Medicinrådet

Bilag til Medicinrådets anbefaling vedrørende tisagenlecleucel til behandling af diffust storcellet B-cellelymfom

Vers. 2.0

Bilagsoversigt

1. Ansøgers notat til Rådet vedr. tisagenlecleucel
2. Forhandlingsnotat fra Amgros vedr. tisagenlecleucel
3. Ansøgers endelige ansøgning vedr. tisagenlecleucel

Den 29. august 2024

Notat vedrørende Udkast til Medicinrådets anbefaling vedr. tisagenlecleucel til behandling af diffust storcellet B-cellelymfom

Vi takker for udkastet til Medicinrådets anbefaling vedr. tisagenlecleucel til behandling af diffust storcellet B-cellelymfom, modtaget fredag den 16. august 2024, og for muligheden for at kommentere.

Indledningsvis vil vi gøre opmærksom på, at der på side 5 (næstsidste afsnit) samt på side 32 linje 4 står "axi-cel". Vi formoder, at der skulle stå "tisa-cel".

Usikkerhed vedr. analyseresultater, ITT vs. Full Analysis Set (FAS) population samt overførbarhed til en dansk population

Medicinrådet anfører, at der er en betydelig usikkerhed vedrørende resultatet af analysen, eftersom der er vist bedre overlevelse i danske patienter efter 3. linje behandling [1], sammenlignet med overlevelsen i CORAL extension studierne, som JULIET studiet er sammenlignet med. Desuden er effekten for tisagenlecleucel baseret på den del af studiepopulationen, der modtog infusion med tisagenlecleucel (FAS-populationen), og ikke alle inkluderede patienter (ITT-populationen), hvorved Medicinrådet mener, at der er risiko for, at effekten af tisagenlecleucel er overestimeret.

I forbindelse med ansøgningen har Novartis haft fokus på at præsentere 5-års data (final data cut). Vi havde ikke mulighed for at få en opdateret analyse på ITT populationen, men kan henvise til, at vi i forbindelse med anmodningen om revurdering indsendte 4 års data for ITT populationen til Medicinrådet. Disse viste en 2-års overall survival (OS) på 34% og en 4-års OS på 29% for IIT populationen. I et nypubliceret registerstudie i danske patienter med DLBCL [1], var 2-års OS 25% efter standard of care (SoC) 3. linje behandling, dvs. knap 10 %-point lavere end for tisagenlecleucel ITT populationen.

Der er få studier, der viser effekten af komparator, dvs. SoC i 3. linje behandling af DLBCL. CORAL extension studierne blev således valgt, fordi der var 5-års data, og fordi Novartis havde adgang til individuelle patientdata, hvilket giver mulighed for at matche og justere patientpopulationer ved sammenligninger. Novartis anerkender, at der er visse usikkerheder ved CORAL extension studierne. Væsentlige baseline værdier, som f.eks. ECOG PS, var ikke registreret i CORAL extension studierne, og populationerne kunne således ikke matches på disse parametre. CORAL extension studierne startede i slut 00-erne, (CORAL patienterne inkluderedes i det primære 2. linje studie mellem 2003 og 2007), og behandlingsregimerne har undergået ændringer siden da. Da analysen blev lavet, var CORAL data de bedst tilgængelige data og vi mener, at den analyse, der indgår i ansøgningen, er den bedst mulige med tanke på muligheden for matching af patienter på individ niveau.

Medicinrådet sammenligner JULIET data med et ny-publiceret dansk registerstudie i DLBCL patienter i 3. linje [1]. Artiklen er publiceret i marts 2024, efter indsendelse og validering af Novartis´ ansøgning, og indeholder 2-års OS data. Patienterne i det danske register studie var generelt ældre end patienterne i JULIET studiet, og SoC behandlingerne adskiller sig på nogle punkter fra dem, der var anvendt i CORAL extension studierne. Novartis anerkender disse forskelle, men uden adgang til individuelle patientdata er det ikke muligt at matche populationerne, hvilket resulterer i en mere usikker sammenligning. Derudover er tidsperspektivet meget forskelligt for de danske real-world data sammenlignet med vores analyse, som er baseret på final data cut for JULIET studiet ved år 5. I CORAL extension studierne var OS lavere i den matchede population end i den ikke-justerede population. Tilsvarende kunne være tilfældet, hvis man lavede en lignende analyse på baggrund af de danske registerdata.

Medicinrådet anfører, at median-alderen i JULIET er lav i forhold til en gennemsnitlig refraktær dansk DLBCL-patient. Dette er reflekteret i Novartis´ sundhedsøkonomiske analyse, da base-case er sat til patienter på 72 år, samme alder som fundet det danske registerstudie (beskrevet i kongres-abstract for reference [1]), og analysen giver derfor et konservativt resultat. I scenarie analysen har vi valgt at tage udgangspunkt i den gennemsnitlige alder fra JULIET (56 år). Medicinrådet tillægger oftest kliniske langtidsstudier større vægt end real-world data, men da der er så stor diskrepans mellem alder, har vi valgt det mere konservative estimat. Den egentlige alder for patienter, som vil blive tilbudt CAR-T behandling formodes imidlertid at ligge imellem de to værdier.

Tid fra leukaferese til infusion i dansk klinisk praksis

Medicinrådet anfører i vurderingsrapporten, at det er afgørende, at den observerede ventetid fra leukaferese til infusion kan reproduceres i dansk klinisk praksis.

Den observerede gennemsnitlige tid fra afhentning af leukaferese-produktet til levering af det færdige produkt (dør til dør) for alle batches i EU (n > 2.750 batches) er 25/26 dage. Denne tidsramme inkluderer situationer, hvor Novartis bliver bedt om at udsætte leveringen af det endelige produkt på grund af patientens tilstand eller kapacitetsproblemer på hospitalets cellelaboratorium, hvilket sker jævnligt. For den seneste danske ALL patient, som blev behandlet på Rigshospitalet i februar 2024, gik der 23 dage fra afhentning af leukaferese-produktet til levering af det endelige produkt.

Patienttal og bridging terapi

Novartis har i ansøgningen taget udgangspunkt i, at 3 patienter årligt vil blive behandlet med tisagenlecleucel, såfremt tisagenlecleucel anbefales som standardbehandling til DLBCL. Medicinrådets estimat er 7 patienter årligt, evt. fordelt på to CAR-T behandlinger.

Novartis er opmærksom på, at der også pågår en vurdering af axicabtagene ciloleucel til DLBCL i 3. linje, og vil i den forbindelse gøre opmærksom på, at tisagenlecleucel er eneste CAR-T, som er godkendt baseret på studier, hvor bridging terapi var tilladt. 92% af patienterne i JULIET studiet fik bridging terapi [2], hvilket også reflekteres i Novartis´ sundhedsøkonomiske model.

Vi ser frem til Medicinrådets endelige beslutning om ibrugtagning af tisagenlecleucel til behandling af diffust storcellet B-cellelymfom d. 25. september 2024.

Med venlig hilsen,
Novartis Healthcare A/S

Alice Brinch Mørch
Value & Access Manager

Asbjørn Toft Hornemann
Nordic HEOR Manager

Referencer

1. AL-Mashhadi AL, Jakobsen LH, Brown P, et al (2024) Real-world outcomes following third or subsequent lines of therapy: A Danish population-based study on 189 patients with relapsed/refractory large B-cell lymphomas. Br J Haematol 204:839–848. https://doi.org/10.1111/bjh.19201

2. Schuster SJ, Bishop MR, Tam CS, et al (2019) Tisagenlecleucel in Adult Relapsed or Refractory Diffuse Large B-Cell Lymphoma. N Engl J Med 380:45–56. https://doi.org/10.1056/NEJMoa1804980

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20.08.2024

MGK/DBS

Forhandlingsnotat

Dato for behandling i Medicinrådet	25.09.2024
Leverandør	Novartis
Lægemiddel	Kymriah (tisagenlecleucel)
Ansøgt indikation	Behandling af voksne patienter med recidiverende eller refraktært diffust storcellet B-celle lymfom (DLBCL) efter to eller flere linjer af systemisk behandling.
Nyt lægemiddel / indikationsudvidelse	Indikationsudvidelse (Advanced Therapy Medicinal Product (ATMP)) (CAR-T behandling) – engangsbehandling

Prisinformation

Amgros har forhandlet følgende pris på Kymriah (tisagenlecleucel):

Tabel 1: Prisinformation

Lægemiddel	Styrke	AIP (DKK)	Nuværende SAIP (DKK)	Forhandlet SAIP*	Rabatprocent ift. AIP
Kymriah	1 behandling CAR-T (genmodificerede hvide blodlegemer)	1.983.462,77	[redacted]	[redacted]	[redacted]
[redacted]					

[redacted]

Prisen er betinget af Medicinrådets anbefaling. Det betyder, at hvis Medicinrådet ikke anbefaler Kymriah, indkøbes lægemidlet til nuværende SAIP.

Tabel 2: Forhandlingsresultat - [redacted]

[redacted]	[redacted]	[redacted]	Lægemiddel	AIP (DKK)	Forhandlet SAIP Pris per patient	Rabatprocent ift. AIP
[redacted]	[redacted]	[redacted]	Kymriah	1.983.462,77	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	Kymriah	1.983.462,77	[redacted]	[redacted]

[redacted]

Tabel 3: Forhandlingsresultat - [redacted]

[redacted]	[redacted]	[redacted]	Lægemiddel	AIP (DKK)	Forhandlet SAIP* Pris per patient	Rabatprocent ift. AIP
[redacted]	[redacted]	[redacted]	Kymriah	1.983.462,77	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	Kymriah	1.983.462,77	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	Kymriah	1.983.462,77	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	Kymriah	1.983.462,77	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	Kymriah	1.983.462,77	[redacted]	[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Aftaleforhold

Amgros har en eksisterende aftale med leverandøren siden 2019, hvor Region Hovedstaden har været eneste behandlingssted (ALL). Hvis Medicinrådet anbefaler Kymriah til DLBCL 3.linje kan flere behandlingssteder tilføjes den eksisterende aftale. Amgros vurderer, at det vil tage cirka tre måneder før nye behandlingssteder er klar til at behandle med Kymriah, da aftalen skal opdateres og certificering af aferese (cellehøst) og træning i relevante procedurer skal være færdiggjort.

[redacted]

Informationer fra forhandlingen

[redacted]

[redacted]

Konkurrencesituationen

Kymriah er indiceret til behandling af pædiatriske og unge voksne patienter op til og med 25 år med B-celle akut lymfoblastær leukæmi (ALL), der er refraktær, i post-transplantations relaps eller i andet eller senere relaps.
Kymriah er indiceret til behandling af voksne patienter med recidiverende eller refraktært diffust storcellet B-celle lymfom (DLBCL) efter to eller flere linjer af systemisk behandling (3. linje).
Kymriah er indiceret til behandling af voksne patienter med recidiverende eller refraktært follikulært lymfom (FL) efter to eller flere linjer af systemisk behandling.

Der er i dag ingen behandlingsvejledning indenfor DLBCL. I september 2023 blev Yescarta anbefalet til DLBCL 2. linje behandling. Der er flere lægemidler på vej igennem EMA og Medicinrådet. I de kommende måneder vurderes fire lægemidler i Medicinrådet, som kan påvirke konkurrencesituationen på området:

- Glofitamab (Columvi) (bispecifikt antistof) er netop blevet vurderet i Medicinrådet til 3. linje behandling af DLBCL. Medicinrådet anbefalede ikke Glofitamab på Rådsmødet den 28.08.2024. [redacted]
- Epcoritamab (Tepkinly) (bispecifikt antistof) vurderes på nuværende tidspunkt i Medicinrådet til 3. linje behandling af DLBCL. Der forventes beslutning om anbefaling 27.11.2024.
- Lisocabtagene maraleucel (Breyanzi) (CAR-T) vurderes på nuværende tidspunkt i Medicinrådet både til DLBCL 2. linje og 3. linje. Der forventes beslutning om anbefaling 29.01.2025.
- Loncastuximab tesirine (Zynlonta) (monoklonalt antistof komb. med et antitoksin) er under vurdering i Medicinrådet til 3. linje behandling af DLBCL. En forventet dato for Medicinrådets anbefaling er endnu ikke fastlagt.

[redacted]
Minjuvi blev i september 2022 vurderet af Medicinrådet i kombination med lenalidomid til behandling af voksne patienter med kræfttypen recidiverende eller refraktær DLBCL, som ikke kan tåle autolog stamcelletransplantation. Minjuvi er ikke anbefalet af Medicinrådet.
Polivy blev i februar 2021 vurderet af Medicinrådet i kombination med bendamustin og rituximab til behandling af voksne patienter med recidiverende/refraktært DLBCL, der ikke er kandidater til hæmatopoietisk stamcelletransplantation. Polivy blev ikke anbefalet af Medicinrådet.

[redacted]

Tabel 3 viser lægemiddeludgifter i relation til andre lægemidler.

Tabel 4: Sammenligning af lægemiddeludgifter pr. patient

Lægemiddel	Styrke	Lægemiddeludgift pr. behandling (SAIP, DKK)
Kymriah	1 behandling	[redacted]

	CAR-T (genmodificerede hvide blodlegemer)	
Yescarta	1 behandling CAR-T (genmodificerede hvide blodlegemer)	[redacted]
[redacted]		

Status fra andre lande

Tabel 5: Status fra andre lande

Land	Status	Link
Norge	Ikke anbefalet	Link til anbefaling
Sverige	Ikke anbefalet	Link til anbefaling
England	Ingen beslutning	Link til information

Konklusion

[redacted]

Application for the reassessment of Kymriah® (tisagenlecleucel) for diffuse large B cell lymphoma (DLBCL) after two or more lines of systemic therapy

Submitted on August 31, 2023. Resubmitted on January 05, 2024

The initial application was assessed in 2019.

This resubmission is based on the final 5-year data from the JULIET study, individual patient data from the CORAL study follow-up and a new price proposal.

Version 1.3

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Color scheme for text highlighting	
Colour of highlighted text	**Definition of highlighted text**
	Confidential information

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1. Basic information

Contact information	
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Overview of the pharmaceutical	
Proprietary name	Kymriah®
Generic name	Tisagenlecleucel
Marketing authorization holder in Denmark	Novartis Healthcare A/S Edvard Thomsens vej 14, 3rd floor DK-2300 Copenhagen S Denmark Company registration number (CVR) 20575786
ATC code	L01XL04
Pharmacotherapeutic group	Other antineoplastic agents.
Active substance(s)	Each ethylene vinyl acetate infusion bag of Kymriah contains tisagenlecleucel cell dispersion at a batch dependent concentration of autologous T cells genetically modified to express an anti CD19 chimeric antigen receptor (CAR positive viable T cells).
Pharmaceutical form(s)	Dispersion for infusion.
Mechanism of action	Tisagenlecleucel is an autologous, immunocellular cancer therapy, which involves reprogramming a patient's own T cells with a transgene encoding a chimeric antigen receptor (CAR) to identify and eliminate CD19 expressing cells. 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 antitumor 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.
Dosage regimen	0.6 to 6 x 10^8 CAR positive viable T cells as a single infusion.
Therapeutic indication relevant for assessment (as defined by the European Medicines Agency, EMA)	Adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) after two or more lines of systemic therapy.

Overview of the pharmaceutical	
Other approved therapeutic indications	Paediatric and young adult patients up to and including 25 years of age with B-cell acute lymphoblastic leukaemia (ALL) that is refractory, in relapse post-transplant or in second or later relapse. *Recommended by the Medicines Council.* Adult patients with relapsed or refractory follicular lymphoma (FL) after two or more lines of systemic therapy.
Will dispensing be restricted to hospitals?	Yes, and also restricted to certified treatment centres.
Combination therapy and/or co-medication	Lymphodepleting chemotherapy is recommended to be administered before Kymriah infusion unless the white blood cell (WBC) count within one week prior to infusion is ≤1,000 cells/µL. Kymriah is recommended to be infused 2 to 14 days after completion of the lymphodepleting chemotherapy. The availability of Kymriah must be confirmed prior to starting the lymphodepleting regimen. If there is a delay of more than 4 weeks between completing lymphodepleting chemotherapy and the infusion and the WBC count is >1,000 cells/µL, then the patient should be re treated with lymphodepleting chemotherapy prior to receiving Kymriah. The recommended lymphodepleting chemotherapy regimen in this indication is: - Fludarabine (25 mg/m^2 intravenous daily for 3 days) and cyclophosphamide (250 mg/m^2 intravenous daily for 3 days starting with the first dose of fludarabine). If the patient experienced a previous Grade 4 haemorrhagic cystitis with cyclophosphamide, or demonstrated a chemo refractory state to a cyclophosphamide containing regimen administered shortly before lymphodepleting chemotherapy, then the following should be used: - Bendamustine (90 mg/m^2 intravenous daily for 2 days). Lymphodepleting chemotherapy may be omitted if a patient's white blood cell (WBC) count is ≤1,000 cells/µL within 1 week prior to Kymriah infusion.
Packaging – types, sizes/number of units, and concentrations	Kymriah 1.2 x 10^6 – 6 x 10^8 cells dispersion for infusion. Each ethylene vinyl acetate (EVA) infusion bag of Kymriah contains tisagenlecleucel cell dispersion at a batch dependent concentration of autologous T cells genetically modified to express an anti CD19 chimeric antigen receptor (CAR positive viable T cells). 10 mL – 50 mL per bag.
Orphan drug designation	Yes.

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2. Abbreviations

AE	Adverse event
AIC	Aikaike information criterion
Allo-SCT	Allogeneic stem cell transplantation
ASCT	Autologous stem cell transplantation
ASH	American Society of Haematology
ATT	Average treatment effect for the primary outcome among treated
BIC	Bayesian information criterion
CAR	Chimeric antigen receptor
CAR-T	Chimeric antigen receptor T-cell
CHMP	Committee for medicinal products for human use
CHOP	Cyclophosphamide, doxorubicin, vincristine, prednisone
CI	Confidence interval
CIBMTR	Center for international blood and marrow transplant research
CNS	Central nervous system
CORAL	Collaborative Trial in Relapsed Aggressive Lymphoma
CPI	Consumer price index
CR	Complete response
CRS	Cytokine release syndrome
CTCAE	Common terminology criteria for adverse events
CVP	Cyclophosphamide, vincristine, prednisone
DHAP	Cisplatin, cytarabine, dexamethasone
DLBCL	Diffuse large B-cell lymphoma
DRG	Diagnose Relaterede Grupper
ECOG	European Cancer Oncology Group
EQ-5D	European quality of life five dimension
FAS	Full analysis set
FPFV	First patient first visit
GDP	Gemcitabine, dexamethasone, cisplatin
GemOx	Gemcitabine, oxaliplatin
HERC	Health Economics Research Centre
HODaR	Health Outcomes Data Repository
HR	Hazard ratio
HRQoL	Health-related quality of Life
HTA	Health technology assessment
ICE	Ifosfamide, carboplatin, etoposide
ICER	Incremental cost effectiveness ratio
ICU	Intensive care unit

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IPI	International prognostic index
ITC	Indirect treatment comparison
ITT	Intention to treat
IVIG	Intravenous immunoglobulin
IWG	International Working Group
KM	Kaplan-Meier curve
LDH	Lactate dehydrogenase
LPFV	Last patient first visit
LYSARC	The lymphoma academic research organisation
MCID	Minimal important difference
NA	Not applicable / Not available
NHL	Non-Hodgkin Lymphoma
OS	Overall survival
PFS	Progression-free survival
PR	Partial response
PS	Propensity score
QoL	Quality of life
QALY	Quality-adjusted life year
R-DHAP	Rituximab, dexamethasone, cytarabine, cyclophosphamide, etoposide
R-EPOCH	Rituximab, doxorubicin, vincristine, etoposide, cyclophosphamide, prednisolone
R-ESHAP	Rituximab, etoposide, methylprednisolone acetate, cytarabine, cisplatin
R-GDP	Rituximab, gemcitabine, dexamethasone, cisplatin
R-ICE	Rituximab, ifosfamide, carboplatin, etoposide
SAE	Serious adverse event
SCT	Stem cell transplantation
SF-36	The 36-item short form survey
SmPC	Summary of Product Characteristics
SMRW	Standardized mortality ratio weight
SoC	Standard of care
UPenn	University of Pennsylvania

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3. Tables and Figures

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4. Summary

4.1 Resumé på dansk

Dette er en genansøgning for vurdering af Kymriah® (tisagenlecleucel) til behandling af diffust storcellet B-celle lymfom (DLBCL) efter to eller flere linjer med systemisk terapi. Medicinrådet valgte i 2019 ikke at anbefale tisagenlecleucel til DLBCL, primært fordi man på det tidspunkt fandt, at der ikke var et rimeligt forhold mellem lægemidlets kliniske merværdi og omkostningerne ved behandling sammenlignet med bedste tilgængelige behandling.

Denne genansøgning er baseret på nye langtidsdata (finale 5-års data), indirekte sammenligninger baseret på individuelle patientdata (CORAL-opfølgningsdata), mere restriktive udvælgelseskriterier for patienter til CAR-T behandling baseret på mere erfaring med tisagenlecleucel fra klinikken, hvilket medfører at færre patienter skal behandles i forhold til ved den tidligere ansøgning samt en ny pris.

Der er ingen etableret standardbehandling for patienter med DLCBL, som er refraktære over for kemoterapi eller som har recidiv efter autolog stamcelletransplantation, og de har generelt en dårlig prognose [1]. Tisagenlecleucel er en autolog, immuncellulær cancerterapi, som involverer om-programmering af en patients egne T-celler med et transgen, der koder for en kimærisk antigenreceptor (CAR) som kan identificere og eliminere CD19-udtrykkende celler, med andre ord en CAR-T-behandling [2]. Den Danske Lymfomgruppe har for nylig defineret udvælgelseskriterier for CAR-T-behandling, og på baggrund heraf vurderes det, at omkring 15 patienter pr. år (2019), med en lille årlig stigning, vil være berettiget til CAR-T-behandling [1]

I 2022 publicerede Maziarz en indirekte sammenligning af tisagenlecleucel og historiske behandlinger for recidiverende/refraktær DLBCL. Sammenligningen var baseret på individuelle patientdata fra det pivotale JULIET-studie (data-cut 20. februar 2020) og opfølgningsdata fra CORAL-studiet [4], hvilket muliggjorde sammenligning mellem balancerede patientgrupper. Hazard ratio (HR) for samlet overlevelse (OS) for tisagenlecleucel vs. standardbehandling var [redacted] i den ujusterede analyse og [redacted] i de justerede analyser.
JULIET-studiet er nu afsluttet med 5-års opfølgning (data-cut december 2022), og Novartis har fået adgang til opfølgningsdata fra CORAL-studiet på patientniveau af Lymphoma Academic Research Organisation (LYSARC) [5]. Denne ansøgning er således baseret på indirekte sammenligninger af data på patientniveau fra JULIET-studiet og opfølgningsdata fra CORAL-studiet, som har givet mulighed for en sammenligning mellem matchede populationer (upublicerede data).

Den sammenlignende analyse viste lignende resultater som allerede offentliggjort af Maziarz. Efter 60 måneder var OS HR for tisagenlecleucel vs. standardbehandling [redacted] i den ujusterede analyse og [redacted] i den justerede analyse.
De resultater viser således, at tisagenlecleucel er forbundet med en signifikant ekstra klinisk fordel, når man sammenligner med historisk kontrol for 3. linje behandling (eller derover) af recidiverende eller refraktær DLBCL, både med og uden justering for forskelle i confoundere.

Der blev ikke påvist nye eller uventede sikkerhedssignaler ved 5-års opfølgningen sammenlignet med, hvad der tidligere er rapporteret.

Resultaterne af den sundhedsøkonomiske model baserer sig, så vidt vi ved, på den bedste tilgængelige sammenligning, eftersom patientniveaudata blev inkluderet fra CORAL-armen, hvilket muliggjorde matchning af hver patient fra sammenligningsarmen. De overordnede resultater viser, at Kymriah® er en omkostningseffektiv behandlingsmulighed for patienter i 3. linje (og derover) i Danmark med en basisomkostning på [redacted] kr. pr QALY.

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4.2 Summary

This is a resubmission for Kymriah® (tisagenlecleucel) for the treatment of diffuse large B cell lymphoma (DLBCL) after two or more lines of systemic therapy. In 2019, the Medicines Council did not recommend tisagenlecleucel for DLBCL, mainly because it was found that the relationship at that time between the medicinal product's clinical added value and the cost of treatment compared to the best available treatment was not reasonable.

This resubmission is based on new long-term data (final 5-year data-cut), indirect comparisons based on individual patient data (CORAL follow-up), more restrictive selection criteria for CAR-T based on more knowledge from real world data (resulting in fewer eligible patients for CAR-T), and a new price.

There is no established standard of care (SoC) for patients who are refractory to chemotherapy or who have recurrence after autologous stem cell transplant, and they generally have a poor prognosis [1]Tisagenlecleucel is an autologous, immunocellular cancer therapy, which involves reprogramming a patient's own T cells with a transgene encoding a chimeric antigen receptor (CAR) to identify and eliminate CD19 expressing cells, in other words a CAR-T treatment [2].The Danish Lymphoma Group have recently defined selection criteria for CAR-T treatment, and based on this it is estimated that about 15 patients per year (2019), with a small yearly increase, will be eligible for CAR-T treatment in general [1]

In 2022, Maziarz published an indirect comparison of tisagenlecleucel and historical treatments for relapsed of refractory (r/r) DLBCL. The comparison was based on individual patient data from the pivotal JULIET study (data-cut February 20, 2020) and CORAL follow-up data [3], allowing comparison between balanced patients groups. The hazard ratio (HR) for overall survival (OS) for tisagenlecleucel vs. standard of care was [redacted] in the unadjusted analysis, and [redacted] in the adjusted analyses.

The JULIET study has now been completed with 5-year follow-up (data-cut December 2022), and Novartis has obtained access to patient-level data from the CORAL extension studies from the Lymphoma Academic Research Organisation (LYSARC) [4]. Thus, this application is based on indirect comparisons of patient level data from the JULIET study (data on file) and the CORAL follow-up data, which allows a comparison between matched populations (data on file).

The comparative analysis showed similar results as already published by Maziarz. At 60 months, the OS HR for tisagenlecleucel vs. SoC was [redacted] in the unadjusted analysis and [redacted] in the adjusted analysis.

Thus, the presented results of the indirect treatment comparison have shown that tisagenlecleucel is associated with a significant added clinical benefit, when comparing to historical control for 3rd line or above treatment of r/r DLBCL, both with and without adjustment for differences in confounders.

No new or unexpected safety signals were detected at the 5-year follow-up, compared with what has previously been reported.

The presented health economic model and the results hereof present, to our knowledge, the best available comparison, since patient level data was included from the CORAL arm enabling matching of each patient from the comparator arm. The overall results show Kymriah® is a cost-effective treatment option for patients in the 3rd line and beyond treatment setting in Denmark with a base case cost of [redacted]

5. The patient population, the intervention and choice of comparator(s)

5.1 The medical condition and patient population

DLBCL is an aggressive subtype of Non-Hodgkin Lymphoma (NHL).

