0.26, 0.579)	<0.0001
CTL019 (B2202 only) vs CEC	0.326 (0.211, 0.505)	<0.0001	0.375 (0.231, 0.608)	0.0001

Table 38 OS Six- and 12-month Survival Probabilities for the ITT population

Scenario	Months	CTL019 Unmatched % (95% CI)	CTL019 Matched % (95% CI)	Comparator % (95% CI)
CTL019 (B2202+B2205J+B2101J) vs CEC	6	79.6 (74.3, 85.2)	77 (70.7, 84)	44.6 (34.2, 58.2)
CTL019 (B2202+B2205J+B2101J) vs CEC	12	69.5 (63.4, 76.2)	66.3 (59, 74.4)	25.9 (17, 39.5)
CTL019 (B2202+B2205J) vs CEC	6	77.1 (70.7, 84.1)	74.2 (66.6, 82.6)	44.6 (34.2, 58.2)
CTL019 (B2202+B2205J) vs CEC	12	66.3 (59, 74.6)	64.3 (55.9, 74)	25.9 (17, 39.5)
CTL019 (B2202 only) vs CEC	6	77.5 (69.5, 86.5)	72.2 (62, 84)	44.6 (34.2, 58.2)
CTL019 (B2202 only) vs CEC	12	69.6 (60.7, 79.7)	67 (56.4, 79.7)	25.9 (17, 39.5)

Table 39 Odds ratios for ORR in the ITT population

Adjustment Scenario	Naïve Comparison		MAIC Comparison	
	OR (95% CI)	p-value	OR (95% CI)	p-value
CTL019 (B2202+B2205J+B2101J) vs CEC	1.946 (1.147, 3.3)	0.0135	1.728 (1, 2.986)	0.0499
CTL019 (B2202+B2205J) vs CEC	1.508 (0.871, 2.61)	0.1423	1.362 (0.771, 2.408)	0.2876
CTL019 (B2202 only) vs CEC	2.144 (1.151, 3.994)	0.0163	1.767 (0.902, 3.463)	0.0971

Since response data was not collected on non-infused patients, it was assumed that all these patients were non-responders.

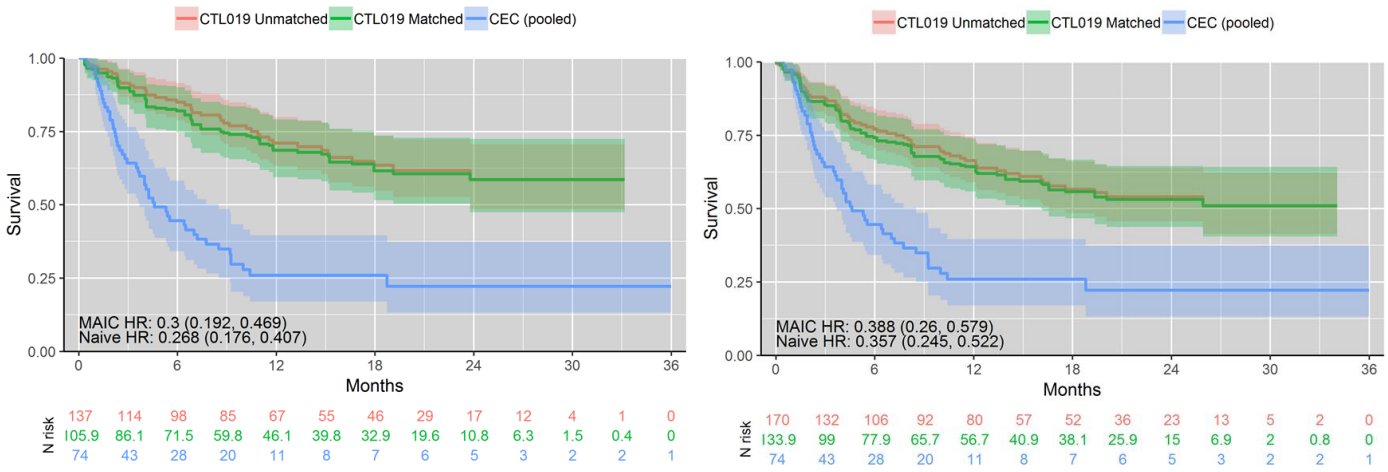


Figure 14 OS of tisagenlecleucel (CTL019) (ELIANA+ENSIGN) vs. CEC in the mITT population (from infusion, left) and the ITT population (from enrollment, right)