DLBCL accounts for about 35% of NHL. In Denmark, approximately 500 patients are diagnosed with DLBCL annually, and the incidence is increasing by approximately 2% per year [5]. The risk of developing DLBCL increases with age, and the median age in Denmark at diagnosis is 69 years [1]

The prognosis is relatively good with a 5-year survival of 65-90% depending on the risk profile (IPI). Patients with DLBCL typically have one or more rapidly growing lymph nodes, often located on the neck, in the mediastinum, and/or in the abdomen. In 40% of patients, however, the disease presents itself with extranodal involvement of for example, the gastrointestinal tract and the central nervous system (CNS) [5]. Multiple extranodal manifestations are associated with a poor prognosis, and certain locations are associated with an increased risk of CNS recurrence.

It is estimated that around 100 patients with DLBCL annually are refractory or experience relapse after two or multiple lines of systemic treatment. In the original assessment of tisagenlecleucel by the Medicines Council it was estimated that approximately 25-50 patients annually would be candidates for treatment with tisagenlecleucel [6]. However, the Danish Lymphoma Group recently defined new, more restrictive, eligibility criteria for use of CAR-T cell therapy [7], which has reduced the number of patients eligible for CAR-T cell therapy (including tisagenlecleucel) to approximately 15 patients per year in total (2019) with a small yearly increase, according to Danish clinical experts.

Table 1 Incidence of DLBCL in the past 5 years

Year	2018	2019	2020	2021	2022
Incidence in Denmark	450	459	468	478	487
Incidence of patients who are refractory or experience relapse after two or multiple lines of systemic treatment	100	102	104	106	108
Global prevalence *	Not applicable				

* For small patient groups, also describe the worldwide prevalence

Source: Reference [5, 6]

Table 2 Estimated number of patients eligible for treatment.

Year	2024	2025	2026	2027	2028
Number of patients in Denmark who are expected to use the pharmaceutical in the coming years	17	17	18	18	18

Based on expert statement following the implementation of the eligibility criteria from the Danish Lymphoma Group [7]

5.1.1 Patient populations relevant for this application

Tisagenlecleucel is indicated for adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) after two or more lines of systemic therapy.

The Danish Lymphoma Group have defined eligibility criteria for CAR-T cell therapy in patients with DLBCL, where they state that CAR-T cell therapy mainly should be considered for patients who, based on comorbidity, performance score and age, would be suitable for high dose chemotherapy with autologous or allogeneic stem cell transplantation (ASCT or allo-SCT). For detailed description of eligibility criteria, please refer to reference [7].

5.1.2 Current treatment options

According to current guidelines, there is no evidence to recommend a specific regimen for 3rd line treatment of patients with r/r DLBCL [1, 8]. This patient group is offered the best available treatment.

If the disease is chemo sensitive, allogeneic bone marrow transplantation is a possibility. The aim it to consolidate treatment and it is potentially curative.

If allogeneic bone marrow transplantation is not a possibility, then it cannot be expected that 3rd line treatment will be curative. It is recommended to consider CAR-T cell therapy (currently not recommended by the Medicines Council, i.e., this requires an evaluation by the national CAR-T committee and permission from the Regional Medicines Committee) or experimental treatment when available [1].

The treatment regimens used after 2nd line have different intensity and side effect profiles. The choice of treatment is assessed for the individual patient and depends, among other things, on the possibility of allo-SCT, performance status, comorbidity, previous treatments, and age.

The following regimens can be considered with the possible addition of CD20 antibody (rituximab), if it is assessed that the patient can tolerate the treatment:

- GDP (gemcitabine, dexamethasone, and cisplatin)
- CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone)
- CVP (cyclophosphamide, vincristine, and prednisone)
- GemOx (gemcitabine and oxaliplatin)
- DHAP (cisplatin, cytarabine, dexamethasone)
- ICE (ifosfamide, carboplatin, etoposide)

Alternatively, the following single-agent treatments can be considered:

- Gemcitabine
- Pixantrone
- Bendamustine

5.1.3 Description of the comparator(s)

The pivotal JULIET study with tisagenlecleucel is a single arm study, and no head-to-head trials have compared the efficacy of tisagenlecleucel vs. standard treatments for adults with r/r DLBCL. For this reason, a comparator was sought in the literature, and the CORAL (Collaborative Trial in Relapsed Aggressive Lymphoma) study was identified [9, 10].

CORAL was a phase 3 clinical study of 2nd therapy that randomly assigned adults with relapsed DLBCL to one of two chemotherapy regimens followed by ASCT when feasible (NCT00137995) [11]. The CORAL investigators collected extensive follow-up data regarding patients' subsequent treatments, i.e., 3rd line and above and long-term survival status, which represent the efficacy of conventional 3rd line treatments (i.e., historical control treatments).

For this analysis, appropriate comparative therapies to tisagenlecleucel were considered as potential index treatments in the CORAL follow-up full analysis set (FAS) population for the comparison with tisagenlecleucel. The treatments were selected based on input from the German health technology assessment (HTA) agency, Gemeinsamer Bundesausschuss and clinical experts:

- Any chemotherapy as mono- or combination therapy
- Rituximab with or without combination treatment
- Lenalidomide with or without combination treatment
- Brentuximab vedotin
- Ibrutinib

- Axicabtagene ciloleucel
- Polatuzumab vedotin with or without bendamustine and rituximab
- Allo-SCT
- Best supportive care

Unknown treatment and ASCT were not considered as appropriate comparators.

Table 3 Description of comparators

Common salvage chemotherapy regimens for R/R DLBCL (Limited to the most commonly used ones)	Dosing schedule	Number of infusions per cycle	Route of administration	Duration of administration (days or hours)	Source for dosing schedule
Regimen: R-ICE					
Etoposide	100 mg/m² on days 3-5	3	IV push		Kewalramani 2004 [12]
Ifosfamide	5000 mg/m² on day 4	1	Continuous 24 hr IV		
Carboplatin	800 mg on day 4	1	IV push		
Rituximab	375 mg/m² on day 1	1	IV	3,75 hour(s)	
Regimen: R-GDP					
Gemcitabine	1000 mg/m² on days 1 and 8	2	IV		Crump 2004 [13]
Dexamethasone	40 mg (oral) daily on days 1-4	4	PO		
Cisplatin	75 mg/m² on day 1	1	IV		
Rituximab	375 mg/m² on day 1	1	IV	3,75 hour(s)	
Regimen: R-ESHAP					
Etoposide	40 mg/m² on days 1-4	4	IV	1,00 hour(s)	Martin 2008 [14]
Methylprednisolone acetate	500 mg on days 1-5	5	IV push	-	
Cytarabine	2000 mg/m² on day 5	1	IV	2,00 hour(s)	
Cisplatin	25 mg/m² on days 1-4	4	Continuous 24 hr IV	4 day(s)	
Rituximab	375 mg/m² on day 1	1	IV	3,75 hour(s)	
Regimen: R-DHAP					
Dexamethasone	40 mg daily on days 3-5	3	IV	-	Oki 2008 [15]
Cytarabine	2000 mg/m² on days 4 and 5	2	IV	2,00 hour(s)	
Cyclophosphamide	1200 mg/m² on day 3	1	IV		
Etoposide	100 mg/m² on days 3-5	3	IV	1,00 hour(s)	
Rituximab	375 mg/m² on day 1	1	IV	3,75 hour(s)	
Regimen: R-EPOCH					

Common salvage chemotherapy regimens for R/R DLBCL (Limited to the most commonly used ones)	Dosing schedule	Number of infusions per cycle	Route of administration	Duration of administration (days or hours)	Source for dosing schedule
Doxorubicin	15 mg/m² on days 2-4	3	Continuous 24 hr IV	-	Jermann 2004 [16]
Vincristine	0.5 mg on days 2-4	3	Continuous 24 hr IV	1,00 hour(s)	
Etoposide	65 mg/m² on days 2-4	3	Continuous 24 hr IV	1,00 hour(s)	
Cyclophosphamide	750 mg/m² on day 5	1	IV		
Prednisolone	60 mg/m² (oral) on days 1-14	14	PO	1 day(s)	
Rituximab	375 mg/m² on day 1	1	IV	3,75 hour(s)	

5.2 The intervention

The following information is derived from the Summary of Product Characteristics for Kymriah [2] and applies to the treatment of DLBCL.

Table 4 Overview of tisagenlecleucel

Dosing	Tisagenlecleucel is intended for autologous use only. Treatment consists of a single dose for infusion containing a dispersion for infusion of CAR-positive viable T cells in one or more infusion bags. The dose is within a range of 0.6 to 6×10^8 CAR-positive viable T cells (non-weight based).
Method of administration	Tisagenlecleucel must be administered in a qualified treatment centre. Therapy should be initiated under the direction of and supervised by a healthcare professional experienced in the treatment of haematological malignancies and trained for administration and management of patients treated with the medicinal product. <u>Preparation for infusion</u> Kymriah is intended for autologous use only. Before administration, it must be confirmed that the patient's identity matches the unique patient information on the Kymriah infusion bags and accompanying documentation. The total number of infusion bags to be administered should also be confirmed with the patient specific information on the batch specific documentation. The timing of thaw of Kymriah and infusion be coordinated. <u>Administration</u> Kymriah should be administered as an intravenous infusion through latex-free intravenous tubing without a leukocyte depleting filter, at approximately 10 to 20mL per minute by gravity flow. If the volume of Kymriah to be administered is ≤20mL, intravenous push may be used as an alternative method of administration.
Treatment duration/criteria for treatment discontinuation	The treatment is given only once.

Should the pharmaceutical be administered with other medicines?	<u>Pre-treatment conditioning (lymphodepleting chemotherapy)</u> The availability of tisagenlecleucel must be confirmed prior to starting the lymphodepleting regimen. Tisagenlecleucel is recommended to be infused 2 to 14 days after completion of the lymphodepleting chemotherapy. Lymphodepleting chemotherapy may be omitted if a patient is experiencing significant cytopenia, e.g., white blood cell (WBC) count ≤1000cells/ill within one week prior to infusion. If there is a delay of more than 4 weeks between completing lymphodepleting chemotherapy and the infusion and the WBC count is >1000cells/µL, then the patient should be re-treated with lymphodepleting chemotherapy prior to receiving tisagenlecleucel. The recommended lymphodepleting chemotherapy regimen is: • Fludarabine (25mg/m2 intravenous daily for 3days) and cyclophosphamide (250mg/m2intravenousdaily for 3days starting with the first dose of fludarabine). If the patient experienced a previous Grade 4 haemorrhagic cystitis with cyclophosphamide, or demonstrated a chemo refractory state to a cyclophosphamide-containing regimen administered shortly before lymphodepleting chemotherapy, then the following should be used: • Bendamustine (90mg/m2intravenousdaily for 2days). <u>Pre-medication</u> To minimise potential acute infusion reactions, it is recommended that patients be pre-medicated with paracetamol and diphenhydramine or another H1 antihistamine within approximately 30 to 60 minutes prior to tisagenlecleucel infusion. Corticosteroids should not be used at any time except in the case of a life-threatening emergency. In the event of cytokine release syndrome (CRS), at least one dose of tocilizumab and emergency equipment must be available per patient prior to infusion. The treatment centre must have access to additional doses of tocilizumab within 8 hours.
Necessary monitoring, during administration, during the treatment period, and after the end of treatment	<u>Clinical assessment prior to infusion</u> Tisagenlecleucel treatment should be delayed in some patient groups at risk (for further details see Section 4.4 in the Summary of Product Characteristics). <u>Monitoring after infusion</u> • Patients should be monitored daily for the first 10 days following infusion for signs and symptoms of potential cytokine release syndrome, neurological events, and other toxicities. Physicians should consider hospitalisation for the first 10 days post infusion or at the first signs/symptoms of cytokine release syndrome and/or neurological events. • After the first 10 days following the infusion, the patient should be monitored at the physician's discretion.

	• Patients should be instructed to remain within proximity (within 2 hours of travel) of a qualified clinical facility for at least 4 weeks following infusion.
Need for diagnostics or other tests (i.e., companion diagnostics)	NA

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6. Literature search and identification of efficacy and safety studies

6.1 Identification and selection of relevant studies

A systematic literature review was conducted to identify relevant publications to assess the efficacy and safety of tisagenlecleucel in DLCBL in connection with the initial application in 2018. This search was conducted on 31st October 2018. In addition, search for publications with tisagenlecleucel clinical trial data from 31st October 2018 to 31st October 2023. The search strategies are provided in Appendix A, and the eligibility criteria used for the systematic literature review are defined in terms of the population, interventions, comparisons, outcomes (PICOs) and study design framework as well as language and time frame (see Table 45 in Appendix A).

The process of study identification and selection is summarised in Figure 12 and Figure 13 with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagrams.

In total, five records were identified in the initial search, and included in the original application. Two of these were excluded in the assessment by the Medicines Council, and one was the original publication of the JULIET study which was published after 31st October 2018, and therefore also appears in the updated search. Three records were identified in the updated search and included in this application.

The initial assessment by the Medicines Council was based on a naïve indirect comparison of tisagenlecleucel data from the JULIET study and the historical treatments from the CORAL extension studies. The data from the CORAL extension studies were derived from two published studies [17, 18] and while the data from the JULIET study were patient-level data, the data from the CORAL extension studies were aggregated patient data. The initial assessment by the Medicines Council was based on a naïve indirect comparison of tisagenlecleucel data from the JULIET study and the historical treatments from the CORAL extension studies. The data from the CORAL extension studies were derived from two published studies [17, 18] and while the data from the JULIET study were patient-level data, the data from the CORAL extension studies were aggregated patient data.

Since the initial application, results from indirect comparisons based on patient level data from both the JULIET (data-cut February 20, 2020) and the CORAL follow-up studies have been published [3]

The JULIET study has now been completed with 5-year follow-up (data-cut December 2022), and Novartis has obtained access to patient-level data from the CORAL extension studies from the Lymphoma Academic Research Organisation (LYSARC) [4]. Thus, this application is based on indirect comparisons of patient level data from the JULIET study (data on file) and the CORAL follow-up data which allows a comparison between matched populations.

Table 5 Relevant studies

Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)
Tisagenlecleucel in Adult Relapsed/Refractory Diffuse Large B-Cell Lymphoma, *Schuster, New England Journal of Medicine, 2018* [19] Long-term clinical outcomes of tisagenlecleucel in patients with relapsed or refractory aggressive B-cell lymphomas (JULIET): a multicentre, open-label, single-arm, phase 2 study *Schuster, Lancet Oncol, 2021* [20]	C2201 / JULIET	NCT02445248	*FPFV: 17 Aug 2015* *LPFV: 22 Dec 2022*

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Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)
Indirect comparison of tisagenlecleucel and historical treatments for relapsed/refractory diffuse large B-cell lymphoma. *Maziarz, Blood Advances, 2022* [3] CCTL019C2201 Final Clinical Study Report. December 2022. *Data on file* Indirect treatment comparison of JULIET vs. CORAL follow-up in relapsed or refractory diffuse large B-cell lymphoma using patient level data. 2023. *Data on file*			
*Salvage regimens with autologous transplantation for relapsed large B-cell lymphoma in the rituximab era. *Gisselbrecht, Journal of Clinical Oncology, 2010* [9] *Rituximab maintenance therapy after autologous stem-cell transplantation in patients with relapsed CD20+ diffuse large B-cell lymphoma: Final analysis of the collaborative trial in relapsed aggressive lymphoma. *Gisselbrecht, Journal of Clinical Oncology, 2012* [10] ***Subgroup follow-up, used in initial application:*** Outcome of patients with relapsed diffuse large B-cell lymphoma who fail second-line salvage regimens in the International CORAL study. (CORAL EXT-2) *Van Den Neste, Bone Marrow Transplantation, 2016* [17] Outcomes of diffuse large B-cell lymphoma patients relapsing after autologous stem cell transplantation: an analysis of patients included in the CORAL study. (CORAL EXT-1) *Van Den Neste, Bone Marrow Transplantation, 2017* [18] ***Indirect comparison of follow-up data (3+ line):*** Indirect comparison of tisagenlecleucel and historical treatments for relapsed/refractory diffuse large B-cell lymphoma. *Maziarz, Blood Advances,* 2022 [21] CORAL follow-up data from the Lymphoma Academic Research Organisation (LYSARC) [4] *Data on file* Indirect treatment comparison of JULIET vs. CORAL follow-up in relapsed or refractory diffuse large B-cell lymphoma using patient level data 2023 *Data on file.*	CORAL	NCT00137995	*The original CORAL study ran from July 2003 to June 2008.* CORAL was a phase 3 clinical study of 2nd line therapy. The CORAL investigators collected extensive follow-up data regarding patients' subsequent treatments (i.e., 3rd line and above). The follow-up time in the analysis for this application was 60 months.

*Publication not identified in the literature search, but included, as they describe the initial CORAL study and outcome

For detailed information about included studies, see Appendix B.

7. Efficacy and safety

7.1 Efficacy and safety of tisagenlecleucel compared to standard of care for adults with DLBCL after two or more lines of systemic therapies

7.1.1 Relevant studies

7.1.1.1 JULIET study

The pivotal JULIET study was an open-label, single arm, multicentre phase 2 study evaluating the efficacy and safety of tisagenlecleucel in adult patients with DLBCL who have r/r disease after ≥ 2 lines of chemotherapy (including rituximab and anthracycline), and who are ineligible for, have failed or are not consenting to ASCT (NCT 02445248) [19, 22].

The study consisted of the following sequential periods: screening including acceptance of leukapheresis product, pre-treatment with bridging- and lymphodepleting chemotherapy, one single dose of tisagenlecleucel infusion (dose range: 1.0-5.0x10^8) and primary follow-up, secondary follow-up, survival follow-up and long-term follow-up (consisting of semi-annual and annual evaluations for up to 15 years from the date of infusion on all patients under a separate long-term follow-up protocol). All patients were allowed to receive bridging therapies constituting standard 3rd line antineoplastic therapy based on the investigators' choice to stabilize the disease while waiting for tisagenlecleucel infusion.

This application is based on the final 5-year data from the JULIET study (data-cut: December 2022).

A total of 167 patients were enrolled (i.e., intention to treat (IIT) population); of these 115 were treated with tisagenlecleucel. One patient with neuroendocrine tumour was initially misdiagnosed and is excluded from the indirect treatment comparison vs. standard of care. The indirect comparison vs. standard of care is based on the full analysis set (FAS) for OS and the FAS main cohort (described below) for ORR. A detailed overview of the various populations included in this application is shown in Table 6 .

Table 6 Overview of populations in the Clinical Study Report (CSR) and the indirect treatment comparison (ITC)

Populations	n	Comments
Clinical study report (data on file) [23]		
IIT	167	All patients enrolled in the study. 52 patients did not receive tisagenlecleucel: Thirteen patients could not have CAR T-cells manufactured, 16 died before infusion, 16 had their treating physician decide against further participation, 4 had an adverse event, 2 decided against further participation, and 1 had a protocol deviation.
FAS	115	All patients who received infusion of tisagenlecleucel
FAS, Main cohort	99	Patients infused with tisagenlecleucel manufactured in the US facility (for primary endpoint)
FAS, Cohort A	16	Patients infused with tisagenlecleucel manufactured in the EU facility
Indirect treatment comparison (data on file) [24]		
FAS (for OS)	114	One patient with neuroendocrine tumour, who was initially misclassified as DLBCL, was excluded
FAS, adjusted analysis based on PS weighting	111	Three patients from JULIET FAS were excluded due to missingness in the selected confounders in the adjusted analysis

FAS, Main cohort (for ORR)	98	One patient with neuroendocrine tumour, who was initially misclassified as DLBCL, was excluded
FAS, adjusted analysis based on PS weighting	95	Three patients from JULIET FAS were excluded due to missingness in the selected confounders in the adjusted analysis
ORR: overall response rate, OS: overall survival, PS: propensity score		

The primary end point was the best overall response rate (ORR, i.e., the percentage of patients who had a complete or partial response), as judged by an independent review committee. Overall survival (OS) was a secondary end point and was defined as the time from the date of tisagenlecleucel infusion for the FAS population to the date of death due to any reason [20]. Other secondary end points were progression free survival (PFS) and the health-related quality of life (HrQoL) outcome SF-36.

Detailed study characteristics are listed in Appendix B. Baseline characteristics are shown in Appendix C. Further description of end points/outcomes can be found in Appendix D.

7.1.1.2 CORAL study

The CORAL study was a phase 3 clinical study of 2nd line therapy that randomly assigned adults with relapsed DLBCL to one of two chemotherapy regimens followed by ASCT when feasible (NCT00137995) [9, 10]. The CORAL investigators collected extensive follow-up data regarding patients' subsequent treatments (i.e., 3rd line and above) and long-term survival status, which represent the efficacy of conventional 3rd line treatments and above (i.e., historical control treatments).

The CORAL enrolled 477 patients with r/r DLBCL (July 2003-June 2008) who received 2nd line treatment [9, 10]. Among them, 297 relapsed or failed to respond to 2nd line treatment [3] and they constituted the basis for the CORAL follow-up population for indirect treatment comparison (ITC) of OS and ORR for this application.

For the current analysis, the CORAL follow-up FAS population (N = 170) included patients from the CORAL follow-up period selected per JULIET criteria. In addition, patients were required to have received one of the following therapies in 3rd line as an index treatment: any chemotherapy, immunotherapy (rituximab/lenalidomide/ofatumumab)-based treatment, brentuximab vedotin, ibrutinib, axicabtagene ciloleucel (axi-cel), polatuzumab vedotin, allo-SCT, or best supportive care. Unknown treatment and ASCT were not considered qualified index treatments as JULIET enrolled patients who had failed, were ineligible for, or did not consent to ASCT. See Table 53 for detailed eligibility criteria. The Expert Committee considered that the treatments used in the CORAL follow-up population corresponds to those used in Danish clinical practice [6].

The indirect comparison (JULIET vs. CORAL follow-up populations) has been done based on the FAS populations, but also on CORAL follow-up populations adjusted on propensity score (PS) weighting. A total of 145 patients were included in the adjusted analysis. Details regarding the PS weighting and analytical methods are described in Appendix F.

Like in the ITC by Maziarz [21], OS was defined as the time from the date of index treatment initiation to the date of death due to any reason.

Detailed study characteristics are listed in Appendix B. Detailed baseline characteristics are shown in Appendix C.

Relevant differences between studies

Baseline characteristics were to a large degree similar for the two studies, with a few exceptions. The proportion of patients with extranodal site involvement in ≥2 extranodal organs was respectively 43.9% and 23.4% in the JULIET and CORAL studies. However, imaging techniques have evolved between the conduct of the CORAL and JULIET studies, which could have an impact. Also, the mean and median number of prior lines of therapies differed significantly with means of 2.8 ± 1.0 vs 2.3 ± 0.7 and medians of 3.0 and 2.0 for the JULIET and CORAL studies, respectively. A higher number of prior lines may indicate a worse prognosis.

In the initial assessment by the Medicines Council, the Expert Committee found that the population in the JULIET study and the CORAL follow-up data was not directly comparable, but the best available data for a comparison. With access to patient level data from CORAL follow-up, it is possible to assign PS matching to each patient from CORAL, thus forming a much more robust comparison. There are a number of confounding differences between the two study populations, making the results of an unadjusted comparison highly uncertain. Therefore, Novartis acquired the patient level data from the CORAL follow-up-study enabling a much more robust comparison between the two patient populations. This analysis is briefly detailed in Section 7.1.3 and Appendix F, and the complete ITC study report is supplied as a confidential reference [24].

For the base case analysis, the standardized mortality ratio weight (SMRW) method has been used. The reasoning behind this is that fine stratification uses quintiles of PS and is useful to avoid large weights of extreme values, whereas SMRW uses propensity scores as continuous variables. In these datasets, there are no variables with extreme values and the precision and better matching obtained through SMRW is therefore favourable. However, the analysis leads to the same HR between CORAL follow-up and JULIET, indicating consistency in the comparison.

7.1.2 Efficacy and safety – results per study

For this application Overall Survival (OS) is the outcome in focus. Overall survival is the gold standard for demonstrating clinical efficacy in studies for cancer, including DBLCL.

In connection with the initial application, the Expert Committee considered it relevant to look at survival after two years. The rationale for this is based on the clinical rationale that after two years of follow-up it can be expected that recurrence would have appeared and that one has knowledge of whether a curative treatment has been successful. The Expert Committee estimated that with the current treatment option, the survival rate would be 20% at two years, and that a clinically relevant difference would be 10 percentage points [25].

For this application, the follow-up time is 5 years. For the JULIET study, OS was defined as the time from the date of tisagenlecleucel infusion to the date of death due to any reason. For the CORAL follow-up OS was defined from the date of index treatment initiation to the date of death due to any reason.

The indirect comparison was made on the full FAS populations, and on adjusted populations based on PS weighting. Results for OS survival for the populations included in the different indirect comparisons are presented below.

In addition to OS, overall response rate (ORR) was assessed for both the JULIET population and the CORAL follow-up population, and also assessed by ITC.

Progression-free survival and health-related quality of life assessed by the SF-36 questionnaire were assessed in the JULIET study, but no data are available for the CORAL follow-up population. The same is the case for detailed safety data.

The endpoints are described in detail in Appendix D.

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7.1.2.1 Results from the JULIET study

Overall survival

For patients treated with tisagenlecleucel, results for median OS and OS at 60 months for the full FAS and the population for the adjusted analyses are shown in Table 7.

Table 7 OS at 60 months. JULIET study

Outcome	N	Result (95% CI)
Median OS (months) Full FAS population	114	[redacted]
Median OS (months) Adjusted analysis	111*	[redacted]
OS at month 60 (%) Full FAS population	114	[redacted]
OS at month 60 (%) Adjusted analysis	111*	[redacted]

Abbreviations: OS: overall survival

* Three patients from JULIET FAS were excluded due to missingness in the selected confounders in the adjusted analysis

The Kaplan-Meier curve (KM) for OS for the adjusted population, including numbers at risk at various time points is shown Figure 1 in Section 7.1.3

The Expert Committee estimated that with the current treatment option, the survival rate would be 20% at 2 years, and that a clinically relevant difference would be 10 percentage points [25]. In the JULIET study, more than 30% of patients treated with tisagenlecleucel were still alive at 5-years follow-up.

Overall response rates (ORR)

ORR was assessed in the FAS, main population, (patients treated with tisagenlecleucel from the US manufacturing site), and the ORR at 60 months was [redacted] in the unadjusted population (excluding one patient with neuroendocrine tumour, who was initially misdiagnosed, n=98) and [redacted] in the adjusted population (n=95).

Progression-free survival (PFS)

PFS was assessed in the FAS, main population [redacted]. The median PFS was [redacted] months, and at 60 months [redacted] had achieved PFS.

SF-36

Health related quality of life was evaluated using SF-36, and results are presented in Table 8.

The number of patients is relatively small, and the mean change from baseline at 60 months met the clinically minimal important difference of 3 [26] for the physical health total score, but not for the mental health total score in the full FAS population. A similar observation was noted amongst responders.

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Table 8 SF-36: Change from baseline. JULIET study

	Full FAS population (N=115)			FAS population, responders (N=61)		
	Baseline (n=110	Month 60 (n=18)	Change from baseline (n=17)	Baseline (n=58)	Month 60 (n=18)	Change from baseline (n=17)
Physical health total score (SD)	[redacted]					
Mental health total score (SD)						

SF-36 = 36-Item Short Form Survey

- Baseline = The most current assessment on or prior to the date of CTL019 infusion.
- n for each time point is the number of patients with non-missing score at that time point.
- n for change from baseline is the number of patients with non-missing score both at baseline and at that post-baseline visit

For detailed efficacy results, please see Appendix D.

Safety

Adverse events

The JULIET study patients were assessed for AEs at each clinic visit: Daily to every third day until day 28, thereafter monthly first 6 months, thereafter every third month until 24 months, thereafter every sixth month until 60 months [22].

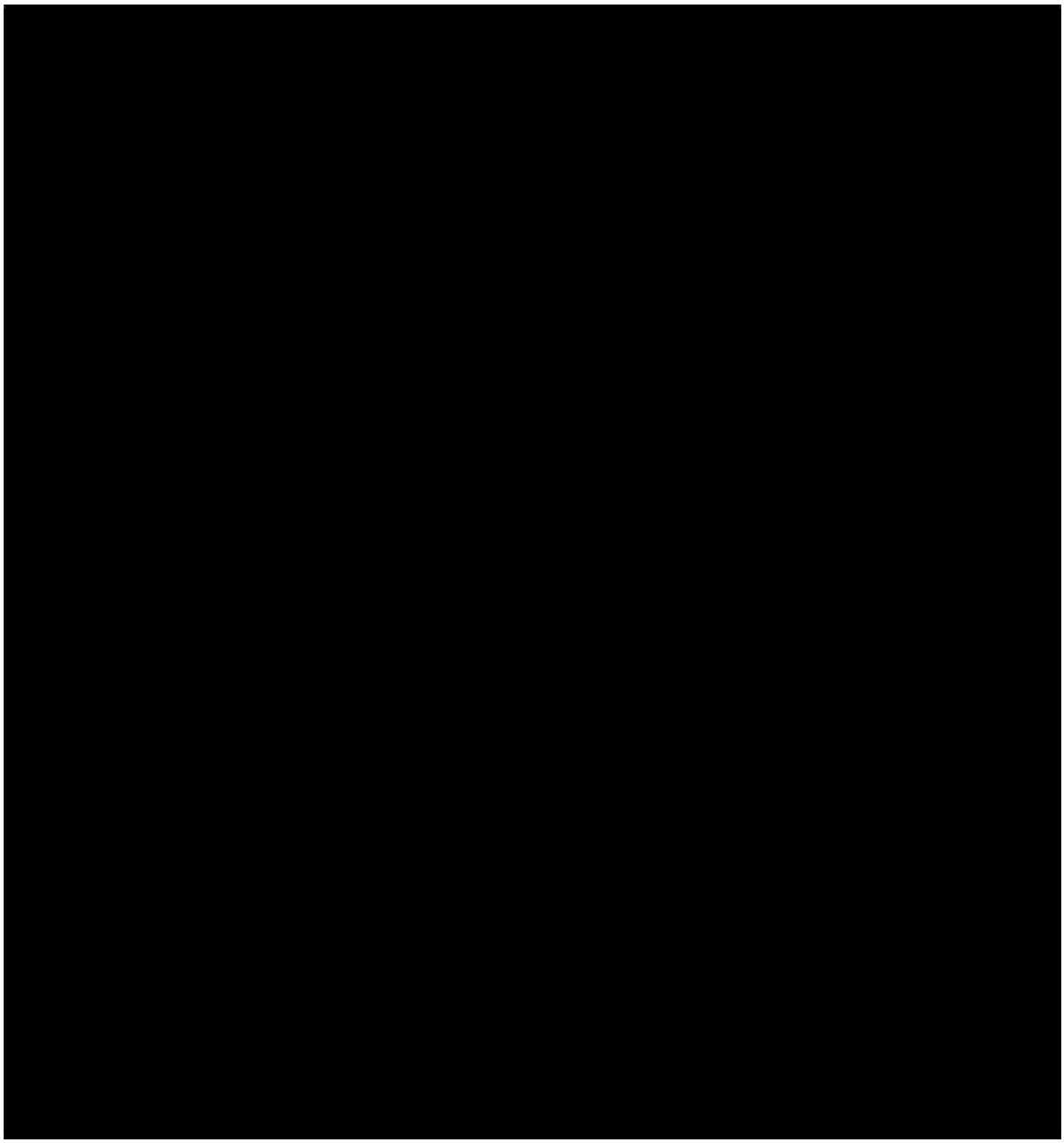
Regardless of study drug relationship, any time post-infusion, all patients experienced at least one AE.

[redacted]

AEs were mainly reported within eight weeks post-tisagenlecleucel infusion and the incidence of AEs decreased substantially after this period. CRS was the most frequently reported AE in the first eight weeks post-tisagenlecleucel infusion. No CRS was reported after that period [23].

An overview of AEs by preferred term, grade and time is shown in Table 9 below.

Table 9 AEs post-tisagenlecleucel infusion (in at least 10% of patients, all grades), by PT and time period.



Source: Clinical Study Report [23] Table 12.4

Serious adverse events

Any time post infusion, SAEs suspected to be related to study drug were reported in 59 patients (51.3%) (see Table 10).

Table 10 SAEs post tisagenlecleucel infusion, suspected to be study drug related.

Source: Clinical Study Report [23] Table 12.9

Cytokine release syndrome (CRS)

[redacted] No AEs of 'CRS' were reported after 8-weeks-post tisagenlecleucel infusion and LPLV [23].

[redacted]

The frequency of CSR is considerably lower with tisagenlecleucel compared with other CAR-T treatments for DLBCL after at least 2 previous treatment lines [27].

No new or unexpected safety signals were detected at the 5-year follow-up, compared with what has previously been reported.

Further details for the safety profile of tisagenlecleucel is described in detail in Appendix F.

7.1.2.2 Results from the CORAL follow-up data

For patients treated with SoC, results for median OS and OS at 60 months for the full FAS and the population for the adjusted analyses are shown in Table 11 below.

Table 11 CORAL follow-up study results, efficacy endpoints

Outcome	N	Result (95% CI)
Median OS (months) Full selected FAS population*	170	[redacted]
Median OS (months) Prior to PS weighting	145	
Median OS (months) Cox regression with fine stratification weight adjusted population	145	
Median OS (months) Cox regression with SMRW adjusted population	145	
OS at 60 months (%) Full selected FAS population*	170	
OS at 60 months (%) Prior to PS weighting	145	
OS at 60 months (%) Cox regression with fine stratification weight adjusted population	145	
OS at 60 months (%) Cox regression with SMRW adjusted population	145	

The KM curve for OS for the adjusted population , including numbers at risk at various time points, is shown in Figure 1 in Section 7.1.3 .

The Expert Committee estimated that with the current treatment option, the survival rate would be 20% at 2 years, and that a clinically relevant difference would be 10 percentage points [25]. In the full FAS population from the CORAL follow-up, [redacted] were alive at 5-years follow-up, and in the adjusted population prior to PS weighting, [redacted]% were alive at 5-years follow-up. In the adjusted population, which is more like the JULIET population, i.e., after PS weighting, only [redacted], respectively, were still alive at 5-year follow-up, depending on the method of adjustment.

Median survival was also lower (respectively [redacted]) in the adjusted population after analysis, compared with the full FAS population and the adjusted population prior to PS weighting. The results are similar regardless of the method used for the adjusted analysis, and in line with the estimation of the survival rates for the current treatment options made by the Expert Committee.

For detailed efficacy results, please see Appendix D.

Overall Response Rate

For the ORR, the results for the FAS population, the adjusted population prior to PS weighting, after PS weighting by fine stratification and PS weighting by SMRW are shown in Table 12 below.

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Table 12 ORR at month 60. CORAL Follow-up

Population	Number of patients	Overall response rate
ORR **Month 60** (%) Full FAS population	170	[redacted]
ORR **Month 60** (%) Prior to PS weighting	145	[redacted]
ORR **Month 60** (%) Fine stratification weight based on PS	145	[redacted]
ORR **Month 60** (%) SMRW based on PS	145	[redacted]

After PS weighting, the ORR is 21% at 60 months, regardless of method.

Other efficacy outcomes

No data for PFS or SF-36 are available for the CORAL follow-up population.

Safety

There are no safety data available from the CORAL follow-up population.

Although safety data of SoC in the population with DLBCL after at least two previous treatment lines is sparse, "traditional" chemotherapy is associated with considerable toxicity, especially hematologic adverse events such as neutropenia, with increased risks for infections, thrombocytopenia, and anaemia, but also fatigue, gastrointestinal adverse events such as nausea, vomiting, diarrhoea and obstipation, and alopecia [28].

7.1.3 Comparative analyses of efficacy and safety

An indirect treatment comparison between tisagencleucel and SoC was done for OS and ORR. No data on PFS or SF-36 are available from the CORAL extension study. There are no safety data available from the CORAL extension study, thus safety is compared narratively.

The indirect treatment comparison compares the efficacy of tisagenlecleucel with historical control for 3rd line or above treatment of relapsed or refractory DLBCL, using patient level data from the single-arm tisagenlecleucel phase 2 study JULIET [19, 29] with data-cut from December 2022 and historical control treatment with patient-level data from the follow-up dataset of the phase 3 CORAL study [9, 10].

To construct a comparable patient population, patients from CORAL follow-up study were selected based on the inclusion and exclusion criteria of the JULIET trial. Patients from the CORAL follow-up may have multiple treatments/index dates that met the inclusion and exclusion criteria of JULIET. The index date had to be selected for CORAL patients. In the unadjusted analysis (Method A), selection of the index treatment based on the number of previous lines was applied without further adjustment for differences in confounders. Adjusted analysis (Method B)

was designed to select an index treatment/date from CORAL follow-up population to reduce the differences in confounders between CORAL follow-up and JULIET populations.

The unadjusted analysis did not account for any differences in confounders. In the adjusted analysis, the comparison was adjusted for identified confounders with <20% missingness of values, using both fine stratification propensity score (PS) weight and SMRW (for details on the PS, and statistical method, see Appendix D and the ICT report [24].

Regarding baseline characteristics, the post PS weighting populations were well balanced for the values included in the PS weighting. However, for the unadjusted as well as the adjusted analyses, patients in the JULIET study had more IPI risk factors at diagnosis compared to the CORAL follow-up population. At baseline, they were older, had a greater number of prior lines of therapies, but a smaller number of IPI risk factors compared to the CORAL follow-up population. Both serum level lactate dehydrogenase (LDH) and European Cancer Oncology Group (ECOG) score were initially included in the PS, however, this was not feasible due to many missing values in the CORAL follow-up population.

Overall survival

OS was defined as the time from the date of tisagenlecleucel infusion (for JULIET) or from the date of index treatment initiation (for the CORAL follow-up) to the date of death due to any reason.

The index date for CORAL follow-up IIT was defined as the date of the selected index treatment initiation, if known, or the date of relapse from last line, if the initiation date of the index treatment was missing.

Results from the analyses are shown in Table 13 below. The health economic evaluation is based on the efficacy of adjusted analysis using the SMRW method, and the KM curves for OS post PS weighting with SMRW are shown in Figure 1 below.

Table 13 Unadjusted and adjusted comparisons of OS between JULIET and CORAL Follow-up

Outcome	Studies included in the analysis	Absolute difference in effect			Relative difference in effect			Method used for quantitative synthesis	Result used in the health economic analysis?
		Difference	CI	*P* value	Difference	CI	*P* value		
Full Analyses Set (Method A)									
Median OS (months)	JULIET CORAL follow-up	[redacted]	NA	NA	[redacted]			Univariable Cox regression	No
Adjusted (Method B)									
Median OS (months)	JULIET CORAL follow-up	[redacted]	NA	NA	[redacted]			Unvariable Cox regression Prior to PS weighting	No
Median OS (months)	JULIET CORAL follow-up		NA	NA				Cox regression with fine stratification based on PS	No

Outcome	Studies included in the analysis	Absolute difference in effect			Relative difference in effect			Method used for quantitative synthesis	Result used in the health economic analysis?
		Difference	CI	*P* value	Difference	CI	*P* value		
Median OS (months)	JULIET CORAL follow-up	[redacted]	NA	NA	[redacted]			Cox regression with SMRW based on PS	Yes

Abbreviations: CI: confidence interval, HR: hazard ratio, NA: not applicable (i.e., available), OS: overall survival, PS: propensity score , SMRW: standardized mortality ratio weight.

Figure 1: JULIET (n=111) vs. CORAL Follow-up (n==145), FAS, Method B, Post PS Weighting with SMRW

Abbreviations: CI: confidence interval; FAS: full analysis set; HR: hazard ratio; KM: Kaplan–Meier; SMRW: standardized mortality ratio weight

Treatment with tisagenlecleucel was associated with a significantly lower hazard of death compared to historical control treatment in both unadjusted (hazard ratio [HR] [95% confidence interval (CI)]: [redacted] and adjusted (HR [95% CI]: [redacted] with fine stratification, [redacted] with SMRW) comparisons [3]

ORR

The ORR was defined as the proportion of patients with a best overall disease response of complete response (CR) or partial response (PR).

In JULIET, response was evaluated by a central independent review committee using the 2014 Lugano Classification [30], in which complete response (CR) did not include unconfirmed CR.

In CORAL, response was measured by an investigator using the 1999 International Working Group (IWG) response criteria [31], in which unconfirmed CR was included under CR.

For both studies, patients with unknown response or without an index treatment were considered non-responders.

To be consistent with the clinical study report of JULIET, response for the JULIET FAS population was assessed among the JULIET main cohort only, i.e., patients treated with tisagenlecleucel from the US manufacturing site.

The results of the analyses are shown in Table 14 below.

Table 14 Unadjusted and adjusted comparisons of ORR between JULIET and CORAL Follow-up

Outcome	Studies included in the analysis	Absolute difference in effect			Relative difference in effect			Method used for quantitative synthesis	Result used in the health economic analysis?
		Difference	CI	*P* value	Difference	CI	*P* value		
Full Analysis Set (Method A)									
ORR at 60 Months (%)	JULIET CORAL follow-up	[redacted]	NA	NA	[redacted]			Unadjusted line selection Univariable logistic regression	No
Adjusted (Method B)									
ORR at 60 Months (%)	JULIET CORAL follow-up	[redacted]	NA	NA	[redacted]			Prior to PS weighting Univariable logistic regression	No
ORR at 60 Months (%)	JULIET CORAL follow-up	[redacted]	NA	NA	[redacted]			Post PS weighting with fine stratification Logistic regression	No
ORR at 60 Months (%)	JULIET CORAL follow-up	[redacted]	NA	NA	[redacted]			Post PS weighting with SMRW Logistic regression	No

Abbreviations: CI: confidence interval, HR: hazard ratio, NA: not applicable (i.e., available), ORR: overall response rate, PS: propensity score , SMRW: standardized mortality ratio weight.

In the unadjusted comparison using Method A sample, tisagenlecleucel was associated with a significantly higher ORR compared to historical control treatment, with a risk difference of [redacted].

Using the Method B sample, before adjustment, tisagenlecleucel was associated with a significantly higher ORR compared to historical control treatment, with a risk difference of [redacted].

After using PS approach to adjust for confounders including age at initial diagnosis, Ann Arbor disease stage, extranodal site involvement, status of disease, time to 2L start after diagnosis, prior HSCT, and number of relapses, tisagenlecleucel was associated with a significantly higher ORR compared to historical control treatment, with a risk difference of [redacted], using either fine stratification weights [redacted] or SMRW [redacted].

Safety

Both tisagenlecleucel and the SoC treatment are associated with high toxicity, which is a burden for patients. However, the side effect profile is significantly different for tisagenlecleucel, in that the most frequent side effect is CRS and neurological side effects that are not seen with current best available treatment.

The Expert Committee previously assessed that overall, the side effect profile for tisagenlecleucel is no worse than for the comparator, and that it is generally acceptable given the patients' prognosis. Moreover, that the side effects are manageable and, for the most part, temporary.

Conclusion

The indirect treatment comparison compared OS and ORR between tisagenlecleucel and historical control treatment with r/r DLBCL using patient-level data from both treatments. Tisagenlecleucel had a statistically significantly lower hazard of death and a higher ORR compared to historical control treatment among the treated populations (i.e. FAS populations), with and without adjustment for differences in confounders.

Both tisagenlecleucel and the SoC treatment are associated with high toxicity, however the characteristics of the adverse events differ.
[redacted]

With more than [redacted] of treated patients still being alive 5 years after tisagenlecleucel infusion, and a safety profile where the adverse events are manageable and, for the most part, temporary, tisagencleucel seems to offer a treatment option for patients with a positive benefit/risk profile vs. SoC.

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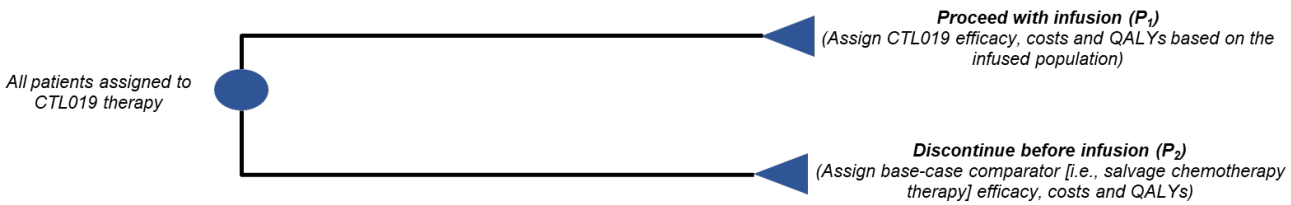
8. Health economic analysis

8.1 Model

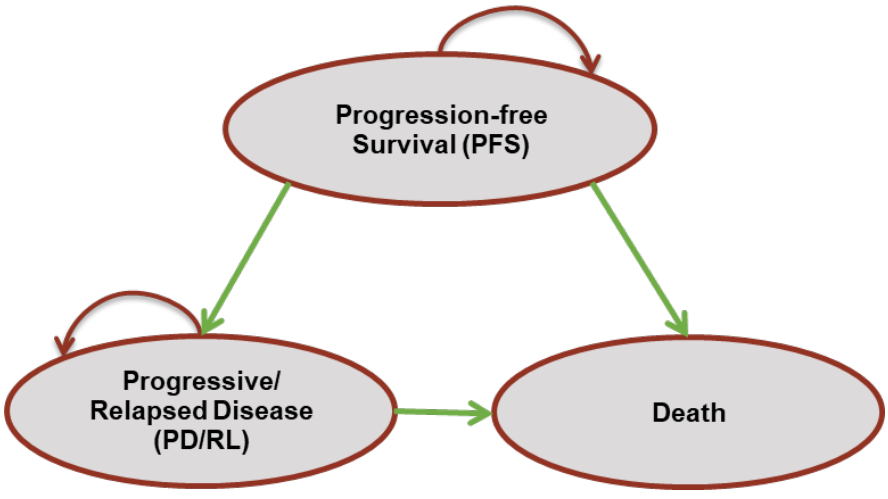
The cost-effectiveness model was developed in Microsoft Excel®. Initially, there is a decision tree structure for patients enrolled in the JULIET trial, i.e., the Kymriah® arm. Based on whether or not the patients receive infusion, they proceed to the infusion arm (with QALYs, efficacy and costs assigned according to the infused population of the JULIET trial) or they are assigned to the comparator arm (with QALYs, efficacy and costs assigned according to the CORAL follow-up population). Relevant costs and outcomes were assigned to the respective relevant branch.

Figure 2: Partitioned survival model structure



After this decision tree structure, the model proceeds as a partitioned survival model A partitioned survival model were chosen as the event data does not follow a constant hazard over time. The model comprised three mutually exclusive health states: (i) Progression-free survival (PFS), (ii) Progressive disease/Relapsed disease (PD/RL) and (iii) Death (Figure 3), as often used for cancer models. PFS was defined as the time from the date of relapse or progression to the date of first documented progression or death due to any cause. A monthly model cycle was used for estimating the proportion of patients in each health state over time, with applied half-cycle correction. All patients began in the PFS state at model start. The proportion of patients in the PFS health state of the model was set to be equal to the PFS curve of each treatment. The progressed/relapsed state included alive patients who had progressed or relapsed. The proportion of patients in the progressed/relapsed health state was set to be equal to the difference between the proportion of living patients (following the extrapolated OS curve of both arms), and the proportion of PFS patients (following the PFS curve for both arms). During each cycle, patients were redistributed among the three health states, with death being the absorbing state. Both costs and effectiveness were discounted at 3.5% annually [32].

Figure 3: Partitioned survival model structure



In the base-case analysis a lifetime horizon was considered since it would comprehensively capture the expected costs and health outcomes of patients. In JULIET, patients had a median age of 56 [2], whereas a recent Danish registration study found a median age in the 3rd line setting of 72 [33]. The latter is used in the base case, whereas the effect of a lower median age, is explored in a scenario analysis.

The discount rate was not changed after 35 years, as the model only runs for 28 years.

8.2 Relationship between the data for relative efficacy, parameters used in the model and relevance for Danish clinical practice

This health economic model is based on a range of data on effectiveness, relative effectiveness, long term survival, use of resources ("quantification of resource use"), quality of life, etc. Unfortunately, Danish guidelines for treatment of DLBCL do not provide detailed information on the 3rd treatment of DLBCL [1]. Several drugs are mentioned in the guidelines, but it is up to the individual clinician to choose therapy. The large variation in treatment seems to be present in this area of medicine as indicated by the CORAL study in which a range of chemotherapy combinations was used in subsequent treatment of patients [18]. Further, a number of patients in 3rd line might not be eligible for treatment with CAR-T [1, 7], which complicates the validation of the comparative evidence.

8.2.1 Presentation of input data used in the model and how they were obtained.

Table 15 Input data used in the health economic model

Name of estimates*	Results from study or indirect treatment comparison	Input value used in the model	How is the input value obtained/estimated**
Overall survival, JULIET	[redacted]	Used for extrapolated curve	ITC [24]
Overall survival, CORAL		Used for extrapolated curve	ITC [24]
Progression free survival, JULIET		Used for extrapolated curve	CSR [23]
Progression free survival,	NA	Based on continuous HR between PFS and OS for JULIET	Calculation
Adverse event, CRS	[redacted]		CSR [23]
Adverse event, B-cell aplasia			CSR [23]
Adverse event, other			CSR [23], Corazzelli 2009 [34]
Patients require hospitalisation after tisagenlecleucel infusion			CSR [23]
Patient with bridging chemotherapy, tisagenlecleucel			CSR [23]
Subsequent stem cell transplant, tisagenlecleucel **ASCT** **Allo-SCT**			CSR [23]
Subsequent stem cell transplant, CORAL **ASCT** **Allo-SCT**	 21.22% 7.55%	 21.22% 7.55%	 Van Den Neste 2016 [17] Van Den Neste 2017 [18]
Health state, pre-progression	[redacted]		CSR [23]
Health state, post progression			CSR [23]

Name of estimates*	Results from study or indirect treatment comparison	Input value used in the model	How is the input value obtained/estimated**
Disutility associated with ICU stay and CRS treatment	[redacted]		Utility assumed to be 0
Disutility during treatment	-0.15	-0.15	Guadagnolo 2006 [35]
Disutility during SCT	-0.30	-0.30	Guadagnolo 2006 [35]

8.2.2 Relationship between the clinical documentation, data used in the model and Danish clinical practice

8.2.2.1 Patient population

In the application for axicabtagene ciloleucel for treatment of patients with DLBCL in 3rd line, the Danish Expert Committee deemed the selected patient pool for comparison from SCHOLAR-1 to not be suitable for comparison and instead used the patient population from CORAL EXT-1 and CORAL EXT-2. The data informing the comparator for this evaluation is based on patient level data from these two studies and denominated as CORAL follow-up in this application. Since, the Expert Committee deemed this population relevant for the comparison and established that the effect shown in CORAL is transferable to Danish clinical practice [36], no further detailing of relevance for the comparator to the Danish population is made.

In the assessment of axicabtagene ciloleucel, the Expert Committee noted that the patient population is a selected subgroup of patients who, in general, are younger and have a higher level of functioning. Thus, there is a subset of patients, where the effects of axicabtagene ciloleucel have not been examined [36]. In parts, this also holds true for tisagenlecleucel. In general, patients were younger and had an ECOG score of 0 or 1 indicating a more fit patient sub-group. However, the patients from JULIET, on average, had more previous lines of treatment, despite being at a young age, which could indicate a more aggressive course disease. Moreover, patients in the JULIET trial [37] were allowed to receive bridging chemotherapy, in contrast to the registration trial for axicabtagene ciloleucel (ZUMA-3) [38], where patients were not allowed to receive bridging chemotherapy, effectively excluding too frail patients to receive treatment. In context of the American Society of Hematology (ASH) presentation from 2022 by Ludvigsen, Al-Mashhadi [33], the median age of 3rd line patients were 72 years, which contrasts the median age from JULIET of 56 [37]. However, since this study is a cross section of all patients treated in the 3rd line setting, a higher median age would be expected. Further, the recently published guideline from the Danish Lymphoma Group [7] dictates that patients must be eligible for SCT to be considered for CAR-T treatment, establishing the difference between all 3rd line treated patients in Denmark and those treated in JULIET. The effect size of treatment with tisagenlecleucel in the Danish setting is likely to be higher than what was observed in JULIET, since one of the exclusion criteria for the JULIET study, was eligibility for an ASCT at enrolment. This is further solidified in the indirect treatment comparison since the effect of the CORAL is lower in the adjusted analysis than in the unadjusted analysis.

8.2.2.2 Relative efficacy outcomes

The clinical data from the indirect treatment comparison show slightly better overall results for both CORAL and JULIET compared to the health economic model. The absolute differences are close to equal and thus the relative difference is negligible. The under-estimation can be explained by the two late events in both the CORAL and the JULIET arm where few people are at risk.

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Table 16 Outcomes data from CORAL and JULIET used in the cost effectiveness model

Clinical efficacy outcome	Clinical documentation	Used in the model (value)
Primary endpoint overall survival, JULIET	Median OS Month 24 OS Month 60 OS	[redacted]
Primary endpoint, overall survival, CORAL	Median OS Month 24 OS Month 60 OS	
Secondary endpoint, progression free survival	median PFS Month 24 PFS Month 60 PFS	

Ref: ITC [24], CSR [23]

8.2.2.3 Adverse events

In the health economic analysis, grade 3 and 4 adverse events (AE) with more than 5% occurrence it included. Of special note, 37.39% patients in JULIET experienced B-cell aplasia and 22.6% experienced cytokine release syndrome, which are both costed individually in the model. The adverse events for tisagenlecleucel are taken directly from JULIET, whereas neither the SCHOLAR-1 nor the CORAL extension studies reported the AE profile of the considered regimens, or the types of regimens included. Therefore, a targeted literature search was conducted to select the most relevant publications for AE rate input for the salvage chemotherapy. Six publications were identified and reviewed for inclusion. Corazzelli 2009 [34] was selected because it captures a comprehensive set of AEs for a common salvage regimen (i.e., Gem-Ox) in a relevant patient population (i.e., r/r B-cell lymphoma patients).