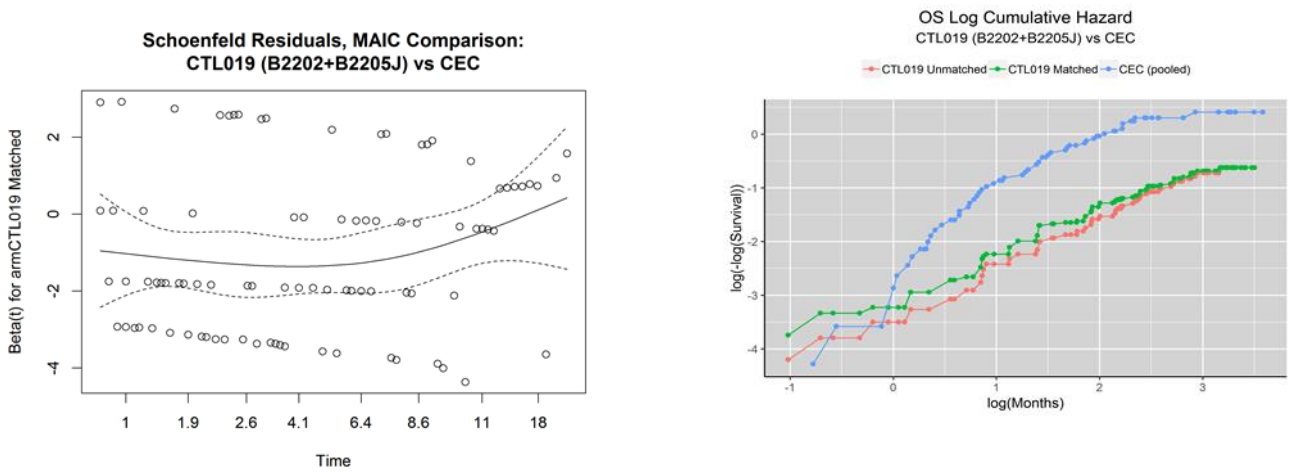


Figure 15 Shoenfeld residuals plots (left) and log cumulative hazard plots (right) for the MAIC comparison between tisagenlecleucel (ELIANA+ENSIGN) vs CEC in the mITT population (left) and the corresponding log cumulative hazard plots (right)

NoMA's assessment of the submitted evidence

Studies included in the MAIC were identified through a Systematic Literature Review (SLR) conducted by Novartis according to the PRISMA guidelines. The SLR was comprehensive and transparent. The search criteria, sources, inclusion and exclusion criteria were clearly stated.

Novartis conducted MAIC based on patient-level data for tisagenlecleucel from the ELIANA, B2205J ENSIGN, and B2101J studies. For B2101J, patients with non-CNS3 ALL were included for the analyses (patients with CNS3 and lymphoma patients were excluded). The results are presented either as a comparison of pooled patients who received tisagenlecleucel, pooled patients from ELIANA and ENSIGN or as ELIANA patients alone. It is noted that trials ELIANA and ENSIGN had a similar single-arm trial design and enrolled identical patient populations. Both were multicentre trial with single infusion with IRC assessment and the requirement for response confirmation. Study B2101J differed, however, in the design as it was a single site trial with wider dose range and multiple infusions allowed. In addition, endpoints were assessed by the investigator without a need for confirmation. For these reasons, NoMA chose to use pooled data from ELIANA and ENSIGN in order to increase the effective sample size and the precision of the estimate.

For the CEC comparison, Novartis chose to pool together a prospective cohort study by Miano 2012 (children with advanced ALL, study size, N=24), a phase II, open label clinical trial as described by Locatelli 2009 (children with advanced ALL, study size, N=25), and Phase II clinical trial in children with r/r ALL as described by Hijiya 2011 (sample size, N=25). Given the small sample size of individual studies an attempt of combining the studies for MAIC could be reasonable. However, it is noted that the differences in study design, various B cell/ T cell phenotype proportions, and unknown prior treatment history makes this combined data source unreliable. In addition, the studies are much older than the tisagenlecleucel studies and the SoC patient charactristics and the study outcomes might have been different nowadays. According to the clinician contacted by the company, Dr. Jochen Büchner from Oslo University Hospital, overall survival chart (Figure 14) from clofarabine combination trials is representative for the Norwegian patients. Chemotherapy given in the relapsed/refractory setting unlikely provides long-term remission and survival and is therefore used as a bridge to transplant. The tail of the OS curve represents survival in those patients who achieved complete remission (CR) and subsequently underwent an alloSCT. NoMA recognizes the challenges of identifying a historical control in the relapsed/refractory paediatric ALL setting such as small number of patients, retrospective design, inhomogeneous treatments.

The MAIC-adjusted comparison vs. CEC was based only on two variables; prior SCT (ranked as high matching importance) and gender (ranked as low matching importance). No other high or medium priority variables were available for matching. Matching by baseline prognostic factors is at the core of MAIC. The reliability of the current comparison appears to be severely compromised due to unavailability of matching variables. The sample size for tisagenlecleucel (ELIANA and ENSIGN) in the mITT comparison dropped from 137 to 106 patients after adjusting for the SCT rate in the CEC studies. The proportion of patients with prior SCT was much higher in ELIANA+ENSIGN (54%) compared to the pooled CEC studies (27%). NoMA expressed their concern regarding the representativeness of the low prior alloSCT rate. In response, Novartis described data from Rikshospitalet in Oslo were 7 paediatric patients have been

treated and 2 (28.5 %) of those had previously had a SCT. Although the proportions appear similar, NoMA acknowledges that it is difficult to draw conclusions based on a such a small Norwegian patient pool.