Table 17 Adverse events in health economic model

Adverse events	Clinical documentation		Used in the model (numerical value)	
	JULIET	CORAL	JULIET	CORAL
Anaemia	[redacted]			
Anorexia				
B-cell aplasia				
CRS				
Fatigue				
Febrile neutropenia				
Hypokalaemia				
Hypophosphatemia				
Hypotension				
Infection				
Neutropenia				
Neutrophil count decreased				
Paraesthesia				
Platelet count decreased				
Pyrexia				

Adverse events	Clinical documentation	Used in the model (numerical value)
Pneumonia	[redacted]	[redacted]
Stomatitis		
Thrombocytopenia		
Vomiting		
White blood cell count decreased		

Source: CSR [23], Corazzelli 2009 [34]

8.3 Extrapolation of relative efficacy

8.3.1 Proportional hazards testing.

Proportional hazards testing was performed to examine the relation between the effect of tisagenlecleucel and chemotherapy. Schoenfeld residuals indicated correlation. The log-cumulative hazards plots maintain separation, with parallelism between the two curves. Further detailed in Appendix G. Consequently, a HR would be suitable for use in the health economic model. In the base case, individually fitted curves are used, but the HR is used when performing the probabilistic sensitivity analysis and in the deterministic sensitivity analysis.

8.3.2 Overall Survival

OS data were available for both JULIET FAS and CORAL follow-up and extrapolated curves could therefore be fitted to both arms. When fitting the KM curves, the spline with 1 knot had the best statistical fit (AIC and BIC) for the chemotherapy arm. For the JULIET data, the spline with 1 and 2 knots had the best BIC and AIC, respectively. Upon visual inspection, the spline with 2 knots appears to have a better fit and was therefore chosen. The proportional hazards assumption did hold and as such a HR between the two would be appropriate for the base case. However, since two different curves was chosen, individual extrapolation of each arm should yield the more accurate OS estimate for both arms and was consequently chosen for the base case analysis. Below in Figure 4, the KM data and fitted curve for OS of JULIET and CORAL follow-up FAS is presented. AIC/BIC statistics and all curves for the examined extrapolation methods are presented in Appendix G.

Figure 4 KM and extrapolated curve for OS of JULIET FAS and CORAL FAS used in the cost effectiveness model

8.3.3 Progression free survival

JULIET full analysis set

For the extrapolation of the PFS KM data for the JULIET arm, the spline with 2 knots best fit the data. Splines with 3 and 4 knots did not converge and is therefore not presented in the health economic model. Albeit Splines with 2 knots presents the best, upon visual inspection, the curve presents a too conservative estimation of the true curve. Due to the curative potential of tisagenlecleucel, the PFS curve flattens and thus converges with the OS curve. Consequently, the PFS curve is capped to the OS curve, which is also applied to the PFS curve of CORAL. The KM curve and the chosen fit is presented below, in Figure 5. A figure of all extrapolated fittings and AIC/BIC statistics can be found in Appendix G.

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Figure 5 Kaplan Meier and extrapolated curve for progression free survival of JULIET FAS used in the health economic model

CORAL follow-up

It was not possible to obtain progression free survival data for CORAL patients. Therefore, the hazard ratio between JULIET OS and JULIET PFS has been used for CORAL follow-up. This was also used in the assessment of axicabtagene ciloleucel for treatment of 3L DLBCL patients [36]. Alternatively, historical data has been used to approximate the relation between OS and PFS. This was estimated based on the average of R-ICE and R-DHAP arms in the Gisselbrecht 2010 study [9]. To estimate an overall cumulative hazard ratio between OS and PFS for each comparator, the ratio was first estimated as the natural log of OS probability divided by the natural log of PFS probability at yearly intervals until the end of the observed period. The overall cumulative hazard ratio between OS and PFS was then calculated as the average of cumulative hazard ratios at all yearly intervals, resulting in a HR of 0.65. This is explored in a scenario analysis.

Long-term survival

In the model, patients were assumed to be cured after 5 years and would follow the mortality rate of the general population, with an adjustment of 1.09. This assumption and value is based on Maurer et al 2014 [39]

8.4 Documentation of health-related quality of life (HRQoL)

As this is a resubmission and the methods in Denmark were changed since the initial application, Novartis has been in dialogue with the secretariat of the Medicines Council and agreed on a slight deviation from Danish methods. Therefore, the HRQoL presented below is based on a recent application to the Norwegian HTA agency based on SF-36 utility values. Hence no attempts to map the SF-36 values, from the JULIET trial to EQ5D-utility weights based on Danish utility weights, have been made.

The utility and disutility inputs of the cost-effectiveness model consisted of utilities of health states, disutility associated with treatment and its AEs, and disutility associated with SCT.

In the JULIET trial SF-36 was an endpoint and the SF-36-scores were translated into QALY-weights by means of mapping to EQ-5D with utility weights from United Kingdom. According to the protocol, SF36 data are collected at screening, at month 0, 3, 6, 12, 18, 24, 36, 48 and 60.

8.5 Summary of Quality of Life weights

The QALY weights for patients prior to tisagenlecleucel treatment in the JULIET trial and their weights after subsequent treatment are presented in Table 18.

Table 18. QALY weights from the JULIET trial based on SF-36 scores and translated to EQ-5D scores by means of mapping

Health States	N patients[a]	N assessments	Mean	SD
Progression-free	[redacted]			
Post progression	[redacted]			

Abbreviations: SD, standard deviation

a. The same patient can have multiple health states at different visits. The statistics presented here reflect the number of patients with at least one assessment with the specified health state

8.6 Quality of life weights used in the cost-effectiveness model

8.6.1 QALY weights from the JULIET trial

Since EQ-5D was not collected in the JULIET trial, but SF-36 was, EQ-5D utility values were derived by mapping SF-36 data to utility values using the UK EQ-5D tariff. According to the Health Economics Research Centre (HERC) database of mapping studies [40], there is no existing mapping algorithm from SF-36 to EQ-5D utility values developed among lymphoma patients. A mapping algorithm that was developed by Rowen (2009)[41] based on a UK hospital database collected from general population in UK, Health Outcomes Data Repository (HODaR) [42], was used in this analysis. HODaR is collected from a prospective survey of inpatients and outpatients at Cardiff and Vale NHS Hospitals Trust, which is a large University hospital in South Wales, UK. The survey includes all subjects aged 18 years or older and excludes individuals who are known to have died or with a primary diagnosis on admission of a psychological illness or learning disability.

In the JULIET trial (data-cut December 2022) [23], Short Form 36 health survey (SF-36) data (version 2, acute form) were collected at screening, month 3, 6, 12, and 18, 24, 36, 48 and 60 for 110, 70, 42, 35, 32, 27, 24, 15, 18 patients, respectively. Based on individual patients' health states at the time of SF-36 evaluation, observed SF-36 values were classified into the following categories corresponding to the health states in the model:

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

EQ-5D utility scores based on UK preference-weights were calculated based on individual dimension scores of SF-36 based on the mapping algorithm reported in Rowen (2009) [41]. This analysis did not impute values for missing evaluations. Descriptive statistics on the mapped EQ-5D utility values and the total sample size by the above health state categories are shown in Figure 6. The utility values associated with each health state were estimated using a

generalised estimating equation (GEE) model with a robust variance estimator to account for correlation within patients' repeated assessments (Figure 6).

Figure 6: Estimated EQ-5D utility score by health states using GEE model

Note: the utility before treatment was not used in the cost-effectiveness model

8.6.2 Literature search for lymphoma QALY weights

A literature review was conducted to identify publications that report quality-of-life (QoL) measures for the target population. Two input sources were considered relevant and used in the health economic model. For the NICE pixantrone single technology assessment a systematic literature review was conducted to identify utility data for patients with aggressive non-Hodgkin's lymphoma (DLBCL is a subgroup of non-Hodgkin disease) or in a similar disease area (NICE, 2014) [43]. The two sets of utility input recommended by the NICE committee and used in the original manufacturer submission were considered as relevant and referenced in the current assessment. Specifically, the utility input based on 2nd line treatment were recommended by the NICE committee, and the self-reported QoL measures during chemotherapy in elderly patients with aggressive non-Hodgkin lymphoma as were used in the original manufacturer submission.

Guadagnolo 2006 [35] developed a decision-analytical model to evaluate follow-up strategies for patients with Hodgkin's disease. Utility and disutility input for patients with Hodgkin's disease were consolidated from prior published studies and used in the analysis. Separate disutility estimates were reported for patients receiving conventional dose salvage chemotherapy and high dose salvage chemotherapy followed by transplantation and were used in the CEA model.

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8.6.3 QALY weights used in the cost-effectiveness model

Utility values in the model were assumed to be dependent on health state and independent of treatment arm. Because none of the utility input from the literature were DBLCL-specific, the utility values derived from the JULIET data were considered in the base-case. EQ-5D estimates from both *PFS* and p*ost-PFS* were used to inform the utility values for the progression-free and progressed health states, respectively.

The utility values obtained from the NICE pixantrone single technology assessment were used in the sensitivity analysis (NICE, 2014) [43]. Two sets of utility values were explored, including the input recommended by the NICE Committee, and the input considered in the original manufacturer submission.

The death state was assumed to have 0 utility (Table 19).

Input for treatment disutility in the treatment phase (chemotherapy induction) were obtained from Guadagnolo 2006 [35]. A decrement of 0.15 for patients undergoing conventional dose salvage chemotherapy is reported and assumed to capture the utility decrements for all short-term AEs associated with the tisagenlecleucel or salvage chemotherapy, except for the cytokine release syndrome (CRS). The treatment disutilities were assumed to apply for the duration of induction chemotherapy for the salvage chemotherapy arm and for the duration of the hospitalisation starting from the pre-treatment lymphodepleting regimen for tisagenlecleucel (Table 19).

For the tisagenlecleucel arm, additional treatment disutilities were considered for grade 3 or 4 cytokine release syndrome (CRS) and intensive care unit (ICU) stays not due to CRS. The CRS rate was derived from the JULIET trial data. For both events, the patients were assumed to have a utility of 0 (a disutility of 0.84) for the duration of the CRS-related or non-CRS-related intensive care unit stay based on the JULIET trial [23].

The model assumed that patients could receive ASCT or allo-SCT subsequent to tisagenlecleucel. The efficacy of subsequent SCT was captured in the PFS and OS estimations. Patients receiving either subsequent ASCT or allo-SCT were assumed to have additional disutility, derived from Guadagnolo 2006 [35]. Because Guadagnolo 2006 [35] did not report any estimate of duration associated with the reported disutility estimates, the disutility associated with SCT was assumed to last for 365 days. The rate of subsequent ASCT or allo-SCT for the tisagenlecleucel arm was derived from the pooled data including JULIET [23] and trials from University of Pennsylvania (UPenn trials) [44]. The rate of subsequent ASCT for the salvage chemotherapy arm was derived from the CORAL trial [17, 18]. Van Den Neste 2016 [17] reported the rate of subsequent allogenic SCT for r/r DLBCL patients receiving 3rd-line treatment without prior SCT; Van Den Neste 2017 [18] reported the rate of subsequent allo-SCT for r/r DLBCL patients receiving 3rd line treatment with prior SCT. The rate used in the model was the weighted average of the two publications based on the proportion of patients with and without prior SCT observed in the pooled data using JULIET and UPenn trials. Table 19 presents subsequent SCT disutilities input, subsequent SCT rates, and the overall subsequent SCT disutilities for each treatment arm.

Table 19: QALY weights used in the cost-effectiveness model

Input	Utility/Disutility input	Duration	% of patients	Source
Health states utility (base-case - JULIET)				
PFS	[redacted]	NA	NA	JULIET data on file
PD/RL	[redacted]			
Health states utility (sensitivity - NICE recommendation for Pixantrone submission)				NICE Pixantrone STA [43]
PFS	0.76	NA	NA	
PD/RL	0.68			
Health states utility (sensitivity - Pixantrone manufacturer submission)				
PFS	0.81	NA	NA	
PD/RL	0.60			
Treatment disutility				
Tisagenlecleucel	-0.15	28 days	NA	Guadagnolo et al. 2006 [35] (disutility), assumption (duration)
Salvage chemotherapy	-0.15	66 days		
Other disutility				
ICU stay due to CRS				Assumption: utility=0 during ICU admission (disutility), CSR [23] (duration and % of patients)
Tisagenlecleucel	[redacted]			
ICU stay not due to CRS				
Tisagenlecleucel	[redacted]			
Subsequent SCT disutility				Guadagnolo et al. 2006 [35]
Tisagenlecleucel – ASCT	[redacted]			JULIET and UPenn trials [23, 44]
Tisagenlecleucel – Allo-SCT	[redacted]			JULIET and UPenn trials [23, 44]
Salvage chemotherapy - ASCT	-0.30	365 days	29.85%	SCHOLAR-1 study [45]
Salvage chemotherapy – Allo-SCT	-0.30	365 days	10.48%	Van Den Neste 2016 [17] Van Den Neste 2017 [18]

Abbreviations: PFS, progression-free survival; PD/RL, progressive/relapsed disease; ICU, intensive care unit; CRS, cytokine release syndrome; ASCT, autologous stem cell transplantation; allo-SCT, allogeneic stem cell transplantation; NA, not applicable; STA, single technology appraisal

8.7 Resource use and costs

The model considered the following cost components: pre-treatment lymphodepleting costs for tisagenlecleucel arm, drug and procedure acquisition costs for tisagenlecleucel and salvage chemotherapy, associated drug administration costs, associated hospitalisation, and Intensive care unit (ICU) costs, AE costs, follow-up cost before progression, subsequent stem cell transplantation (SCT) costs, follow-up and monitoring costs, cost post progression and terminal care costs.

For all pharmaceuticals, we used pharmacy purchase price and prices were found on medicinpriser.dk [46]. The website was accessed on August 17th, 2023, and lowest cost drug was always chosen. DRG rates were sourced from the DRG list from 2023 [47]. When costs were obtained from the literature, they were converted to DKK at the time of publication using valutakurser.dk [48] and then inflated to 2023 costs using the general consumer price index (CPI) from time of publication using data from Danmarks Statistik [49].

Per DMC request, patient cost has been added to the model. When available, the time usage has been sourced from the application for treatment of 2nd line DLBCL patients with Yescarta [50]. If not available, the time usage has been assumed. The cost of a patient hour was set to DKK 203 and transportation was set equal 20km drive at equating to 140 DKK per visit [51]. Due to time constraints, these were added to the costs associated with hospital visits and was not added as new cells in the health economic model. If the patient stayed a full day or more in the hospital, this was costed with 16 hours per day. For each visit, 1 patient hour for transportation was added to the patient costs, i.e. if the patient visited the hospital for 4 hour, the patient cost for that particular visit would be 5 hours.

8.7.1 Pre-treatment cost

Patients treated with tisagenlecleucel typically receive lymphodepleting agents before infusion. Lymphodepletion was included as pre-treatment costs in the model. The administration cost of tisagenlecleucel was conservatively set to the DRG 17MP07 "Biologisk modificerende stoffer på svulster i lymfatisk og bloddannende væv, pat. mindst 18 år". It could be argued that this would encompass the cost of lymphodepletion. Cost of lymphodepleting is based on two regimens: Regimen 1, including fludarabine and cyclophosphamide, and Regimen 2, including bendamustine. The distribution of patients to each regimen is based on the JULIET trial, in which 73.91% of patients received Regimen 1, 19.13% received regimen 2 [11] and the last 8% did not receive lymphodepletion prior to infusion. For an overview of the cost, see Table 20 and Table 21.

Table 20 Dosing schedule and costs associated with the two lymphodepletion regimens

	Defined dosing	Price per package or vial	Number of vials per infusion	Number of infusions per cycle	Admin cost per day of infusion	Number of infusion days within the cycle and time per infusion
Regimen 1						
Fludarabine	25 mg/m² daily for 3 doses	6 551	0.19	3	2 551	3

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Cyclophosphamide	250 mg/m² daily for 3 doses	257	0.96	3		1 hour
Regimen 2						
Bendamustine	90mg/m² daily for 2 days	1 174	0.34	2	2 551	2

Sources: [46, 47]. All costs in DKK

Table 21 Average cost of Lymphodepletion regimen prior to tisagenlecleucel infusion

	Total drug cost	Total outpatient admin cost	Distribution of patients
Regimen 1	4 511	7 653	
Regimen 2	811	5 102	
Total treatment cost	**3 489**	**6 633**	

All costs in DKK

8.7.2 Treatment costs

Treatment costs consisted of drug/procedure acquisition costs, hospitalisation, and ICU costs. Vial sharing for drugs other than Kymriah® was considered when estimating drug costs.

8.7.3 Tisagenlecleucel

The list price of Kymriah® is DKK 2 028 084.54 [46]. In addition to the cost of treatment, T-cell cell harvesting is carried out, which involves two days in-hospital care with central vein apheresis. The DRG rate for "afereser" 17MP18 was used, costing DKK 30 622 [47].

Table 22 Kymriah® price

	Pharmacy purchase price
Kymriah®	2 028 080.54

All costs in DKK

It is assumed that all patients are treated in the hospital setting. The cost of infusion was assumed to cover the first 20 days of hospitalisation associated with treatment, costed with 17MP09, "Biologisk modificerende stoffer på svulster i lymfatisk og bloddannende". And 16 x 20 x DKK 203 in patient cost equaling DKK 61 146. The remaining days was costed with DKK 2 240, which is the "langliggertakst" as of 2023 [47]. Therefore, patients were costed with an additional DKK 41 716, due to hospitalisation following infusion.

On average, tisagenlecleucel patients had 0.90 days in intensive care unit (ICU) for reasons other than cytokine release syndrome. The cost of intensive care unit could not be sourced from the cost list for the hospitals of the Capital Region and set to DKK 33 312 after inflation to the current cost year [52].

In JULIET and in the real-world treatment setting, patients receive chemotherapy as bridging before tisagenlecleucel infusion. This was included in the model and applied to all patients who received tisagenlecleucel infusion and costed with the same as one cycle of the average chemotherapy regimens used for the comparator. Patients who did not

receive infusion with tisagenlecleucel, were assumed to be treated with chemotherapy and thus were costed equal to the comparator arm, as described in the following section.

8.7.3.1 Salvage chemotherapy

The treatment cost of salvage chemotherapy is estimated using weighted average costs of different regimens (R-ICE, R-GDP and R-DHAP). The model allows the user to choose the proportion of patients receiving rituximab, which is set to 100% in the base case. Two costing options can be chosen. Costing using DRG, where the cost is weighted to the two DRGs 17MP10 and 17MP11 depending on the proportion of patients chosen to receive rituximab, costing DKK 58 135 and DKK 41 510, respectively (Table 25) [47]. When costing using DRG rates, hospitalisations are omitted as it is believed to be captured in the DRG rate. Alternatively, it is possible to use administration costs which are set equal to an outpatient visit per infusion day (DRG 17MA98) [47], the cost of each chemotherapy regimen with pharmacy purchase price of drugs collected from medicinpriser.dk [46] (Table 23 and Table 24). Finally, the cost of hospitalisation was conservatively costed with the cost of a "langliggertakst" of DKK 2 240 for the average of 11.4 days and average hospitalisation rate of 1.1 from Huntington 2018 [53] resulting in a cost of DKK 29 201. The total treatment cost for salvage chemotherapy calculated at DKK 200 566 and DKK 97 631, when using the two methods, respectively. As with the other costs, patient time was added to treatment and hospitalizations related to chemotherapy treatment. This was not included for the costs using DRG rates, as the DMC preferred the other costing approach.

Table 23 Overview of cost and posology of each chemotherapy regimen included in the cost effectiveness model

	Defined dosing	Price per package or vial DKK	Number of vials per infusion	Number of infusions per cycle	Admin cost per day of infusion DKK	Number of infusion days within the cycle
Regimen: (R)-ICE						
Etoposide	100 mg/m² on days 3-5	71	1.91	3	2 005	4
Ifosfamide	5000 mg/m² on day 4	380	9.56	1		
Carboplatin	800 mg on day 4	226	1.78	1		
Rituximab	375 mg/m² on day 1	6 687	1.43	1		
Regimen: (R)-GDP						
Gemcitabine	1000 mg/m² on days 1 and 8	420	0.87	2	2 005	2
Dexamethasone	40 mg (oral) daily on days 1-4	1 490	0.10	4		
Cisplatin	75 mg/m² on day 1	100	2.87	1		
Rituximab	375 mg/m² on day 1	6 687	1.43	1		
Regimen: (R)-ESHAP						
Etoposide	100 mg/m² on days 3-5	71	1.91	3	2 005	5
Methylprednisolone acetate	500 mg on days 1-5	132	2,50	5		
Cytarabine	2000 mg/m² on day 5	150	1.91	1		
Cisplatin	75 mg/m² on day 1	100	2.87	1		
Rituximab	375 mg/m² on day 1	6 687	1.43	1		
Regimen: (R)-DHAP						
Dexamethasone	40 mg (oral) daily on days 1-4	1 490	0.10	4	2 005	4
Cytarabine	2000 mg/m² on day 5	150	1.91	1		

Cyclophosphamide	1200 mg/m² on day 3	180	4.59	1		
Etoposide	100 mg/m² on days 3-5	71	1.91	3		
Rituximab	375 mg/m² on day 1	6 687	1.43	1		
Regimen: (R)-EPOCH						
Doxorubicin	15 mg/m² on days 2-4	120	0.57	3	2 005	5
Vincristine	0.5 mg on days 2-4	390	0.50	3		
Etoposide	100 mg/m² on days 3-5	71	1.91	3		
Cyclophosphamide	1200 mg/m² on day 3	180	4,59	1		
Prednisolone	60 mg/m² (oral) on days 1-14	17	0,46	14		
Rituximab	375 mg/m² on day 1	6 687	1,43	1		

Table 24 Drug and administration cost of chemotherapy included in the cost effectiveness model and the average calculated cost (all costs in DKK)

	Drug cost per cycle	Admin cost per cycle	Average number of cycles	Cycle length (days)	Usage rate for each regimen %
Regimen: (R)-ICE	14 027	18 107	3	14	25%
Regimen: (R)-GDP	11 197	7 601	2	21	15%
Regimen: (R)-DHAP	11 702	21 355	4	21	60%
Weighted average of regimens	**12 164**	**19 453**	**3**	**19**	
Total cost of chemotherapy	**41 964**	**67 113**			

Table 25 Costs associated with chemotherapy treatment, using DRG rates (all costs in DKK)

	DRG rates and rituximab use for different chemotherapy regimens considered				Average number of cycles	Usage rate for each regimen %
	DRG cost	Rituximab use	DRG cost	Rituximab use		
Regimen: (R)-ICE	58 135	100%	41 510	0%	3	25%
Regimen: (R)-GDP	58 135	100%	41 510	0%	2	15%
Regimen: (R)-ESHAP	58 135	100%	41 510	0%	3	0%
Regimen: (R)-DHAP	58 135	100%	41 510	0%	4	60%

Regimen: (R)-EPOCH	58 135	100%	41 510	0%	4	0%
Weighted average of regimens			**58 135**		**3.45**	
Total cost for chemotherapy	**200 566**					

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Subsequent stem cell transplantation costs

The model assumes that patients can receive subsequent allo-SCT or ASCT after initial treatment. The cost and disutility of subsequent SCT were added separately for the proportion of patients who received subsequent SCT for each treatment arm and is presented in Table 26 below. The subsequent SCT rate for tisagenlecleucel with efficacy defined as starting from relapse is based on the JULIET data alone [23]. The subsequent SCT rate for chemotherapy is based on use from the CORAL study [17, 18].

Table 26 Subsequent SCT Rate used in health economic model

	Subsequent allo-SCT rate (%)	Subsequent autologous SCT rate (%)
Tisagenlecleucel		
Salvage Chemotherapy		

Abbreviation: SCT: stem cell transplant, Source: Van Den Neste 2016 [17], Van Den Neste 2017[18], CSR [23]

The cost of SCT (allo-SCT and ASCT) were based on DRG rates [47]. The cost associated with allo-SCT treatment procedure was based on DRG 26MP22 with a cost of DKK 768 062. For ASCT treatment, the cost was based on 26MP24 costing DKK 102 366. Cost of follow-up post-transplant was taken from a previous submission on axicabtagene ciloleucel and inflated to current cost year [6]. Cost of patient time was added and using the assessed time from the Yescarta report [50].

Table 27 Cost of stem cell transplantation

Treatment	Cost DKK	Source
Cost associated with allo-SCT procedure	847 981	26MP22 "Allogen stamcelletransplantation" [47]
Cost associated with ASCT procedure	182 285	26MP24 "Kemoterapi, højdosis, m. autolog stamcellestøtte" [47]
Follow-up cost after SCT	50 555	DMC assessment report for axicabtagene ciloleucel [6]

Abbreviations: allo-SCT: allogeneic stem cell transplant; ASCT: autologous stem cell transplant. All costs in DKK

8.7.4 Follow-up costs

Follow-up costs consisted of the costs of the outpatient visits, laboratory tests and procedures (e.g., full blood count and bone marrow biopsy). The costs of taking the blood panels were derived from the labportal of Rigshospitalet at labportal.rh.dk [54]. Each individual test was added to the cost of an outpatient visit. Additionally, the cost of a CT scan was included in the follow-up costs [47]. Also. The cost of patient time was added to the consultant visit and assumed to be 4 hours.

The follow-up unit costs are described in Table 28 and detailed schedules are available in the Excel model (sheet "Follow-Up Costs input").

Table 28: Unit costs for follow-up procedures

Description	Input (cost) DKK	Code	Source
Consultant visit	3 160	17MP98	DRG [47]
Haematology panel	238	ASERY, reti, HBA1C	labportal.rh.dk [54]
Coagulation panel	43	APTT	labportal.rh.dk [54]
Chemistry panel	20	CRP	labportal.rh.dk [54]
Bone marrow biopsy and/or aspirate	6 603	CSVMRK	labportal.rh.dk [54]
Comprehensive metabolic panel	236	ALB, BASP, ALAT, ASAT, CARB, CA, CO2, CL, CREA, K, N, BILI, PROMKOMP	labportal.rh.dk [54]

Serum lactate dehydrogenase (LDH)	16	LDH	labportal.rh.dk [54]
Uric acid	21	UURAT	labportal.rh.dk [54]
CT scan	2 440	30PR06	DRG [47]

Abbreviations: CT: computed tomography

The follow-up costs were assigned to both treatment arms with the frequency shown in Table 29 below. The follow-up and frequency were taken from the guideline on treatment of DLBCL in Denmark by the Danish Lymphoma Group [1].