After adjusting for prior SCT and gender via MAIC, tisagenlecleucel was estimated to have superior OS and ORR over CEC. The OS HRs were 0.3 (95%CI: 0.192, 0.469) for the mITT population and 0.388 (95%CI: 0.26, 0.579) for the ITT population. The results for the adjusted and naïve comparisons were fairly similar.

Novartis claims that the PH assumption was not violated. However, the Schoenfeld residuals and log-cumulative hazard plot (Figure 15) do not support the proportional hazard assumption. The mechanism of action between tisagenlecleucel and CEC is also very different, and does not provide a rationale for a constant proportional treatment effect. NoMA concludes that there is no evidence to support the use of a constant HR.

In summary, there are many methodological issues underlying the provided comparison. The component studies of the CEC comparison are heterogenous and the overall patient number is small. Furthermore, the matching of ELIANA+ENSIGN to CEC is based on too few prognostic factors and effect modifiers. As the result, the comparison vs. CEC is considered more as a naïve comparison rather than an adjusted comparison. Overall, this comparison is subject to potential bias due to unobserved or unmeasurable confounding. At the same time it is noted that the degree of benefit observed was largely consistent regardless of whether the comparison was made using ELIANA only or using the pooled tisagenlecleucel studies and was largely consistent across all the endpoints and between the mITT and the ITT populations. However, although the superior efficacy of tisagenlecleucel over CEC is clear, the magnitude of this benefit is highly uncertain.

VEDLEGG 1 KOMMENTARER FRA PRODUSENT (VEDLAGT SEPARAT)

Novartis takker for muligheten til å kommentere på Legemiddelverket sin rapport i forbindelse med hurtig metodevurdering av Kymriah (tisagenlecleucel) til behandling av pediatriske og unge voksne pasienter opptil 25 år med akutt lymfoblastisk B-celleleukemi (B ALL) som er refraktær, i residiv etter transplantasjon eller med to eller flere tilbakefall.

Legemiddelverket har utarbeidet en god og grundig rapport, og Novartis er enig i Legemiddelverkets konklusjon om at Kymriah kan være et kostnadseffektivt alternativ til denne pasientgruppen.

Vi registrerer at Legemiddelverket har gjort noen endringer i den innsendte analysen som hovedsakelig går i disfavør av Kymriah. Vi mener det er sannsynlig at reell kostnad per vunnet kvalitetsjusterte leveår vil være lavere enn i Legemiddelverkets hovedanalyse.

Antagelsene til Legemiddelverket er godt begrunnet, men noen av valgene er vi uenige i:

- Kostnad til leukaferese er satt svært høyt og er basert på et estimat fra OUS beregnet for kliniske studier der det er lagt inn en betydelig profitt i prisen. Kostnaden i andre Europeiske land er betydelig lavere.
- Apotekavanse vil i dette tilfellet være en overføring fra sykehuset til sykehusapoteket og således ingen kostnad. Apoteket skal ikke håndtere eller oppbevare legemiddelet, og de har heller ingen kapitalbinding eller finansiell risiko ved Kymriah. En apotekavanse på kr 85 000 for en jobb som kanskje har et omfang på 2 timer er etter vår mening urimelig høyt.
- Livskvalitetstapet ved allogen stamcelle transplantasjon er underestimert ved at pasientene kun får et tap i livskvalitet i 2 måneder. Det er ikke tatt hensyn til eventuelle komplikasjoner etter transplantasjonen.
- På den annen side mener vi at livskvaliteten for pasienter på Kymriah er satt urimelig lavt ved å anta at disse pasientene ikke kan få høyere livskvalitet enn 0,8 frem til år 5 etter infusjon.

Dette er en sykdom som er svært alvorlig med et estimert helsetap på 51 kvalitetsjusterte leveår, og pasientene kan potensielt ha svært stor nytte av Kymriah. For disse pasientene finnes det ingen andre effektive behandlingsalternativer, og selv om man gjerne skulle hatt enda lengre oppfølgingstid i de kliniske studiene for å dokumentere langtidsoverlevelse, så har det første barnet som ble behandlet med Kymriah nå vært kreftfri i mer enn 6 år.

Novartis har tilbudt norske pasienter gratis behandling med Kymriah i kliniske studier siden 2015, og vi håper at Beslutningsforum kan ta en rask avgjørelse i denne saken slik at norske barn og unge voksne med B ALL fortsatt kan få tilgang til denne behandlingen.

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