Table 29 Frequency of resource use used in the cost effectiveness model

Description	Frequency of follow-up during PFS for comparators			
	Yearly frequency (Year 1)	Yearly frequency (Year 2)	Yearly frequency (Year 3-5)	Yearly frequency (Year 5+)
Bone marrow biopsy and/or aspirate	1	0	0	0
Chemistry panel	4	2	2	2
Coagulation panel	4	2	2	2
Comprehensive metabolic panel	4	2	2	2
Consultant visit	4	2	2	2
CT scan	1	0	0	0
Haematology panel	4	2	2	2
Serum lactate dehydrogenase (LDH)	4	2	2	2
Serum test	0	0	0	0
Uric acid	4	2	2	2
placeholder	4	2	2	2
Monthly cost	**1 998 DKK**	**622 DKK**	**622 DKK**	**622 DKK**

8.7.5 Adverse event costs

AE costs were calculated for tisagenlecleucel, and salvage chemotherapy based on rates of AEs and their unit costs. The rates were obtained from the JULIET trial data for tisagenlecleucel and Corazzelli 2009 for salvage chemotherapy [34]. Because neither the SCHOLAR-1 nor the CORAL extension studies reported the AE profile of the considered regimens or the types of regimens included, a targeted literature search was conducted to select the most relevant publications for AE rate input for the salvage chemotherapy. Six publications were identified and reviewed for inclusion. Corazzelli 2009 [34] was selected because it captures a comprehensive set of AEs for a common salvage regimen (i.e., Gem-Ox) in a relevant patient population (i.e., r/r B-cell lymphoma patients).

8.7.5.1 Cytokine release syndrome costs

In the cost effectiveness model, cytokine release syndrome (CRS) costs based on resource use in JULIET has been included. The cost of CRS is calculated by using the mean stay in the ICU, ICU costs, tocilizumab use, and average

doses given. The mean duration of ICU stays was taken from real world evidence, from the CIMBTR registry [55]. The mean duration of ICU stays was sourced from real world data in the CIMBTR registry. The cost of CRS can be costed in two ways. Either as a DRG: 17MA02 "Patienter med hæmatologiske komplikationer" or as a per day ICU cost of DKK 33 312 timed by the average days spend in the ICU (5 days). The cost of tocilizumab was sourced from medicinpriser.dk [46] and the DRG 17MA98 was used for the administration cost [47] An overview of the costs associated with a CRS event is detailed in Table 30 below.

Table 30: Overview of cytokine release syndrome costs using detailed costs (all costs in DKK)

	Daily cost/unit cost per infusion [8]/ DKK	Duration (days) /# of doses	Total cost per CRS event DKK
ICU admission	36 700	5 days	183 507
Tocilizumab treatment	6 367	1.08 doses	6 857
Tocilizumab administration	3 600	1.08 doses	3 403

Sources: DRG: [47]; CSR: [23]; CIMBTR: [55]
Abbreviation: CRS: Cytokine release syndrome

The costing of each AE was based on their grade 3 and 4 definition as listed in the Common Terminology Criteria for Adverse Events (CTCAE). This was done to estimate whether each AE would likely be captured in other identified AEs, required hospitalisation or if they could be managed in the outpatient setting. AEs experienced by more than 5% of patients in either arm were included. A full list of AEs included in the model, their DRG codes, costs and frequencies are detailed in Table 31 below. A detailed description on choices of costs can be found in sheet "AE cost Input" of the attached health economic model.

Table 31: Detailed overview of costs and frequency of Grade 3/4 AEs included in the model (all costs in DKK)

Grade 3/4 AEs	Tisagenlecleucel	CORAL	Cost per AE event	Code	Year of cost	Description
Anaemia	[redacted]		9 030	16PR02	2023	"Transfusion af blod, øvrig" costed twice. 1 hour per infusion
Anorexia	[redacted]		0			Assumed without cost. Common side effect and managed through routine follow-up or treatment stop.
CRS	[redacted]		183 507			See Section 8.7.5.1 above.
Fatigue	[redacted]		0			CTACE classifies as "not relieved by rest". Assumed to be part of routine follow-up and infers no additional costs.
Febrile neutropenia	[redacted]		17 165	18MA09	2023	Febrile neutropenia is a serious side effect and is managed through examination of underlying causes. These additional costs are assumed to be

	[redacted]				captured in other reported AEs. DRG text: "observation for infektion eller parasitær sygdom". 4 hour patient time
Hypokalaemia	[redacted]	21 236	05MA07	2023	Hospitalisation is indicated. Indicative of arythmia. "Hjertearytmi og synkope" is used. 1 day patient time
Hypophosphatemia	[redacted]	68 629	16MA11	2023	Hospitalisation is indicated "Observation for sygdom i blod og bloddannende organer". 3 days patient time
Hypotension	[redacted]	21 326	05MA07	2022	Hospitalisation is indicated "Hjertearytmi og synkope" is chosen, as fainting is a symptom of Hypotension. 1 day patient time
Infection	[redacted]	65 531	04MA06	2023	Hospitalisation is indicated "Infektioner og betændelse i luftveje, pat. 0-64 år". 3 days patient time
Neutropenia	[redacted]	0			Reference value, it is assumed that symptomatic occurrences is captured in other reported AEs like infection and is therefore not costed.
Neutrophil count decreased	[redacted]	0			Reference value, it is assumed that symptomatic occurrences are captured in other reported AEs.
Paraesthesia	[redacted]	0			Treatment consists of lowering chemo dose. Assumed to be managed as part of routine follow-up.
Platelet count decreased	[redacted]	3 969	16PR02	2023	Reference value. Assumed to be managed as part of routine follow-up. A single DRG for transfusion of blood is costed. "Transfusion af blod, øvrig"
Pyrexia	[redacted]	0			Assumed to be part of other reported AEs. Has not been costed to avoid double counting. For reference Grade 3 is 40,0 C fever for less than 24 hours. Grade 4 is 40,0 C fever for more than 24 hours.

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Pneumonia	[redacted]	65 531	04MA06	2023	Hospitalisation indicated. "Infektioner og betændelse i luftveje, pat. 0-64 år". 3 days patient time
Stomatitis	[redacted]	51 949	18MA08	2023	Hospitalisation indicated "Andre infektioner eller parasitære sygdomme". 3 days patient time
Thrombocytopenia	[redacted]	3 969	16PR02	2023	Reference value. Assumed to be managed during routine follow-up. Costed with "Transfusion af blod, øvrig"
Vomiting	[redacted]	45 056	06MP15	2023	Grade 3 advises tube-feeding. Grade 4 is life-threatening. "Øvrige indgreb på spiserør, mavesæk og tolvfingertarm, pat. mindst 18 år". 3 days patient time
White blood cell count decreased	[redacted]	3 969	16PR02	2023	Reference value. Assumed to be managed as part of routine follow-up. A single DRG for transfusion of blood is costed. "Transfusion af blod, øvrig"
Total AE costs (not including B-cell aplasia or CRS)	**27 510**	**18 094**			

Sources: DRG: [8]; JULIET [16]; Corazzelli et al. 2009 [34]

Abbreviation: AE Adverse event

8.7.5.2 Long term adverse event

The cost applied to B cell aplasia was estimated by multiplying drug costs of intravenous immunoglobulin (IVIG), administration costs, percentage of patient using IVIG and the number of administrations per patient on average. The calculated average cost per patient was estimated at DKK 32 493 [23, 46, 47]

Table 32: Drug costs, administration cost and vial distribution of IVIG treatment

Defined dosing	Package size /mg	Price per vial or package /DKK [7]	Average dose per infusion /mg	Number of vials per infusion [18]	Number of infusions per cycle	Administration cost per infusion /DKK [8]
400mg/kg every 4 weeks	10000	6 200	31 404	3.14	1	3 160
	1000	620		0		

Source: [46, 47]

Table 33: Estimated average cost of IVIG treatment for tisagenlecleucel patients

Percentage of patients with IVIG	Total monthly drug cost/DKK	Total monthly admin cost/DKK [8]	Mean number of IVIG use	Total IVIG cost/DKK

[redacted]	19 470	3 160	4.0	[redacted]

Source: [23, 46, 47]
Abbreviation: IVIG: intravenous immunoglobulin

8.7.6 Post progression costs

Monthly post progression costs were sourced from Muszbek 2016 [56], converted to DKK with exchange rates at publication and inflated to 2023 costs using valutakurser.dk [48] and CPI index from Danmarks Statistik [49]. The estimated post progression cost was DKK 33 211.

8.7.7 Terminal care costs

All patients who transitioned to death were assumed to incur terminal care costs for the last cycle before death. Terminal care cost was based on Round 2015 [57] which estimated end-of-life treatment costs for four large cancers: breast, colorectal, lung, and prostate. The cost estimate for end-of-life treatment was weighted evenly across all four types of cancer, converted to DKK using valutakurser.dk [48], exchange rates at time of publication and inflated to current DKK values using CPI data from Danmarks Statistik [49] and resulted in an end-of-life cost of DKK 119 289.

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8.8 Results

8.8.1 Base case overview

Table 34 Base case overview

	Included
Comparator	Chemotherapy
Type of model	Decision tree and partitioned survival model
Time horizon	28 years (lifetime)
Treatment line	3rd line +. Subsequent treatment lines not included.
Measurement and valuation of health effects	Health-related quality of life measured with SF-36 in JULIET mapped to EQ-5D
Included costs	Pharmaceutical costs Follow-up costs Hospital costs Costs of AEs
Parametric function for PFS	Intervention: Spline with two knots Comparator: HR between OS and PFS for intervention
Parametric function for OS	Intervention: Spline with two knots Comparator: Spline with single knot
Other important assumptions	OS is set equal to background mortality with SMR adjustment at month 61 Costs are based on DRG rates when available

8.8.2 Base case results

[redacted]

Table 35 Base case results, confidential rebate (all costs in DKK)

Per patient	Intervention	Comparator	Difference
Life years gained			
Total life years gained	[redacted]		
Life years gained, pre-progression			
Life years gained, post-progression			
QALYs			
Total QALYs	[redacted]		
QALYs, pre-progression			
QALYs, post progression			

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Per patient	Intervention	Comparator	Difference
QALYs, adverse events	[redacted]		
QALYs, stem cell transplant			
Costs			
Total costs	[redacted]		
Pre-treatment			
Treatment			
• *Drug/procedure*			
• *Administration*			
• *Hospitalisation*			
AEs			
Follow-up cost before progression			
Subsequent SCT3			
Cost post progression			
Terminal care			
Incremental results	Intervention vs. Comparator		
Cost per life year gained	[redacted]		
ICER (per QALY)			

Table 36 Base case results, list price, PPP (DKK)

Per patient	Intervention	Comparator	Difference
Life years gained			
Total life years gained	[redacted]		
Life years gained, pre-progression			
Life years gained, post-progression			
QALYs			
Total QALYs	[redacted]		
QALYs, pre-progression			
QALYs, post progression			
QALYs, adverse events			
QALYs, stem cell transplant			
Costs			

Per patient	Intervention	Comparator	Difference
Total costs	[redacted]		
Pre-treatment			
Treatment			
• *Drug/procedure*			
• *Administration*			
• *Hospitalisation*			
AEs			
Follow-up cost before progression			
Subsequent SCT3			
Cost post progression			
Terminal care			
Incremental results	**Intervention vs. Comparator**		
Cost per life year gained	[redacted]		
ICER (per QALY)			

8.9 Sensitivity analyses

Select inputs were included in scenario analysis to show their overall impact on the results. Below in Table 37, these scenario analyses are presented.

8.9.1 Deterministic sensitivity analyses

Below, in Table 37 the results of the scenario analysis and select one way sensitivity analyses are presented. In the two-way sensitivity analysis, the parameters that had the highest impact on the results are the HR between JULIET and CORAL, the treatment cost of tisagenlecleucel, the discounting and the starting age Figure 7. From the two-way sensitivity analysis, the model is robust and varying key parameters does not change the ICER significant. Overall, the ICER remain within a reasonable threshold. For the scenario analysis, choosing the HR between PFS of OS from the literature, a short time horizon and using observed KM data for the trial period has the largest impact on the overall results. As with the two-way sensitivity analysis, the scenario analyses did not show any major changes to the ICER, when changing key inputs.

Table 37 Scenario analysis

	Change	Reason / Rational / Source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY)
Base case	-	-			
Hazard Ratio (HR) Overall Survival (OS)		Lower CI from ITC [24]			
		HR from ITC [24]			
		Upper CI from ITC [24]			
SMR of long-term survivors	0.69	Lower CI			
	1.74	Upper CI			
Health state utility - PFS (95% CI)		-SE*1.96			
		+SE*1.96			
Treatment cost tisagenlecleucel		- 25%			
		+ 25%			
Post progression cost	24 909	- 25%			
	45 514	+ 25%			
Discount weights rate for cost and effectiveness	0%				
	6%				
Starting age	60				
	84				
HR between CORAL OS and PFS from literature	HR = 0.65	Gisselbrecht 2010 [9]			
Health state utility - NICE pixantrone STA, manufacturer submission		Validation of utility weights			
Health state utility - NICE pixantrone STA, NICE recommendation		Validation of utility weights			
Health state utility - Chen 2017 [58]		Validation of utility weights			
Time horizon - 20 years		Impact of time			
Time horizon - 10 years		Impact of time			
Efficacy per parametric functions (weighted AIC) during trial period		Validation of parametric fit			
Use HR adjusted curve instead of observed data for CTL019 OS extrapolation from month 0 till year 5		Validation of parametric function			
Use observed ITT data from trial for tisagenlecleucel		Impact of extrapolation of KM data			

	Change	Reason / Rational / Source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY)
Consider continuous use of IVIG until median time to B-cell recovery		Maximum potential impact B-cell aplasia	[redacted]		

Figure 7 Two-way sensitivity analysis of top 20 impactful parameters

[redacted]

Below, in

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In Table 38 the ICER, when comparing tisagenlecleucel to chemotherapy, is depicted. At cost 0, the ICER remains in the upper west quarter (more costly and more effective), which is due to the longer time alive patients experience when treated with tisagenlecleucel, thereby accruing more costs.

Table 38 Overview of ICERs at different price points of tisagenlecleucel (DKK)

Cost of intervention DKK	ICER DKK/QALY

8.9.2 Probabilistic sensitivity analyses

The probabilistic sensitivity analysis (PSA). Showed a tight spread in the 5 000 iterations that were run with an average ICER of xxxxxxxxxxx and the deterministic result almost perfectly centred. Further, the cost-effectiveness acceptability plot showed almost 0% acceptability, until it quickly rises between xxxxxxxxxxx in willingness to pay and xxxxxxxxxxx. in willingness to pay to an acceptability of more than 90%. A full overview of the parameters included in the PSA are detailed in Appendix J.

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Figure 8 scatter plot of the probabilistic sensitivity analysis of tisagenlecleucel vs. chemotherapy

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Figure 9 Cost effectiveness acceptability curve the probabilistic sensitivity analysis of tisagenlecleucel vs. chemotherapy

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9. Budget impact analysis

The budget impact analysis was based on the assumption that 3 patients yearly would receive Kymriah for the treatment of DLBCL in the 3rd line setting and beyond. This is in line with the discounted price offer sent to AMGROS. If more patients are treated, this would effectively lower the price of Kymriah® changing the relative budget impact of Kymriah® per patient, but also lower the ICER related to treatment with Kymriah®. In the cost effectiveness model, a dynamic budget impact model is included. In the budget impact sheet, the budget impact, the total budget of eligible 3rd line DLBCL patients and the budget of those expected to be treated with Kymriah® in case of a positive reimbursement decision, is presented.

Number of patients

Table 39 Number of patients expected to be treated over the next five-year period - if the pharmaceutical is introduced

	Year 1	Year 2	Year 3	Year 4	Year 5
For the pharmaceutical under consideration					
Kymriah ®	3	3	3	3	3
SoC	14	14	15	15	15
Total number of patients	17	17	18	18	18

Table 40 Number of patients expected to be treated over the next five-year period - if the pharmaceutical is NOT introduced

	Year 1	Year 2	Year 3	Year 4	Year 5
For the pharmaceutical under consideration					
Kymriah ®	0	0	0	0	0
SoC	17	17	17	17	17
Total number of patients	17	17	17	17	17

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Expenditure per patient

The costs included in the budget impact model are the same as those included in the health economic analysis, but with undiscounted costs. For both arms, the majority of the costs occur in year one, with approximately 95% of the costs associated with Kymriah® treatment and 85% associated with chemotherapy, largely due to the cost of chemotherapy, but also subsequent stem cell transplant and end of life treatment.

Table 41 Costs per patient per year (DKK) - if the pharmaceutical is recommended

	Year 1	Year 2	Year 3	Year 4	Year 5
Kymriah® cost per patient					
Pre-treatment	[redacted]				
Treatment					
Drug/procedure					
Administration					
Hospitalization					
AEs					
Follow-up cost before progression					
Subsequent SCT					
Cost post progression					
Terminal care					
Total costs					

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Table 42 Costs per patient per year (DKK) - if the pharmaceutical is NOT recommended

	Year 1	Year 2	Year 3	Year 4	Year 5
Chemotherapy cost per patient					
Pre-treatment					
Treatment					
Drug/procedure					
Administration					
Hospitalisation					
AEs					
Follow-up cost before progression					
Subsequent SCT					
Cost post progression					
Terminal care					
Total costs					

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Budget impact

The budget impact of Kymriah is expected to be approximately [redacted], if a positive reimbursement decision is reached. The relative low budget impact is due to the low number of patients treated. Conversely, in an extreme scenario, if all 18 eligible patients were treated, the total budget impact would be approximately [redacted].

Table 43 Expected budget impact of recommending the pharmaceutical for the current indication (DKK)

	Year 1	Year 2	Year 3	Year 4	Year 5
The pharmaceutical under consideration is recommended	[redacted]				
Of which: Drug costs	3 775 386	3 775 386	3 775 386	3 775 386	3 775 386
Of which: Hospital costs	1 588 442	1 764 324	1 881 241	1 962 301	2 019 995
Of which: Adverse event costs	236 808	236 808	236 808	236 808	236 808
Minus: **The pharmaceutical under consideration is NOT recommended**	[redacted]				
Of which: Drug costs	125 893	125 893	125 893	125 893	12 5893
Of which: Hospital costs	1 351 834	1 455 270	1 526 125	1 572 004	1 603 102
Of which: Adverse event costs	54 281	54 281	54 281	54 281	54 281
Budget impact of the recommendation	[redacted]				

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10. Discussion on the submitted documentation

This reapplication is based on an indirect comparison between data from a single arm clinical study with tisagenlecleucel and historical real-world data. The lack of a comparator arm in the pivotal tisagenlecleucel study is due to the fact that there is no established 3rd line treatment option for patients with r/r DLBCL, and these patients in general have a very poor prognosis.

This application is based on unpublished and including 5-year data (data-cut December 2022). However, the results are consistent with similar analyses which was published by Maziarz in 2022, which was based on data-cut for the JULIET study in 2020.

With the access to individual patient data from the CORAL study follow-up population it has now been possible to conduct an indirect comparison between balanced patient populations, and to further adjust the CORAL follow-up population to reflect the JULIET population. By including the patient level data from CORAL patients, the matched indirect treatment comparison generates a robust comparison, compared to the comparison rejected in the originally submitted comparison, as this enables weighting the individual patients and their base line characteristics. Thereby the observed effect size from both studies more accurately assesses the endpoints from the CORAL study, as each unique patient would be assigned a weight based on each prognostic factor present for each patient.

More than [redacted] of patients were still alive at 60 months in the JULIET study, and with a HR of [redacted] vs. SoC in the unadjusted analysis, tisagenlecleucel was shown to provide substantial benefit to patients with r/r DLBCL. In addition, when the CORAL FAS population was further adjusted, considering confounding factors, the benefit was even better, with a HR of [redacted], regardless of method of adjustment. Thus, the results seem robust.

As described in the re-assessment form, there was a recent presentation at ASH 2022 on patients treated in Denmark for r/r DLBCL in the 3rd line setting. The findings of this review show a greater survival rate, than observed in the comparator arm used in the health economic model. A key driver for a positive OS outcome among the patients in the Danish abstract was chemotherapy treatment with DHAP or ICE. These regimens are often used as conditioning before ASCT, indicating the inclusion of patients not comparable to JULIET patients. Since ASCT eligible patients were excluded from the JULIET trial, this would skew the baseline patient characteristics to favour a positive outcome in the Danish population. Additionally, 11% of the Danish patients were treated in a clinical trial setting, which also could have an impact on the OS from the Danish registry study.

According to the Danish Lymphoma group treatment guidelines for treatment with CAR-T, only patients who are eligible for ASCT treatment, should be considered for treatment with CAR-T. This imposes a situation, where the patient population in scope for treatment in Denmark have not been studied in a clinical study setting. The effect size of treatment with tisagenlecleucel in the Danish setting is likely to be higher than what was observed in JULIET, since one of the exclusion criteria for the JULIET study, was eligibility for an ASCT at enrolment. This is further solidified in the indirect treatment comparison since the effect of the CORAL is lower in the adjusted analysis than in the unadjusted analysis.

Overall, the presented health economic model and the results hereof presents, to our knowledge, the best available comparison, since patient level data was included from the CORAL arm. The overall results show Kymriah® is a cost-effective treatment option for patients in the 3rd line and beyond treatment setting in Denmark with a base case cost of [redacted] per QALY.

11. List of experts

NA

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13. Appendix A

Literature search for efficacy and safety of intervention and comparator(s)

The literature search presented below for this reapplication, consists of the systematic literature search conducted for the initial application on 31 October 2018, and a search for publications with tisagenlecleucel clinical trial data from 31 October 2018 to 31 October 2023. [4]

Search strategy

Original literature search

Table 44 Bibliographic databases included in the literature search

Database	Platform	Relevant period for the search	Date of search completion
MEDLINE	Ovid	Until date of search	31.10.2018
CENTRAL	Cochrane	Until date of search	31.10.2018

The search strategy developed to meet the objective of the literature search was defined by the inclusion and exclusion criteria in Table 45.

Table 45 Inclusion and exclusion criteria for literature selection

Inclusion criteria
• Population: Adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) after two or more lines of systemic therapy • Intervention: Kymriah (tisagenlecleucel) • Comparator(s): Salvage chemotherapy, including GDP±R (gemcitabine, dexamethasone, cisplatin ± rituximab), DHAP±R (cisplatin, cytarabine, dexamethason ± rituximab), ICE±R (ifosfamide, carboplatine, etoposide ± rituximab) • Outcomes: overall survival (OS), adverse events (AEs), health-related quality of life (HRQoL), complete remission (CR) rate, transplant-related mortality (TRM), duration of response (DoR), and event-free survival (EFS). • Study design: Randomized clinical trial, single arm trials, prospective studies • Language restrictions: English, Danish, Swedish, and Norwegian
Exclusion criteria
• Population: paediatric DLBCL patients, PMBCL patients, Mantle-cell lymphoma patients, Burkitt's lymphoma patients and, DLBCL patients in 1st salvage attempt (refractory only, or in first relapse) • Intervention: Not the CAR-T cells of interest • Comparator(s): no use of salvage chemotherapy combinations: GDP±R, DHAP±R, or ICE±R • Outcomes: No outcomes of interest • Study design: case reports, editorials, opinion pieces, reviews, retrospective studies • Language restrictions: Any other language than English, Danish, Swedish, and Norwegian • Other: records published prior to 2007

The search strings for the original search are shown in Table 46 and Table 47 below.

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Table 46 Search strategy and results for Medline via OVID

Line no.	Search terms	Number of records
1	exp Lymphoma$, Large B-Cell, Diffuse/	18119
2	(diffuse large b cell lymphoma? or DLBCL).ti,ab.	11387
3	(primary and (mediastinal or mediastinum) and large b-cell lymphoma?).ti,kw.	183
4	(1 or 2) not 3	22964
5	exp Adult/ or adult?.ti,ab.	7214380
6	(juvenil* or paediatric* or pediatric* or child*).ti,kw.	908474
7	exp Child/	1793785
8	5 not (6 or 7)	472734
9	Recurrence/ or Neoplasm Recurrence, Local/	278072
10	(relaps* or refractory or recurren* or treatment failure or (failed adj3 (treatment or therap*))).ti,ab.	748178
11	9 or 10	838542
12	4 and 8 and 11	2061
13	exp Animals/ not Humans/	4510078
14	12 not 13	2061
15	limit 14 to (english or danish or norwegian or swedish)	1828
16	(review or editorial or letter or case reports or comment or meeting abstracts or news or technical report).pt. or (case report or review).ti.	6007397
17	15 not 16	1094
18	limit 17 to (clinical study or clinical trial, all or comparative study or multicenter study or observational study)	407
19	17 not 18	687
20	journal article.pt.	27134083
21	19 and 20	687
22	((clinical or randomi#ed or controlled or comparative or single arm or multicent* or multi-cent* or single cent* or intervention or interventional or observational or prospective or retrospective) adj4 (trial? or study or studies)).ti,ab.	1656354
23	((phase 2 or phase 3 or phase 4) adj4 (trial? or study or studies)).ti,ab.	12524
24	(phase adj (II or two or III or three or IV or four) adj4 (trial? or study or studies)).ti,ab.	57750
25	(open study or open label or ((single or doubl* or triple) adj (blind* or mask*))).ti,ab.	195232
26	Retrospective study/ or Prospective study/	1180208
27	or/22-26	2441333
28	21 and 27	308
29	18 or 28	715
30	limit 29 to yr="2007-Current"	511
31	(tisagenlecleucel or kymriah* or CTL019 or "CTL 019").ti,ab,kf,nm.	87
32	(GDP or RGDP or R-GDP).ti,ab,kf. or GDP protocol.px,nm.	13618
33	Deoxycytidine/aa or (deoxycytidine or gemcitabine).ti,ab,kf,nm.	27097
34	Dexamethasone/ or dexamethasone.ti,ab,kf,nm.	67596
35	Cisplatin/ or cisplatin.ti,ab,kf,nm.	69609
36	(DHAP or RDHAP or R-DHAP).ti,ab,kf. or DHAP protocol.px,nm.	682
37	Cytarabine/ or (cytarabine or ara-c or arabinocytidine or cytosine arabinoside).ti,ab,kf,nm.	18868
38	(ICE or RICE or R-ICE).ti,ab,kf. or ICE protocol 3.px,nm.	74832
39	Ifosfamide/ or (ifosfamide or iphosphamide).ti,ab,kf,nm.	6924

40	Carboplatin/ or carboplatin.ti,ab,kf,nm.	16263
41	Etoposide/ or etoposide.ti,ab,kf,nm.	24189
42	(salvage adj3 (treat* or therap* or chemotherap*)).ti,ab. or Salvage Treatment/ or (autologous stem cell transplant*).ti,ab.	24707
43	or/31-42	306575
44	30 and 43	207

Table 47 Search strategy and results for CENTRAL via Cochrane Library

Line no.	Search terms	Number of records
1	[mh "Lymphoma, Large B-Cell, Diffuse"]	328
2	(diffuse large b cell lymphoma* or DLBCL):ti,ab,kw	1140
3	(primary and (mediastinum or mediastinal) and large and "b cell" and lymphoma*):ti,kw	30
4	(#1 or #2) not #3	1122
5	[mh Adult] or adult*:ti,ab,kw	509182
6	#4 and #5	519
7	[mh Child] or (juvenil* or paediatric* or pediatric* or child* or juvenile or adolescent*):ti,kw	183959
8	#6 not #7	411
9	[mh recurrence] or [mh "neoplasm recurrence, local"]	15074
10	("recurrent disease" or relaps* or refractory or recurren* or "treatment failure"):ti,ab,kw or (failed near/2 (treatment or therap*)):ti,ab,kw	87214
11	#9 or #10	87237
12	#8 and #11	220
13	("tisagenlecleucel T" or tisagenlecleucel or kymriah* or CTL019 or "CTL 019"):ti,ab,kw	18
14	(GDP or RGDP or R-GDP):ti,ab,kw	195
15	(deoxycytidine or gemcitabine):ti,ab,kw	4549
16	dexamethasone:ti,ab,kw	8673
17	cisplatin:ti,ab,kw	10814
18	(DHAP or RDHAP or R-DHAP):ti,ab,kw	136
19	(cytarabine or ara-c or arabinocytidine or cytosine arabinoside):ti,ab,kw	2873
20	(ICE or RICE or R-ICE):ti,ab,kw	2667
21	(ifosfamide or iphosphamide):ti,ab,kw	1208
22	carboplatin:ti,ab,kw	4934
23	etoposide:ti,ab,kw	3474
24	(salvage near/3 (treat* or therap* or chemotherap*)):ti,ab,kw or [mh "Salvage Treatment"] or (autologous stem cell transplant*):ti,ab,kw	4534
25	#13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24	34122
26	#12 and #25	102
27	conference abstract:pt or nct*:au	246643
28	#26 not #27 with Publication Year from 2007 to 2018, in Trials	32

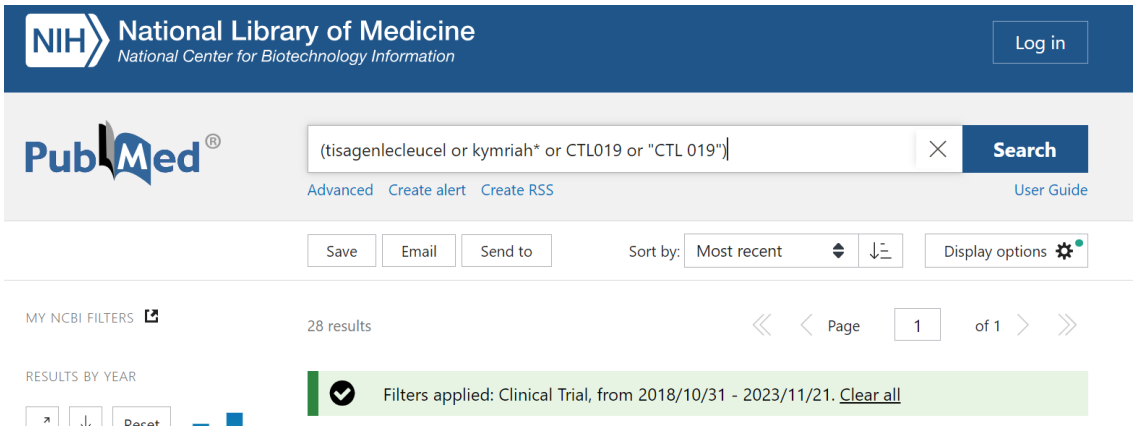
In addition, the peer-reviewed journal article of the pivotal phase II trial JULIET (C2201), was not published yet at the search date, and was identified through other sources. It is included in the updated literature search.

Updated literature search

Table 48 Bibliographic databases included in the literature search

Database	Platform	Relevant period for the search	Date of search completion
MEDLINE	Pubmed	31.10.2018	31.10.2023
CENTRAL	Cochrane	31.10.2018	31.10.2023

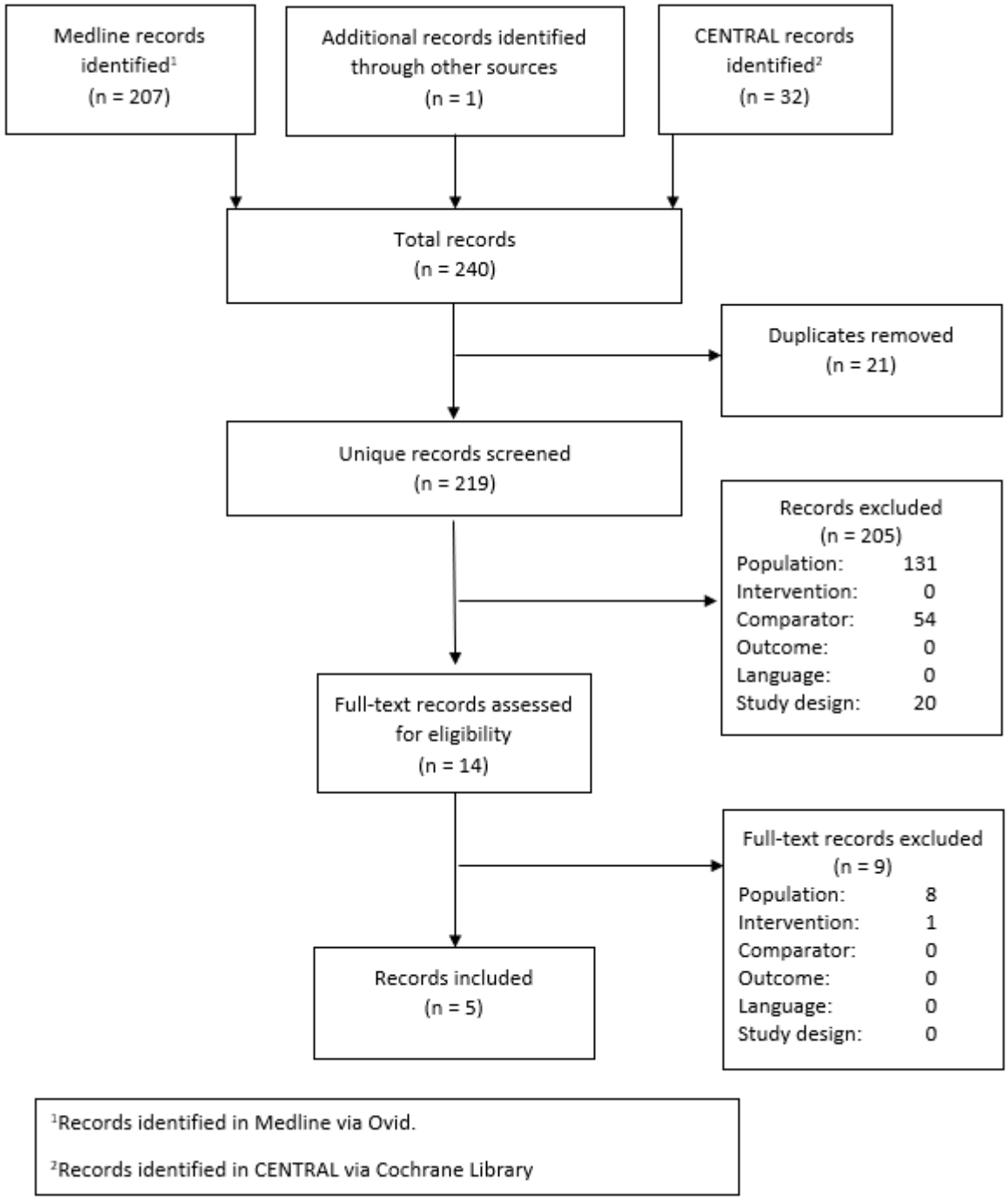
Due to the limited number of published articles with tisagenlecleucel since 2018, the search team was limited to for (tisagenlecleucel or kymriah* or CTL019 or "CTL 019") for the MEDLINE database, and to ("tisagenlecleucel T" or tisagenlecleucel or kymriah* or CTL019 or "CTL 019") for the CENTRAL database.



Systematic selection of studies

The outcome of the searches is shown in the PRISMA flow in Figure 12 and Figure 13 below..

Figure 12 PRISMA diagram of the original literature search



Note: Two of the records included were subsequently excluded in the assessment by the Medicines Council (see Table 49), thus leaving three included records. One of the included records was the publication of the JULIET study (identified through other sources, not yet published). This record was also included based on the updated literature search below.

Table 49 References not included in the application. Original search.

Reference	Reason for exclusion
Witzig TE, et al. Salvage chemotherapy with rituximab DHAP for relapsed non-Hodgkin lymphoma: A phase II trial in the North Central Cancer Treatment Group. Leuk Lymphoma 2008;49:1074–80.	Non-DLBCL patients included
Simpson L, et al. Effectiveness of second line salvage chemotherapy with ifosfamide, carboplatin, and etoposide in patients with relapsed diffuse large B-cell lymphoma not responding to cis-platinum, cytosine arabinoside, and dexamethasone. Leuk Lymphoma 2007;48:1332–7.	Single center study (Mayo clinic), 1/3 had no prior rituximab. Patients included from 1998 to 2005.
Sarid N, et al. Reduced-dose ICE chemotherapy ± rituximab is a safe and effective salvage therapy for fit elderly patients with diffuse large B-cell lymphoma. Leuk Lymphoma 2016;57:1633–9	1st salvage attempt, elderly patients on dose reduced ICE±R
Nagle SJ, et al. Outcomes of patients with relapsed/refractory diffuse large B-cell lymphoma with progression of lymphoma after autologous stem cell transplantation in the rituximab era. Am J Hematol 2013;88:890–4.	Single center (UPenn) restrospective study, confirms CORAL ext-1, e.g. 9.9 vs 10.0 months median OS, but the study is smaller and hence inferior to CORAL ext-1
Kuruvilla J, et al. Salvage chemotherapy and autologous stem cell transplantation for transformed indolent lymphoma: a subset analysis of NCIC CTG LY12. Blood 2015;126:733-738.	1st salvage attempt
Kochenderfer JN, et al. Lymphoma remissions caused by anti-CD19 chimeric antigen receptor T cells are associated with high serum interleukin-15 levels. J Clin Oncol 2017;35:1803–13.	Not the CAR-T of interest
Cuccuini W, et al. MYC+ diffuse large B-cell lymphoma is not salvaged by classical R-ICE or R-DHAP followed by BEAM plus autologous stem cell transplantation. Blood 2012;119:4619-4624.	1st salvage attempt
Crump M, et al. Outcomes in refractory diffuse large B-cell lymphoma: Results from the international SCHOLAR-1 study. Blood 2017;130:1800–8.	Included non-DLBCL patients
Calvo-Villas JM, et al. Effect of addition of rituximab to salvage chemotherapy on outcome of patients with diffuse large B-cell lymphoma relapsing after an autologous stem-cell transplantation. Ann Oncol 2010;21:1891–7.	Approximately 3 out of 4 patients did not receive prior rituximab
Schuster SJ, Svoboda J, Chong EA, Nasta SD, Mato AR, Anak Ö, et al. Chimeric Antigen Receptor T Cells in Refractory B-Cell Lymphomas. N Engl J Med 2017;377:2545–54.	Excluded by the Medicines Council, due to study design (case-series-study)
Van Imhoff GW, McMillan A, Matasar MJ, Radford J, Ardeshna KM, Kuliczkowski K, et al. Ofatumumab versus rituximab salvage chemoimmunotherapy in relapsed or refractory diffuse large B-cell lymphoma: The ORCHARRD study. J Clin Oncol 2017;35:544–51.	Excluded by the Medicines Council due to patient population (one previous treatment line)

Figure 13 PRISMA diagram of the updated literature search

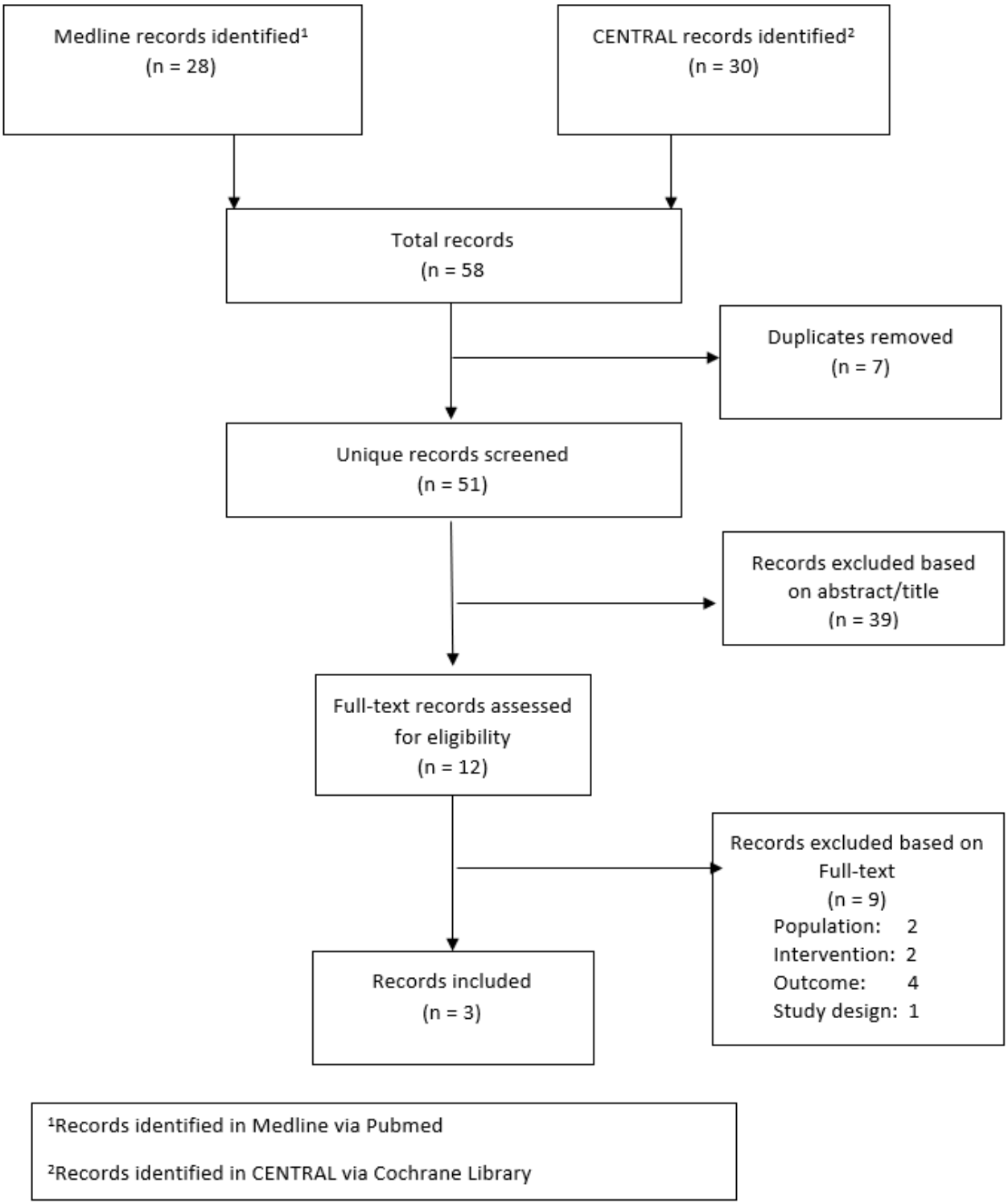


Table 50 References not included in the application. Updated search

Reference	Reason for exclusion
Thudium Mueller K, Grupp SA, Maude SL, et al (2021) Tisagenlecleucel immunogenicity in relapsed/refractory acute lymphoblastic leukemia and diffuse large B-cell lymphoma. Blood Adv 5:4980–4991. https://doi.org/10.1182/bloodadvances.2020003844	No relevant outcome
Sesques P, Ferrant E, Safar V, et al (2020) Commercial <scp>anti-CD19 CAR</scp> T cell therapy for patients with relapsed/refractory aggressive B cell lymphoma in a European center. Am J Hematol 95:1324–1333. https://doi.org/10.1002/ajh.25951	Retrospective real world data (study design)
Park JH, Nath K, Devlin SM, et al (2023) CD19 CAR T-cell therapy and prophylactic anakinra in relapsed or refractory lymphoma: phase 2 trial interim results. Nat Med 29:1710–1717. https://doi.org/10.1038/s41591-023-02404-6	Mixed populations and interventions
Maziarz RT, Schuster SJ, Romanov V V., et al (2020) Grading of neurological toxicity in patients treated with tisagenlecleucel in the JULIET trial. Blood Adv 4:1440–1447. https://doi.org/10.1182/bloodadvances.2019001305	Focus on grading method (outcome)
Jaeger U, Worel N, McGuirk JP, et al (2023) Safety and efficacy of tisagenlecleucel plus pembrolizumab in patients with r/r DLBCL: phase 1b PORTIA study results. Blood Adv 7:2283–2286. https://doi.org/10.1182/bloodadvances.2022007779	All patients received combination treatment (intervention)
Goto H, Makita S, Kato K, et al (2020) Efficacy and safety of tisagenlecleucel in Japanese adult patients with relapsed/refractory diffuse large B-cell lymphoma. Int J Clin Oncol 25:1736–1743. https://doi.org/10.1007/s10147-020-01699-6	Subgroup analysis for JULIET population. Not relevant in a Danish setting
Fan L, Wang L, Cao L, et al (2022) Phase I study of CBM.CD19 chimeric antigen receptor T cell in the treatment of refractory diffuse large B-cell lymphoma in Chinese patients. Front Med 16:285–294. https://doi.org/10.1007/s11684-021-0843-8	Not tisagenlecleucel
Awasthi R, Pacaud L, Waldron E, et al (2020) Tisagenlecleucel cellular kinetics, dose, and immunogenicity in relation to clinical factors in relapsed/refractory DLBCL. Blood Adv 4:560–572. https://doi.org/10.1182/bloodadvances.2019000525	Outcomes not relevant
Chen AJ, Zhang J, Agarwal A, Lakdawalla DN (2022) Value of Reducing Wait Times for Chimeric Antigen Receptor T-Cell Treatment: evidence From Randomized Controlled Trial Data on Tisagenlecleucel for Diffuse Large B-Cell Lymphoma. Value in health 25:1344-1351. https://doi.org/10.1016/j.jval.2022.02.007	Outcomes not relevant

Table 51 References included in the application. Original and updated search

Reference
Outcome of patients with relapsed diffuse large B-cell lymphoma who fail second-line salvage regimens in the International CORAL study. (CORAL EXT-2) *Van Den Neste, Bone Marrow Transplantation, 2016* [17]
Outcomes of diffuse large B-cell lymphoma patients relapsing after autologous stem cell transplantation: an analysis of patients included in the CORAL study. (CORAL EXT-1) *Van Den Neste, Bone Marrow Transplantation, 2017* [18]
Tisagenlecleucel in Adult Relapsed/Refractory Diffuse Large B-Cell Lymphoma, *Schuster, New England Journal of Medicine, 2018* [19]
Long-term clinical outcomes of tisagenlecleucel in patients with relapsed or refractory aggressive B-cell lymphomas (JULIET): a multicentre, open-label, single-arm, phase 2 study *Schuster, Lancet Oncol, 2021* [20]
Indirect comparison of tisagenlecleucel and historical treatments for relapsed/refractory diffuse large B-cell lymphoma. *Maziarz, Blood Advances, 2022* [3]

Internal validity of selected studies

Both studies are uncontrolled, single arm studies, thus the internal validity of the studies is low.

Quality assessment

The literature search for the original application was performed and documented in accordance with the methodology recommended by the Medicines Council. As the reapplication concerns the final 5-year data from the JULIET study, the updated search has been limited to identify clinical trial data for tisagencleucel.

Unpublished data

The JULIET study has now been completed with 5-year follow-up (data-cut December 2022), and Novartis has obtained access to patient-level data from the CORAL extension studies from the Lymphoma Academic Research Organisation (LYSARC) [4]. Thus, this application is based on indirect comparisons of patient level data from the JULIET final study report (data on file) and the CORAL follow-up data (data on file), allowing a comparison between matched populations.

An indirect treatment comparison of patient-level data from the JULIET study, with data-cut February 20, 2020, vs. CORAL follow-up data was published in 2022 [3]

Presentation of the data based on 60-month data is planned at the European Hematology Association congress in June 2024 with subsequent publication in a peer-reviewed journal.

Appendix B

Main characteristics of included studies

Table 52 Main characteristics of the JULIET study

Trial name: JULIET	**NCT number: NCT02445248**
Objective	Evaluate the efficacy of tisagenlecleucel in r/r DLBCL defined as the overall response rate (ORR), which includes complete response and partial response based on the Lugano Classification [30] as determined by a central independent review committee.
Publications – title, author, journal, year	Tisagenlecleucel in Adult Relapsed or Refractory Diffuse Large B-Cell Lymphoma. Schuster SJ, et al. NEJM 2019 [19] Long-term clinical outcomes of tisagenlecleucel in patients with relapsed or refractory aggressive B-cell lymphomas (JULIET): a multicentre, open-label, single-arm, phase 2 study. Schuster SJ, et al. Lancet Oncol 2021 [20] Indirect comparison of tisagenlecleucel and historical treatments for relapsed/refractory diffuse large B-cell lymphoma. Maziarz RT, et al. Blood Adv [25]2022 [3] CCTL019C2201 Final Clinical Study Report. December 2022. Data on file
Study type and design	This pivotal study (C2201 – JULIET) is a single arm, open-label, multi-center, Phase 2 study conducted to determine the efficacy and safety of tisagenlecleucel in adult patients with r/r DLBCL
Sample size (n)	Included in the study (IIT) n=166 Treated with tisagenlecleucel (Safety population): n=115 Full Analysis Set: n=114 (one patient was excluded due to wrong diagnosis)

Main inclusion and exclusion criteria	**Inclusion Criteria:**
	
	1. Written informed consent was obtained prior to any screening procedures
	2. Patients were ≥ 18 years of age
	3. Histologically confirmed DLBCL at last relapse (by central pathology review before enrolment).
	   a. Sufficient formalin-fixed paraffin-embedded tumour samples were available for histological and molecular subtype (cell of origin) testing along with a corresponding pathology report. A recent tumour sample obtained for the purpose of the study was submitted; however, if not clinically feasible, an archival tumour biopsy from the most recent relapse was submitted instead. Excisional biopsies were submitted wherever possible; in cases where this was not possible, a core needle biopsy was allowed. Fine needle aspiration was not allowed.
	4. Relapsed or refractory disease after ≥ 2 lines of chemotherapy, including rituximab and anthracycline, and either having failed autologous SCT, or being ineligible for or not consenting to autologous SCT.
	5. Measurable disease at time of enrolment:
	   a. Nodal lesions greater than 20 mm in the long axis, regardless of the length of the short axis
	   b. Extranodal lesions (outside lymph node or nodal mass, but including liver and spleen) ≥ 10 mm in long AND short axis
	6. Life expectancy ≥ 12 weeks

7. Eastern Cooperative Oncology Group (ECOG) performance status that was either 0 or 1 at screening
8. Adequate organ function:
    a. Renal function defined as:
        - A serum creatinine of ≤ 1.5×upper limit of normal (ULN) OR
        - Estimated glomerular filtration rate ≥ 60 mL/min/1.73 m^2
    b. Liver function defined as:
        - alanine aminotransferase (ALT) ≤ 5 times the ULN for age
        - Bilirubin ≤ 2.0 mg/dl with the exception of patients with Gilbert–Meulengracht syndrome; patients with Gilbert-Meulengracht syndrome may be included if their total bilirubin is ≤ 3.0×ULN and direct bilirubin ≤ 1.5×ULN
    c. Must have a minimum level of pulmonary reserve defined as ≤ Grade 1 dyspnoea and pulse oxygenation >91% on room air
    d. Hemodynamically stable and left ventricular ejection fraction ≥ 45% confirmed by echocardiogram or multiple uptake gated acquisition
    e. Adequate bone marrow reserve without transfusions defined as:
        - Absolute neutrophil count >1.000/mm^3
        - Absolute lymphocyte count >300/mm^3, and absolute number of CD3+ T-cells >150/mm^3
        - Platelets ≥ 50.000/mm^3
        - Haemoglobin >8.0 g/dL
9. Must have an apheresis product of non-mobilized cells accepted for manufacturing.
10. Women of child-bearing potential defined as all women physiologically capable of becoming pregnant, and all male participants used highly effective methods of contraception for at least 12 months following tisagenlecleucel infusion and until CAR T-cells were no longer present by quantitative polymerase chain reaction (qPCR) on two consecutive tests.
11. Sexually active males accepted to use a condom during intercourse for 12 months after treatment and they did not father a child in this period. A condom was used also by vasectomized men (as well as during intercourse with a male partner or sterile female partner) as white blood cells (WBCs) are a normal part of semen and transmission of tisagenlecleucel transduced cells may occur.

Exclusion Criteria:

1. Prior treatment with any prior anti-CD19/anti-CD3 therapy, or any other anti-CD19 therapy
2. Treatment with any prior gene therapy product
3. Active central nervous system (CNS) involvement by malignancy
4. Prior Allo-SCT
5. Eligible for and consenting to autologous SCT
6. Chemotherapy other than LD chemotherapy within 2 weeks of infusion
7. Investigational medicinal product within the last 30 days prior to screening. Note: Investigational therapies were not used at any time while on study until the first progression following tisagenlecleucel infusion.
8. The following medications were excluded:
    a. **Steroids:** Therapeutic doses of steroids were stopped >72 hours prior to leukapheresis and >72 hours prior to tisagenlecleucel

infusion. However, the following physiological replacement doses of steroids were allowed: <12 mg/m^2/day hydrocortisone or equivalent

b. **Immunosuppression:** Any other immunosuppressive medication was stopped ≥ 2 weeks prior to leukapheresis and ≥ 2 weeks prior to tisagenlecleucel infusion. This could include check point inhibitors (monoclonal antibodies and small molecule modulators).
c. **Antiproliferative therapies** other than LD chemotherapy within 2 weeks of leukapheresis and 2 weeks prior to infusion

- Short acting drugs used to treat leukaemia or lymphoma (e.g. TKIs, and hydroxyurea) was stopped >72 hour prior to leukapheresis and >72 hours prior to tisagenlecleucel infusion
- Other cytotoxic drugs, including low dose daily or weekly maintenance chemotherapy, were not given within two weeks prior to leukapheresis and within two weeks prior to tisagenlecleucel infusion.
- Fludarabine may be associated with prolonged lymphopenia. This was taken into consideration when evaluating the optimal timing for leukapheresis collection.

d. **Antibody use** including anti-CD20 therapy within four weeks prior to infusion or five half-lives of the respective antibody, whichever is longer. Note: Rituximab is excluded within four weeks prior to infusion.
e. **CNS disease prophylaxis** must be stopped >1 week prior to tisagenlecleucel infusion (e.g., intrathecal methotrexate)

9. Prior radiation therapy within 2 weeks of infusion
10. Active replication of or prior infection with hepatitis B or active hepatitis C (hepatitis C virus ribonucleic acid-positive)
11. Human immunodeficiency virus-positive patients
12. Uncontrolled acute life threatening bacterial, viral or fungal infection (e.g., blood culture positive ≤ 72 hours prior to infusion)
13. Unstable angina and/or myocardial infarction within 6 months prior to screening
14. Previous or concurrent malignancy with the following exceptions:

    a. Adequately treated basal cell or squamous cell carcinoma (adequate wound healing is required prior to study entry)
    b. In situ carcinoma of the cervix or breast, treated curatively and without evidence of recurrence for at least 3 years prior to the study
    c. A primary malignancy which has been completely resected and in complete remission for ≥ 5 years

15. Pregnant or nursing (lactating) women. Note: female study participants of reproductive potential had a negative serum or urine pregnancy test performed within 24 hours before lymphodepletion
16. Intolerance to the excipients of the tisagenlecleucel cell product
17. Cardiac arrhythmia not controlled with medical management
18. Prior treatment with any adoptive T cell therapy
19. Patients with T-cell rich/histiocyte rich large B-cell lymphoma, primary cutaneous large B-cell lymphoma, primary mediastinal B-cell lymphoma, Epstein-Barr virus-positive DLBCL of the elderly, Richter's transformation, and Burkitt lymphoma
20. Patients with active neurological auto immune or inflammatory disorders (e.g., Guillain-Barré Syndrome, amyotrophic lateral sclerosis.

Trial name: JULIET	NCT number: NCT02445248
Intervention	A single dose of 1 to 5 x 10^8 of autologous CTL019 transduced cells.
Comparator(s)	Single arm study
Follow-up time	For the December 2022 data-cut, the maximum follow-up time was 60.1 month. Median follow-up time was 14.55 months.
Is the study used in the health economic model?	Yes
Primary, secondary and exploratory endpoints	**Endpoints included in this application:** • Overall survival (OS) **Other endpoints:** Primary Outcome Measures: • Overall Response Rate (ORR) Secondary Outcome Measures: • Incidence and severity of adverse events (AEs) • Time to response (TTR) • Duration of overall response (DOR) • Event free survival (EFS) • Progression free survival (PFS) • In vivo cellular Pharmacokinetic (PK) profile of CTL019 transduced cells into target tissues • Incidence of immunogenicity to CTL019 • Number of Participants with presence of exposure to replication-competent lentivirus (RCL) as Assessed by quantitative polymerase chain reaction (qPCR) • Prevalence of immunogenicity to CTL019
Method of analysis	All efficacy analyses were per-protocol analyses. Overall survival, event-free survival and duration of overall response were estimated with the use of the Kaplan–Meier method. The ORR was estimated with the use of 95% confidence intervals.
Subgroup analyses	All efficacy analyses were prespecified per-protocol analyses of the population that received the study intervention.
Other relevant information	None

Table 53 Main characteristics of the CORAL study and CORAL follow-up data

Trial name: CORAL study and CORAL follow-up data	NCT number: NCT00137995
Objective	The main objective of the CORAL study was to compare two salvage regimens (R-DHAP (rituximab, dexamethasone, cytarabine, cisplatinum) or R-ICE (rituximab, ifosfamide, carboplatinum, etoposide)), followed by ASCT when feasible. Follow-up data: The CORAL investigators collected extensive follow-up data regarding patients' subsequent treatments (ie, third line and above) and long-term survival status.
Publications – title, author, journal, year	Salvage regimens with autologous transplantation for relapsed large B-cell lymphoma in the rituximab era. Gisselbrecht, Journal of Clinical Oncology, 2010 [9] Rituximab maintenance therapy after autologous stem-cell transplantation in patients with relapsed CD20+ diffuse large B-cell lymphoma: Final analysis of the collaborative trial in relapsed aggressive lymphoma. Gisselbrecht, Journal of Clinical Oncology, 2012 [10] **Subgroup follow-up, used in initial application:** Outcome of patients with relapsed diffuse large B-cell lymphoma who fail second-line salvage regimens in the International CORAL study. (CORAL EXT-2). Van Den Neste, Bone Marrow Transplantation, 2016 [17] **Subgroup follow-up, used in initial application:** Outcomes of diffuse large B-cell lymphoma patients relapsing after autologous stem cell transplantation: an analysis of patients included in the CORAL study. (CORAL EXT-1). Van Den Neste, Bone Marrow Transplantation, 2017 [18] **Indirect comparison of follow-up data (3+ line):** Indirect comparison of tisagenlecleucel and historical treatments for relapsed/refractory diffuse large B-cell lymphoma. Maziarz, Blood Advances, 2022 [3] CORAL follow-up data from the Lymphoma Academic Research Organisation (LYSARC) [4] Data on file
Study type and design	**CORAL:** Open label, randomized phase 3 trial **Follow-up data:** Prospective observational study
Sample size (n)	**CORAL:** 477 patients received 2nd line treatment **Follow-up data:** Full Analysis Set: n=170 Adjusted population: n=145
Main inclusion and exclusion criteria	**For CORAL:** Inclusion Criteria: • Patients with CD20-positive diffuse large B-cell lymphoma. Disease must be histologically proven in case of relapse or partial response. • Aged 18 to 65 years • First relapse after complete remission (CR), less than partial remission (PR) or partial response to first line treatment not achieving documented or confirmed complete remission. • Eligible for transplant

- Previously treated with chemotherapy regimen containing anthracyclines with or without rituximab.
- ECOG performance status 0 to 2.
- Minimum life expectancy of 3 months.
- Signed written informed consent prior to randomization.

Exclusion Criteria:

- Burkitt, mantle-cell and T-cell lymphoma.
- CD20-negative diffuse large cell lymphoma
- Documented infection with HIV and hepatitis B virus [HBV] (in the absence of vaccination)
- Central nervous system or meningeal involvement by lymphoma.
- Not previously treated with anthracycline-containing regimens
- Prior transplantation
- Contra-indication to any drug contained in the chemotherapy regimens.
- Any serious active disease or co-morbid condition (according to the investigator's decision and information provided in the Investigational Drug Brochure [IDB]).
- Poor renal function (creatinine level > 150µmol/l or 1.5-2.0 x upper limit of normal [ULN]); poor hepatic function (total bilirubin level > 30mmol/l [> 1.5 x ULN], transaminases > 2.5 maximum normal level) unless these abnormalities are related to the lymphoma; poor bone marrow reserve as defined by neutrophils < 1.5G/l or platelets < 100G/l, unless related to bone marrow infiltration.
- Any history of cancer during the last 5 years with the exception of non-melanoma skin tumours or stage 0 (in situ) cervical carcinoma.
- Treatment with any investigational drug within 30 days before planned first cycle of chemotherapy and during the study.
- Pregnant women
- Adult patients unable to provide informed consent because of intellectual impairment.

For the follow-up:

The inclusion/exclusion criteria from JULIET trial were considered in selecting patients from the CORAL follow-up data. The following criteria were used to select patients from CORAL follow-up data for the current analysis:

Inclusion criteria

- 18 years of age or older on potential index date (index date is defined in ICT Report [24])
- 18 years of age or older with non-missing potential index date (index date is defined in ICT Report [24])

- Histologically confirmed DLBCL or transformed lymphoma
- Relapsed or refractory disease after ≥2 lines of chemotherapy, including rituximab, and previous autologous stem cell transplantation (ASCT) was allowed
- Eastern Cooperative Oncology Group (ECOG) performance status that was either 0 or 1 within a month prior to or on the potential index date. A large proportion of patients in CORAL follow-up did not have an ECOG assessment during this period; those with a missing or unknown ECOG status during this period were included in the analyses

Exclusion criteria

- Had active central nervous system (CNS) involvement of their DLBCL. A large proportion of patients in CORAL follow-up did not have CNS assessment; those with a missing or unknown CNS involvement were not excluded in the analyses
- Had previously received an allo-SCT prior to index date
- With primary mediastinal large B-cell lymphoma
- Lastly, the CORAL follow-up FAS patients were restricted to those with qualified index treatments (see intervention below.

CORAL follow-up FAS population:

CORAL patients who met the inclusion and exclusion criteria specified above and who received a qualified index treatment, which was a 3rd line or above treatment listed under interventions below.

- 3rd line and above treatments in CORAL follow-up were considered for potential index treatments for comparison with tisagenlecleucel FAS population
- For patients in CORAL follow-up who had several treatment lines that met the criteria for potential index treatments, the selection of the index treatment and the respective index date for CORAL follow-up FAS is described in Appendix F.

Intervention

For CORAL:

R-DHAP (rituximab, dexamethasone, cytarabine, cisplatinum) or R-ICE (rituximab, ifosfamide, carboplatinum, etoposide)), followed by ASCT when feasible.

For the follow-up data:

The treatments were selected based on input from the German HTA agency, Gemeinsamer Bundesausschuss and clinical experts:

- Any chemotherapy as mono- or combination therapy
- Rituximab with or without combination treatment
- Lenalidomide with or without combination treatment
- Brentuximab vedotin
- Ibrutinib
- Axicabtagene ciloleucel
- Polatuzumab vedotin with or without bendamustine and rituximab
- Allo-SCT
- Best supportive care

Trial name: CORAL study and CORAL follow-up data	NCT number: NCT00137995
	Unknown treatment and ASCT were not considered as appropriate comparators.
Comparator(s)	NA
Follow-up time	**Follow-up data:** The primary endpoint in the ICT was OS at 60 months.
Is the study used in the health economic model?	Yes
Primary, secondary and exploratory endpoints	**Endpoints included in this application:** OS. Overall survival **Other endpoints:** Overall response rate, ORR
Method of analysis	All analyses were carried out among JULIET FAS vs. CORAL follow-up FAS. Both unadjusted and adjusted analyses were conducted. The unadjusted analyses used index treatment line selected from Method A (specified in Appendix F). The adjusted analyses used index treatment line selected from Method B (specified in Appendix F). For the adjusted analyses, a list of potential confounders was selected. These confounders were used in two steps: 1) selecting treatment line and/or index date, and 2) using as covariates for adjusted comparisons. More details can be found in Appendix F.
Subgroup analyses	Analyses on the follow-up data were made for the unadjusted full FAS population as well as adjusted populations. Selection criteria for the adjusted population are described in Appendix J.
Other relevant information	None

Appendix C

Baseline characteristics of patients in studies used for the comparative analysis of efficacy and safety

In Table 54, baseline characteristics are shown for patients included in the unadjusted analyses (Method A). In Table 55, baseline characteristics are shown for patients included in the adjusted analysis (Method B) prior to propensity score (PS) weighing, and in Table 56, baseline patient characteristics are shown for patients included in the adjusted analysis (Method B) after PS weighing.

Statistical comparisons were made between tisagenlecleucel vs. historical control treatment using t-tests for mean and Wilcoxon rank sum tests for median for continuous variables, and Chi-squared tests for categorical variables non-missing data, unless frequency was < 5, in which case Fisher's exact test was used.

Table 54 Patient Characteristics for JULIET FAS and CORAL Follow-up FAS (Method A)

	JULIET (N=114)	CORAL Follow-up (N=170)	P-value[4]
Confounders:			
Demographics			
Age at initial diagnosis (years)			0.119
≤ 60, n (%)	82 (71.9%)	137 (80.6%)	
> 60, n (%)	32 (28.1%)	33 (19.4%)	
Mean (SD)	51.1 (12.9)	50.1 (11.2)	0.527
Median (min, max)	52.6 (14.3, 74.0)	53.4 (12.0, 64.2)	0.407
Disease characteristics			
Ann Arbor disease stage, n (%)			0.161
I or II	26 (22.8%)	45 (31.5%)	
III or IV	88 (77.2%)	98 (68.5%)	
Missing value		*27*	
Extranodal site involvement, n (%)			0.001*
0 - 1	64 (56.1%)	111 (76.6%)	
≥ 2 extranodal organs	50 (43.9%)	34 (23.4%)	
Missing value		*25*	
Status of disease, n (%)			0.359
Relapsed after last line	51 (44.7%)	89 (52.4%)	
Refractory to all lines	22 (19.3%)	24 (14.1%)	
Refractory to last line but not to all lines	41 (36.0%)	57 (33.5%)	
Time to 2nd line start after diagnosis (months)[5], n (%)			0.417
< 12	62 (55.9%)	82 (48.2%)	
≥ 12 and ≤ 24	27 (24.3%)	45 (26.5%)	
> 24	22 (19.8%)	43 (25.3%)	
Serum LDH level[6], n (%)			0.411
Normal	46 (40.4%)	48 (34.5%)	
Elevated	68 (59.6%)	91 (65.5%)	
Missing value		*31*	
ECOG[7], n (%)			--
0 - 1	114 (100.0%)	33 (100.0%)	
Missing value		*137*	
Prior therapies			

	JULIET (N=114)	CORAL Follow-up (N=170)	P-value[4]
Prior HSCT[8], n (%)			0.678
Yes	56 (49.1%)	78 (45.9%)	
No	58 (50.9%)	92 (54.1%)	
Number of relapses (excluding refractory)[9]			0.109
0, n (%)	22 (19.3%)	24 (14.1%)	
1, n (%)	38 (33.3%)	56 (32.9%)	
2, n (%)	38 (33.3%)	76 (44.7%)	
3, n (%)	14 (12.3%)	13 (7.6%)	
4, n (%)	2 (1.8%)	0 (0.0%)	
5, n (%)	0 (0.0%)	1 (0.6%)	
Mean (SD)	1.4 (1.0)	1.5 (0.9)	0.703
Median (min, max)	1.0 (0.0, 4.0)	2.0 (0.0, 5.0)	0.583
Other Baseline Variables			
Demographics			
Age (years)			0.001*
< 40, n (%)	17 (14.9%)	26 (15.3%)	
≥ 40 and < 65, n (%)	72 (63.2%)	132 (77.6%)	
≥ 65, n (%)	25 (21.9%)	12 (7.1%)	
Mean (SD)	53.7 (13.1)	53.0 (11.3)	0.629
Median (min, max)	56.0 (22.0, 76.0)	56.2 (20.2, 68.7)	0.538
Gender, n (%)			0.659
Female	44 (38.6%)	60 (35.3%)	
Male	70 (61.4%)	110 (64.7%)	
Disease characteristics			
Ann Arbor disease stage at diagnosis, n (%)			0.106
I or II	33 (30.3%)	69 (40.6%)	
III or IV	76 (69.7%)	101 (59.4%)	
Missing value	*5*		
IPI at diagnosis[10], n (%)			0.014
< 2 risk factors	27 (29.0%)	72 (45.6%)	
≥ 2 risk factors	66 (71.0%)	86 (54.4%)	
Missing value	*21*	*12*	
IPI[10], n (%)			0.012
< 2 risk factors	30 (26.3%)	14 (12.3%)	
≥ 2 risk factors	84 (73.7%)	100 (87.7%)	
Missing value		*56*	
BM involvement at diagnosis, n (%)			0.104
Yes	20 (18.3%)	16 (10.5%)	
No	89 (81.7%)	136 (89.5%)	
Missing value	*5*	*18*	
BM involvement, n (%)			<.001*
Yes	8 (7.0%)	16 (28.6%)	
No	106 (93.0%)	40 (71.4%)	

	JULIET (N=114)	CORAL Follow-up (N=170)	P-value[4]
Missing value		*114*	
CNS involvement, n (%)			--
No	114 (100.0%)	70 (100.0%)	
Missing value		*100*	
Histological subtype, n (%)			--
DLBCL	92 (80.7%)	170 (100.0%)	
Transformed lymphoma	22 (19.3%)	0 (0.0%)	
Time since most recent relapse / progression to index date (month)[11], n (%)			<.001*
≤ Median of JULIET	63 (55.3%)	146 (98.6%)	
> Median of JULIET	51 (44.7%)	2 (1.4%)	
Missing value		*22*	
Mean (SD)	5.8 (2.8)	0.9 (1.5)	<.001*
Median (min, max)	5.4 (1.6, 21.5)	0.5 (0.0, 12.1)	<.001*
Prior therapies			
Number of prior lines of therapies			
Mean (SD)	2.8 (1.0)	2.3 (0.7)	<.001*
Median (min, max)	3.0 (1.0, 6.0)	2.0 (2.0, 6.0)	<.001*

** Denotes p-value <0.05; -- denotes p-value not calculated*

Abbreviations: BM: bone marrow; CNS: central nervous system; DLBCL: diffuse large B cell lymphoma; ECOG: Eastern Cooperative Oncology Group; HSCT: hematopoietic stem cell transplantation; IPI: International Prognostic Index; LDH: lactate dehydrogenase; SD: standard deviation

Notes:

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

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

[3] Unless otherwise indicated, numbers and percentages of data availability were only summarized where missing data availability occurred.

[4] P-values comparing CORAL follow-up vs. JULIET were calculated using t-tests for mean and Wilcoxon rank sum tests for median for continuous variables, and Chi-squared tests for categorical variables non-missing data, unless frequency was < 5, in which case Fisher's exact test was used.

[5] For the JULIET patients who had one prior line, the 2nd line start date was defined as the JULIET enrolment date. For the JULIET patients with more than one prior lines, the 2nd line start date was defined as the 2nd line initiation date. For the CORAL follow-up group, the 2nd line start date was defined as the 2nd line initiation date.

[6] Normal serum LDH level was defined as LDH less than or equal to ULN, while elevated serum LDH level was defined as LDH greater than ULN.

[7] ECOG performance status were assessed within a month prior to or on the index date for CORAL follow-up.

[8] Prior HSCT only included prior ASCT because records with an allo-SCT prior to index date were excluded.

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

[10] The IPI includes the following risk factors: age > 60 years, elevated lactate dehydrogenase level, stage III or IV disease, ECOG performance status ≥ 2, and two or more extranodal sites.

[11] Time since most recent relapse / progression to index date was defined as time from most recent relapse to infusion date in JULIET, time from most recent relapse / progression to treatment start date in CORAL follow-up.

Table 55 Patient Characteristics for JULIET FAS and CORAL Follow-up FAS (Method B Prior to PS Weighting)

	JULIET (N=111)	CORAL Follow-up (N=145)	P-value[4]
Confounders Included (Relevant for Method B)			
Demographics			
Age at initial diagnosis (years)			0.366
≤ 60, n (%)	81 (73.0%)	114 (78.6%)	
> 60, n (%)	30 (27.0%)	31 (21.4%)	
Mean (SD)	50.9 (12.9)	50.4 (11.4)	0.790
Median (min, max)	52.5 (14.3, 74.0)	53.5 (12.0, 64.2)	0.726
Disease characteristics			
Ann Arbor disease stage, n (%)			0.186
I or II	26 (23.4%)	46 (31.7%)	
III or IV	85 (76.6%)	99 (68.3%)	
Extranodal site involvement, n (%)			0.003*
0 - 1	63 (56.8%)	109 (75.2%)	
≥ 2 extranodal organs	48 (43.2%)	36 (24.8%)	
Status of disease, n (%)			0.250
Relapsed after last line	50 (45.0%)	80 (55.2%)	
Refractory to all lines	20 (18.0%)	19 (13.1%)	
Refractory to last line but not to all lines	41 (36.9%)	46 (31.7%)	
Time to 2L start after diagnosis (months)[5], n (%)			0.158
< 12	62 (55.9%)	64 (44.1%)	
≥ 12 and ≤ 24	27 (24.3%)	41 (28.3%)	
> 24	22 (19.8%)	40 (27.6%)	
Prior therapies			
Prior HSCT[6], n (%)			0.853
Yes	56 (50.5%)	76 (52.4%)	
No	55 (49.5%)	69 (47.6%)	
Number of relapses (excluding refractory)[7]			0.047*
0, n (%)	20 (18.0%)	19 (13.1%)	
1, n (%)	38 (34.2%)	42 (29.0%)	
2, n (%)	38 (34.2%)	73 (50.3%)	
3, n (%)	13 (11.7%)	10 (6.9%)	
4, n (%)	2 (1.8%)	0 (0.0%)	
5, n (%)	0 (0.0%)	1 (0.7%)	
Mean (SD)	1.5 (1.0)	1.5 (0.9)	0.456
Median (min, max)	1.0 (0.0, 4.0)	2.0 (0.0, 5.0)	0.331
Confounders Excluded Due to Missing (Relevant for Method B)[8]			
Serum LDH level[9], n (%)			0.250

	JULIET (N=111)	CORAL Follow-up (N=145)	P-value[4]
Normal	46 (41.4%)	47 (33.6%)	
Elevated	65 (58.6%)	93 (66.4%)	
Missing value		*5*	
ECOG[10], n (%)			--
0 - 1	111 (100.0%)	32 (100.0%)	
Missing value		*113*	
Other Baseline Variables			
Demographics			
Age (years)			0.012*
< 40, n (%)	17 (15.3%)	20 (13.8%)	
≥ 40 and < 65, n (%)	71 (64.0%)	113 (77.9%)	
≥ 65, n (%)	23 (20.7%)	12 (8.3%)	
Mean (SD)	53.7 (13.1)	53.0 (11.3)	0.978
Median (min, max)	56.0 (22.0, 76.0)	56.2 (20.2, 68.7)	0.951
Gender, n (%)			0.473
Female	44 (39.6%)	50 (34.5%)	
Male	67 (60.4%)	95 (65.5%)	
Disease characteristics			
Ann Arbor disease stage at diagnosis, n (%)			0.141
I or II	33 (30.8%)	59 (40.7%)	
III or IV	74 (69.2%)	86 (59.3%)	
Missing value	*4*		
IPI at diagnosis[11], n (%)			0.028*
< 2 risk factors	27 (30.0%)	61 (45.5%)	
≥ 2 risk factors	63 (70.0%)	73 (54.5%)	
Missing value	*21*	*11*	
IPI[11], n (%)			0.007*
< 2 risk factors	30 (27.0%)	14 (12.1%)	
≥ 2 risk factors	81 (73.0%)	102 (87.9%)	
Missing value		*29*	
BM involvement at diagnosis, n (%)			0.070
Yes	20 (18.9%)	13 (9.8%)	
No	86 (81.1%)	119 (90.2%)	
Missing value	*5*	*13*	
BM involvement, n (%)			0.001*
Yes	8 (7.2%)	15 (27.3%)	
No	103 (92.8%)	40 (72.7%)	
Missing value		*90*	

	JULIET (N=111)	CORAL Follow-up (N=145)	P-value[4]
CNS involvement, n (%)			--
No	111 (100.0%)	70 (100.0%)	
Missing value		*75*	
Histological subtype, n (%)			--
DLBCL	89 (80.2%)	145 (100.0%)	
Transformed lymphoma	22 (19.8%)	0 (0.0%)	
Time since most recent relapse / progression to index date (month)[12], n (%)			<.001*
≤ Median of JULIET FAS	61 (55.0%)	143 (98.6%)	
> Median of JULIET FAS	50 (45.0%)	2 (1.4%)	
Mean (SD)	5.8 (2.8)	0.9 (1.5)	<.001*
Median (min, max)	5.4 (1.6, 21.5)	0.5 (0.0, 12.1)	<.001*
Prior therapies			
Number of prior lines of therapies			
Mean (SD)	2.7 (1.0)	2.3 (0.7)	<.001*
Median (min, max)	3.0 (1.0, 6.0)	2.0 (2.0, 6.0)	<.001*

** denotes p-value <0.05; -- denotes p-value not calculated*

Abbreviations: BM: bone marrow; CNS: central nervous system; DLBCL: diffuse large B cell lymphoma; ECOG: Eastern Cooperative Oncology Group; FAS: full analysis set; HSCT: hematopoietic stem cell transplantation; IPI: International Prognostic Index; LDH: lactate dehydrogenase; SD: standard deviation

Notes:

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

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

[3] Unless otherwise indicated, numbers and percentages of data availability were only summarized where missing data availability occurred.

[4] P-values comparing CORAL follow-up vs. JULIET were calculated using t-tests for mean and Wilcoxon rank sum tests for median for continuous variables, and Chi-squared tests for categorical variables non-missing data, unless frequency was < 5, in which case Fisher's exact test was used.

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

[6] Prior HSCT only included prior ASCT because records with an allo-SCT prior to index date were excluded.

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

[8] Serum LDH level was not included in method B adjustment due to missing percentage >20%.

[9] Normal serum LDH level was defined as LDH less than or equal to ULN, while elevated serum LDH level was defined as LDH greater than ULN.

[10] ECOG performance status were assessed within a month prior to or on the index date for CORAL follow-up. [11] The IPI includes the following risk factors: age > 60 years, elevated lactate dehydrogenase level, stage III or IV disease, ECOG performance status ≥ 2, and two or more extranodal sites.

[12] Time since most recent relapse / progression to index date was defined as time from most recent relapse to infusion date in JULIET, time from most recent relapse / progression to treatment start date in CORAL follow-up.

Table 56 Patient Characteristics for JULIET FAS and CORAL Follow-up FAS (Method B Post PS Weighting)

	JULIET (N=111)	CORAL Follow-up (N=145)		Standardized mean difference (JULIET vs. CORAL Follow-up)		Variance ratio (JULIET vs. CORAL Follow-up)	
		Fine stratification weight	SMRW	Fine stratification weight	SMRW	Fine stratification weight	SMRW
Confounders Included (Relevant for Method B)							
Demographics							
Age at initial diagnosis (years)							
≤ 60	73.0%	71.1%	71.4%	0.041	0.035	0.960	0.966
> 60	27.0%	28.9%	28.6%	-0.041	-0.035	0.960	0.966
Mean	50.9	51.4	51.4	-0.043	-0.042	1.355	1.365
Disease characteristics							
Ann Arbor disease stage							
I or II	23.4%	23.9%	24.1%	-0.011	-0.015	0.986	0.981
III or IV	76.6%	76.1%	75.9%	0.011	0.015	0.986	0.981
Extranodal site involvement							
0 - 1	56.8%	55.9%	56.5%	0.018	0.004	0.995	0.999
≥ 2 extranodal organs	43.2%	44.1%	43.5%	-0.018	-0.004	0.995	0.999
Status of disease							
Relapsed after last line	45.0%	49.5%	47.4%	-0.089	-0.048	0.990	0.993
Refractory to all lines	18.0%	17.6%	17.6%	0.012	0.010	1.021	1.017
Refractory to last line but not to all lines	36.9%	33.0%	34.9%	0.083	0.042	1.054	1.025
Time to 2L start after diagnosis (months)[5]							
< 12	55.9%	53.3%	54.6%	0.051	0.026	0.991	0.995
≥ 12 and ≤ 24	24.3%	24.2%	23.2%	0.004	0.027	1.004	1.033

	JULIET (N=111)	CORAL Follow-up (N=145)		Standardized mean difference (JULIET vs. CORAL Follow-up)		Variance ratio (JULIET vs. CORAL Follow-up)	
		Fine stratification weight	SMRW	Fine stratification weight	SMRW	Fine stratification weight	SMRW
> 24	19.8%	22.5%	22.2%	-0.066	-0.059	0.911	0.919
Prior therapies							
Prior HSCT[6]							
Yes	50.5%	52.4%	51.0%	-0.038	-0.010	1.002	1.000
No	49.5%	47.6%	49.0%	0.038	0.010	1.002	1.000
Number of relapses (excluding refractory)[7]							
0	18.0%	17.6%	17.6%	0.012	0.010	1.021	1.017
1	34.2%	30.4%	30.0%	0.083	0.091	1.065	1.073
2	34.2%	43.3%	43.7%	-0.186	-0.195	0.917	0.915
3	11.7%	7.2%	7.0%	0.155	0.163	1.551	1.591
4	1.8%	--	--	--	--	--	--
5	--	1.7%	1.7%	--	--	--	--
Mean	1.5	1.5	1.5	-0.017	-0.019	1.009	1.003
Confounders Excluded Due to Missing (Relevant for Method B)[8]							
Serum LDH level[9]							
Normal	58.6%	71.7%	72.3%	-0.279	-0.293	1.197	1.213
Elevated	41.4%	28.3%	27.7%	0.279	0.293	1.197	1.213
ECOG[10]							
0 - 1	100.0%	100.0%	100.0%	--	--	--	--
Other Baseline Variables							

	JULIET (N=111)	CORAL Follow-up (N=145)		Standardized mean difference (JULIET vs. CORAL Follow-up)		Variance ratio (JULIET vs. CORAL Follow-up)	
		Fine stratification weight	SMRW	Fine stratification weight	SMRW	Fine stratification weight	SMRW
Demographics							
Age (years)							
< 40	15.3%	12.6%	12.5%	0.080	0.080	1.181	1.182
≥ 40 and < 65	64.0%	78.5%	79.8%	-0.326	-0.357	1.366	1.429
≥ 65	20.7%	8.9%	7.7%	0.336	0.381	2.020	2.320
Mean	53.5	54.1	54.1	-0.045	-0.044	1.407	1.427
Gender							
Female	39.6%	34.5%	34.3%	0.108	0.110	1.059	1.061
Male	60.4%	65.5%	65.7%	-0.108	-0.110	1.059	1.061
Disease characteristics							
Ann Arbor disease stage at diagnosis							
I or II	30.8%	35.3%	35.3%	-0.095	-0.096	0.934	0.933
III or IV	69.2%	64.7%	64.7%	0.095	0.096	0.934	0.933
IPI at diagnosis[11]							
< 2 risk factors	30.0%	39.3%	39.8%	-0.196	-0.207	0.881	0.876
≥ 2 risk factors	70.0%	60.7%	60.2%	0.196	0.207	0.881	0.876
IPI[10]							
< 2 risk factors	27.0%	7.0%	7.0%	0.551	0.555	3.010	3.048
≥ 2 risk factors	73.0%	93.0%	93.0%	-0.551	-0.555	3.010	3.048
BM involvement at diagnosis							
Yes	18.9%	8.5%	8.4%	0.307	0.309	1.977	1.993
No	81.1%	91.5%	91.6%	-0.307	-0.309	1.977	1.993
BM involvement							

	JULIET (N=111)	CORAL Follow-up (N=145)		Standardized mean difference (JULIET vs. CORAL Follow-up)		Variance ratio (JULIET vs. CORAL Follow-up)	
		Fine stratification weight	SMRW	Fine stratification weight	SMRW	Fine stratification weight	SMRW
Yes	7.2%	28.0%	27.8%	-0.566	-0.563	0.332	0.333
No	92.8%	72.0%	72.2%	0.566	0.563	0.332	0.333
CNS involvement							
No	100.0%	100.0%	100.0%	--	--	--	--
Histological subtype							
DLBCL	80.2%	100.0%	100.0%	-0.703	-0.703	--	--
Transformed lymphoma	19.8%	--	--	--	--	--	--
Time since most recent relapse / progression to index date (month)[12]							
≤ Median of JULIET FAS	55.0%	99.2%	99.2%	-1.237	-1.239	30.168	31.639
> Median of JULIET FAS	45.0%	0.8%	0.8%	1.237	1.239	30.168	31.639
Mean	5.8	0.9	0.9	2.244	2.270	4.429	4.657
Prior therapies							
Number of prior lines of therapies, mean	2.7	2.4	2.4	0.367	0.353	1.418	1.401

-- denotes p-value not calculated

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

Notes:

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

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

[3] Three patients from JULIET and twenty-five patients from CORAL follow-up were excluded due to missingness in the covariates used in the PS model.

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

	JULIET (N=111)	CORAL Follow-up (N=145)			Standardized mean difference (JULIET vs. CORAL Follow-up)			Variance ratio (JULIET vs. CORAL Follow-up)	
		Fine stratification weight	SMRW		Fine stratification weight	SMRW		Fine stratification weight	SMRW
[5] For the JULIET patients who had one prior line, the second-line start date was defined as the JULIET enrolment date. For the JULIET patients with more than one prior lines, the second-line start date was defined as the second-line initiation date. For the CORAL follow-up group, the second-line start date was defined as the second-line initiation date. [6] Prior HSCT only included prior ASCT because records with an allo-SCT prior to index date were excluded. [7] The number of relapses was defined as the total number of lines prior to the index treatment where patient had a CR or PR as the response and relapsed later. [8] Serum LDH level was not included in method B adjustment due to missing percentage >20%. [9] Normal serum LDH level was defined as LDH less than or equal to ULN, while elevated serum LDH level was defined as LDH greater than ULN. [10] ECOG performance status were assessed within a month prior to or on the index date for CORAL follow-up. [11] The IPI includes the following risk factors: age > 60 years, elevated lactate dehydrogenase level, stage III or IV disease, ECOG performance status ≥ 2, and two or more extranodal sites. [12] Time since most recent relapse / progression to index date was defined as time from most recent relapse to infusion date in JULIET, time from most recent relapse / progression to treatment start date in CORAL follow-up.									

Comparability of patients across studies

The baseline characteristics for JULIET FAS and CORAL follow-up FAS from Method A

These are presented in Table 54. Most baseline characteristics were balanced between the JULIET FAS and CORAL follow-up FAS population. At baseline, JULIET FAS, compared with CORAL follow-up FAS, had

- a higher proportion of patients with greater than or equal to two extranodal sites involvement (43.9% vs. 23.4%, p=0.001),
- a higher proportion of patients aged 65 and older (21.9% vs. 7.1%, p=0.001),
- a lower proportion of patients with BM involvement (7% vs. 28.6%, p<0.001),
- a lower proportion of patients with greater than or equal to two IPI risk factors at index date (73.7% vs. 87.7%, p=0.012),
- a longer time since most recent relapse or progression to index date (mean: 5.8 vs. 0.9 months, p<0.001), and
- a greater number of prior lines of therapies (median: 3 vs. 2, p<0.001).

At diagnosis, a higher proportion of patients in JULIET FAS had

- greater than or equal to two IPI risk factors (71.0% vs. 54.4%, p=0.014) than CORAL follow-up FAS.

All the above comparisons and p-values were estimated among non-missing observations only.

The baseline characteristics for JULIET FAS and CORAL follow-up FAS prior to PS weighting

These are presented in Table 55 Most baseline characteristics were balanced between the JULIET FAS and CORAL follow-up FAS prior to PS weighting adjustment. At baseline, JULIET FAS had

- a higher proportion of patients with greater than or equal to two extranodal sites involvement (43.2% vs. 24.8%, p=0.003),
- a higher proportion of patients with fewer than two relapses (excluding refractory) (52.2% vs. 42.1%, p=0.047),
- a higher proportion of patients aged 65 and older (20.7% vs. 8.3%, p=0.012),
- a lower proportion of patients with BM involvement (7.2% vs. 27.3%, p=0.001),
- a lower proportion of patients with greater than or equal to two IPI risk factors (73.0% vs. 87.9%, p=0.007),
- a longer time since most recent relapse or progression to index date (mean: 5.8 vs. 0.9 months, p<0.001), and
- greater number of prior lines of therapies (median: 3 vs. 2, p<0.001) than CORAL follow-up FAS.

At diagnosis, a higher proportion of patients in JULIET FAS also had

- greater than or equal to two IPI risk factors (70.0% vs. 54.4%, p=0.028) than CORAL follow-up FAS.

All the above comparisons and p-values were estimated among non-missing observations only.

The baseline characteristics for JULIET FAS and CORAL follow-up FAS post PS weighting

These are presented in Table 56. JULIET FAS and CORAL follow-up FAS were well balanced on the list of variables that are used to estimate PS in both PS fine stratification weighting and SMRW approaches. These were reflected by the values of standardized mean differences after weighting were all below 0.1, and the variance ratios were all close to 1, indicating the two cohorts were well balanced.

For the variables not included in the PS adjustment, some variables were not balanced between JULIET FAS and CORAL follow-up FAS with the absolute values of the standardized mean difference being above 0.1. At baseline, JULIET FAS, compared with CORAL follow-up FAS, had

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- a higher proportion of patients with elevated serum LDH level (41.4% in JULIET FAS vs. 28.3% and 27.7% in CORAL follow-up FAS using fine stratification and SMRW, respectively),
- a higher proportion of patients aged 65 and older (20.7% vs. 8.9% and 7.7% using fine stratification and SMRW, respectively),
- a lower proportion of patients with greater than or equal to two IPI risk factors (73.0% vs. 93.0% and 93.0% using fine stratification and SMRW, respectively),
- a lower proportion of patients with BM involvement (7.2% vs. 28.0% and 27.8% using fine stratification and SMRW, respectively), and
- greater number of prior lines of therapies (mean: 2.7 vs. 2.4 and 2.4 using fine stratification and SMRW, respectively).

At diagnosis,

- a higher proportion of patients in JULIET FAS had greater than or equal to two IPI risk factors (70.0% vs. 60.7% and 60.2% using fine stratification and SMRW, respectively) than CORAL follow-up FAS;
- a higher proportion of patients in JULIET FAS had BM involvement at diagnosis in JULIET FAS than CORAL follow-up FAS (18.9% vs. 8.5% and 8.4% using fine stratification and SMRW, respectively).

In conclusion, for both the unadjusted and adjusted analyses, patients in the JULIET study had more IPI risk factors at diagnosis compared to the CORAL follow-up population. At baseline, they were older, had a greater number of prior lines of therapies, but a smaller number of IPI risk factors compared to the CORAL follow-up population.

The post PS weighting populations were well balanced for the values included in the PS weighting (see Appendix F).

Comparability of the study populations with Danish patients eligible for treatment

In the initial assessment by the Medicines Council of tisagenlecleucel, the Expert Committee assessed that the populations in the JULIET and CORAL follow-up studies were overall comparable to the Danish patient population, although Danish patients are generally older and with poorer performance status compared to the study population. The Expert Committee considered that the treatments used in the CORAL follow-up population correspond to those used in Danish clinical practice [6]. For further discussion on patient populations, see Section 8.2.2.1.

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Appendix D

Efficacy and safety results per study

Definition, validity, and clinical relevance of included outcome measures

Table 57 Definition, validity, and clinical relevance of included outcome measures

Outcome measure	Definition	Validity	Clinical relevance
Overall survival (OS)	OS was defined as the time from the date of tisagenlecleucel infusion (for JULIET) or from the date of index treatment initiation (for the CORAL follow-up) to the date of death due to any reason. The index date for CORAL follow-up ITT was defined as the date of the selected index treatment initiation, if known, or the date of relapse from last line if the initiation date of the index treatment was missing. For completeness, OS rate at 60 months is presented for the JULIET study and the CORAL follow-up data.	OS is the gold standard for demonstrating clinical efficacy in studies for cancer, including DBLCL.	OS is highly clinically relevant for patients. The clinically minimal important difference (MCID) was considered to be 10% points after 2 years, according to the protocol for the initial assessment of tisagenlecleucel by the Medicines Council [6]
Overall response rate (ORR)	The ORR was defined as the proportion of patients with a best overall disease response of complete response (CR) or partial response (PR). In JULIET, response was evaluated by a central independent review committee using the 2014 Lugano Classification [30],- in which CR did not include unconfirmed CR. In CORAL, response was measured by an investigator using the 1999 International Working Group (IWG) response criteria [31], in which unconfirmed CR was included under CR.	See clinical relevance	Response rates have been suggested as an important outcome by the Expert Committee in a previous CAR T-cell therapy protocol [25], where the MCID was 10% points

Outcome measure	Definition	Validity	Clinical relevance
	For both studies, patients with unknown response or without an index treatment were considered non-responders. To be consistent with the clinical study report of JULIET, response for the JULIET FAS population were assessed among the JULIET Main cohort only, i.e. patients treated with tisagenlecleucel or intended to receive tisagenlecleucel from the United States (US) manufacturing facility in Morris Plains, New Jersey.		
Progression free survival (PFS)	PFS Is defined as the time from initiation of treatment to progression or death regardless of cause. In the main analysis of PFS, patients who proceeded to HSCT after tisagenlecleucel infusion were censored at the time of HSCT. PFS was estimated using the KM method and the median PFS is presented along with 95% CI in the Main cohort, only.	See clinical relevance	PFS is a frequently used outcome for demonstrating efficacy in cancer studies. In previous DMC evaluations of CAR T-cell therapy in DLBCL, the Expert Committee has stated that based on their vast experience with the currently available treatments for DLBCL, an improvement of 3 months in median PFS is clinically relevant [25]
SF-36 questionnaire	The SF-36 is a generic instrument based on 36 questions designed to assess quality of life. The questionnaire is divided into 8 health-related domains: physical function, physical limitations, mental limitations, social function, physical pain, mental health, energy and general health. The score is measured on a scale from 0-100, where higher scores represent better quality of life [26]. The results are shown as change from baseline for the two overall summary scores, the physical health total score and the mental health total score.	See clinical relevance	SF-36 is a widely used and validated QoL questionnaire. For the SF-36, MCIDs were estimated to be 3 for both the physical and mental health total scores [26]

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Results per study

Table 58 Results from the JULIET study (NCT02445248)

Tisagencecleucel											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
Median OS (months) Full FAS population	Tisagen-lecleucel	114[1]	[redacted]	NA	NA	NA	NA	NA	NA	Kaplan-Meyer method	ITC report [24]
OS rate Month 60 (%) Full FAS population	Tisagen-lecleucel	114	[redacted]	NA	NA	NA	NA	NA	NA	Observed data	ITC report [24]
Median OS (months) Adjusted analysis With PS weighting	Tisagen-lecleucel	111[2]	[redacted]	NA	NA	NA	NA	NA	NA	Kaplan-Meyer method	ITC report [24]
OS rate Month 60 (months) Adjusted analysis	Tisagen-lecleucel	111	[redacted]	NA	NA	NA	NA	NA	NA	Observed data	ITC report [24]

Tisagencecleucel											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
With PS weighting			[redacted]								
ORR Month 60 (%) FAS, main cohort	Tisagen-lecleucel	98[3]	[redacted]	NA	NA	NA	NA	NA	NA	Observed data.	ITC report [24]
ORR Month 60 (%) Adjusted analysis With PS weighting	Tisagen-lecleucel	95	[redacted]	NA	NA	NA	NA	NA	NA	Observed data	ITC report [24]
Median PFS (months) FAS, main cohort	Tisagen-lecleucel	99	[redacted]							Kaplan-Meyer method	Clinical study report [23]
PFS rate Month 60 (%) Full FAS population	Tisagen-lecleucel	99	[redacted]	NA	NA	NA	NA	NA	NA	Observed data	Clinical study report [23]
SF-36 Physical score	Tisagen-lecleucel	115	[redacted]	NA	NA	NA	NA	NA	NA	Observed data	Clinical study report [23]

Tisagencecleucel											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Change from baseline at month 60 (mean (SD))			[redacted]								
SF-36 Mental score Change from baseline at month 60 (mean (SD))	Tisagen-lecleucel	115	[redacted]	NA	NA	NA	NA	NA	NA	Observed data	Clinical study report [23]

Abbreviations: CI: confidence interval, FAS: full analysis set, NA: not applicable, ORR: overall response rate, OS: overall survival, PS: propensity score, SD. standard deviation
[1]In the Clinical Study Report, the FAS included the one patient who was misdiagnosed (had endocrine carcinoma), i.e., n=115. OS was measured as time from infusion to death.
[2]Three patients from JULIET FAS were excluded due to missingness in the selected confounders in the adjusted analysis.
[3]As per protocol, only the main cohort, i.e., patients who received tisagenlecleucel from the US manufacturing site were included in the analyses of ORR.
A full overview of study populations is presented in Table 6.

Table 59 Results from the CORAL study follow-up (NCT00137995)

Standard of care											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
Median OS (months) Full selected FAS population*	SoC	170	[redacted]	NA	NA	NA	NA	NA	NA	Kaplan-Meyer method Patient population after sample selection and identification of presence of valid index treatment	ITC report [24]
Median OS (months) Prior to PS weighting	SoC	145	[redacted]	NA	NA	NA	NA	NA	NA	Kaplan-Meyer method Patient population after sample selection and identification of presence of valid index treatment and missingness in values of identified confounders	ITC report [24]
Median OS (months) Fine stratification weight adjusted population	SoC	145	[redacted]	NA	NA	NA	NA	NA	NA	Kaplan-Meyer method Patient population after sample selection and identification of presence of valid index treatment and missingness in values of identified confounders	ITC report [24]
Median OS (months) SMRW adjusted population	SoC	145	[redacted]	NA	NA	NA	NA	NA	NA	Kaplan-Meyer method Patient population after sample selection and identification of presence of valid index treatment and missingness in values of identified confounders	ITC report [24]

Standard of care											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
OS rate Month 60 (%) Full selected FAS population*	SoC	170	[redacted]	NA	NA	NA	NA	NA	NA	Observed data. Patient population after sample selection and identification of presence of valid index treatment	ITC report [24]
OS at 60 months (%) Prior to PS weighting	SoC	145	[redacted]	NA	NA	NA	NA	NA	NA	Observed data. Patient population after sample selection and identification of presence of valid index treatment and missingness in values of identified confounders	ITC report [24]
OS at 60 months (%) Fine stratification weight adjusted population	SoC	145	[redacted]	NA	NA	NA	NA	NA	NA	Observed data. Patient population after sample selection and identification of presence of valid index treatment and missingness in values of identified confounders	ITC report [24]
OS at 60 months (%) SMRW adjusted population	SoC	145	[redacted]	NA	NA	NA	NA	NA	NA	Observed data. Patient population after sample selection and identification of presence of valid index treatment and missingness in values of identified confounders	ITC report [24]

Standard of care											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
ORR Month 60 (%) Full FAS population	SoC	170	[redacted]	NA	NA	NA	NA	NA	NA	Observed data	ITC report [24]
ORR Month 60 (%) Prior to PS weighting	SoC	145	[redacted]	NA	NA	NA	NA	NA	NA	Observed data	ITC report [24]
ORR Month 60 (%) Fine stratification weight based on PS	SoC	145	[redacted]	NA	NA	NA	NA	NA	NA	Observed data	ITC report [24]
ORR Month 60 (%) SMRW based on PS	SoC	145	[redacted]	NA	NA	NA	NA	NA	NA	Observed data	ITC report [24]

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Standard of care												
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		

Abbreviations: CI: confidence interval, FAS: full analysis set, NA: not applicable, ORR: overall response rate, OS: overall survival, PS: propensity score
SoC: standard of care, SMRW: standardized mortality ratio weight
There were 170 total patients included in the CORAL follow-up study patient-level data, and OS was measured as time from treatment initiation to death.
Age at initial diagnosis, Ann Arbor disease stage, extranodal site involvement, status of disease, time to 2L start after diagnosis, prior HSCT, and number of relapses were included to adjust in the PS model.
Average treatment effect among the treated population fine stratification weight was assigned to CORAL follow-up patients. Stratums were based on the quintiles of the PS distribution from the whole cohort. Weights were calculated based on the ratio of percentage of patients residing within the same stratum between two treatments. 25 patients from CORAL follow-up were excluded due to missingness in the covariates.
Average treatment effect among the treated population SMRW was assigned to CORAL follow-up patients. Weights were calculated based on the odds of PS. 25 patients from CORAL follow-up were excluded due to missingness in the covariates.

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Appendix E

Safety data for intervention and comparator(s)

There is only limited published data on the safety of SoC for patients with DLBCL after at least 2 treatment lines. For this reason, only safety data for tisagenlecleucel is presented in this re-application.

The safety profile of tisagenlecleucel observed in this long-term follow-up analysis was largely consistent with previous reports, (on which the Summary of Product Characteristics (SmPC) for Kymriah is based). No new or unexpected safety signals were detected.

The following information is based on the SmPC for Kymriah (data-cut December 2022)) [2]. In addition, relevant tables from the final clinical study report (CSR) [23] (5-year follow-up) are shown below.

In the JULIET study, the most common non-haematological adverse reactions were cytokine release syndrome (57%), Infections (58%), pyrexia (35%), diarrhoea (31%), nausea (29%), fatigue (27%) and hypotension (25%).

The most common haematological laboratory abnormalities were decreased lymphocytes (100%), decreased white blood cells (99%), decreased haemoglobin (99%), decreased neutrophils (97%), and decreased platelets (95%).

Grade 3 and 4 adverse reactions were reported in 88% of patients. The most common Grade 3 and 4 non-haematological adverse reactions were infections (34%) and cytokine release syndrome (23%).

The most common (>25%) Grade 3 and 4 haematological laboratory abnormalities were lymphocyte count decreased (95%), neutrophil count decreased (82%), white blood cell count decreased (78%), haemoglobin decreased (59%) and platelet count decreased (56%).

Grade 3 and 4 adverse reactions were more often observed within the initial 8 weeks post-infusion (82%) compared to after 8 weeks post-infusion (48%).

Description of selected AEs:

Cytokine release syndrome

In the ongoing clinical study in DLBCL (N=115), cytokine release syndrome was reported in 57% of patients (23% with Grade 3 or 4). Cytokine release syndrome was graded per Penn criteria as follows: Grade 1: mild reactions, reactions requiring supportive care; Grade 2: moderate reactions, reactions requiring intravenous therapies; Grade 3: severe reactions, reactions requiring low-dose vasopressors or supplemental oxygen; Grade 4: life-threatening reactions, those requiring high-dose vasopressors or intubation; Grade 5: death.

Infections and febrile neutropenia

In DLBCL patients, severe infections (Grade 3 and higher), which can be life-threatening or fatal, occurred in 34% of patients. The overall incidence (all grades) was 58% (unspecified 48%, bacterial 15%, fungal 11% and viral 11%). 37% of the patients experienced an infection of any type within 8 weeks.

Prolonged cytopenias

Cytopenias are very common based on prior chemotherapies and Kymriah therapy. All adult DLBCL patients had Grade 3 and 4 cytopenias at some time after Kymriah infusion. Grade 3 and 4 cytopenias not resolved by day 28 based on laboratory findings included decreased count of thrombocytes (39%), lymphocytes (29%), neutrophils (25%), and white blood cells (21%) and decreased haemoglobin (14%).

Neurological adverse reactions

The majority of neurotoxic events occurred within 8 weeks following infusion and were transient. In DLBCL patients, manifestations of encephalopathy and/or delirium occurred in 20% of patients (11% were Grade 3 or 4) within 8 weeks after Kymriah infusion.

Hypogammaglobulinemia

Hypogammaglobulinemia was reported in 17% of patients with r/r DLBCL. Pregnant women who have received Kymriah may have hypogammaglobulinemia. Immunoglobulin levels should be assessed in newborns of mothers treated with Kymriah.

Immunogenicity

In clinical studies, humoral immunogenicity of tisagenlecleucel was measured by determination of anti-murine CAR19 antibodies (anti-mCAR19) in serum pre- and post-administration. The majority of patients in the JULIET study (93,9%) tested positive for pre-dose anti-mCAR19 antibodies. Treatment-induced anti-mCAR19 antibodies were found in 8.7% of adult DLBCL patients. Pre-existing and treatment-induced antibodies were not associated with an impact on clinical response, nor did they have an impact on the expansion and persistence of tisagenlecleucel. There is no evidence that the presence of pre-existing and treatment-induced anti-mCAR19 antibodies impacts the safety or effectiveness of tisagenlecleucel. T-cell immunogenicity responses were not observed.

The tables below are based on the safety population (n=115) in the JULIET study at the final data-cut (CSR) [23]. The safety population included one patient with neuroendocrine carcinoma. The tables show AEs post-tisagenlecleucel infusion, suspected to be study drug related, by PT and maximum CTC grade in more than 5% of all grades (Table 60), Serious adverse events (SAEs) post-tisagenlecleucel infusion, suspected to be study drug (Table 61) and deaths by preferred term and time period (Table 62).

Table 60 AEs post-tisagenlecleucel infusion, suspected to be study drug related, by PT and maximum CTC grade in more than 5% of all grades patient (safety set).

Source: Clinical Study Report [23] Table 12.5

Table 61 SAEs post tisagenlecleucel infusion, suspected to be study drug related.

Source: Clinical Study Report [23] Table 12.9

Table 62 Deaths by preferred term and time period (Enrolled set).

Source: Clinical Study Report [23] Table 12.7

Appendix F

Comparative analysis of efficacy and safety

Indirect treatment comparisons were done for the outcomes OS and ORR. Safety is described narratively in Section 7.1.3 and Appendix E.

The indirect treatment comparison compares the efficacy of tisagenlecleucel with historical control for 3rd line or above treatment of relapsed or refractory DLBCL, using patient level data from the single-arm tisagenlecleucel phase 2 study JULIET [19, 29] with data-cut from December 2022 and historical control treatment with patient-level data from the follow-up dataset of the phase 3 CORAL study [9, 10].

To construct a comparable patient population, patients from CORAL follow-up study were selected based on the inclusion and exclusion criteria of the JULIET trial, (see Table 53). Patients from the CORAL follow-up may have multiple treatments/index dates that met the inclusion and exclusion criteria of JULIET. The index date had to be selected for CORAL patients. In the unadjusted analysis (Method A), selection of the index treatment based on the number of previous lines was applied without further adjustment for differences in confounders. Adjusted analysis (Method B) was designed to select an index treatment/date from CORAL follow-up population to reduce the differences in confounders between CORAL follow-up and JULIET populations. Following sample selection and index treatment/date selection, OS and ORR was compared among the infused JULIET patients vs. CORAL follow-up. To construct a comparable patient population, patients from CORAL follow-up study were selected based on the inclusion and exclusion criteria of the JULIET trial, (see Table 53). Patients from the CORAL follow-up may have multiple treatments/index dates that met the inclusion and exclusion criteria of JULIET. The index date had to be selected for CORAL patients. In the unadjusted analysis (Method A), selection of the index treatment based on the number of previous lines was applied without further adjustment for differences in confounders. Adjusted analysis (Method B) was designed to select an index treatment/date from CORAL follow-up population to reduce the differences in confounders between CORAL follow-up and JULIET populations. Following sample selection and index treatment/date selection, OS and ORR was compared among the infused JULIET patients vs. CORAL follow-up.

[redacted]

1. [redacted]
2. [redacted]
3.

Table 63 Overview of identified confounders and their relevance in the Indication

Potential confounders (identified by systematic literature research)	Relevance[1] for adults with r/r DLBCL (by medical experts)
[redacted]	

3. [redacted]

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[redacted]

[redacted]

[redacted]

Results from the analyses are shown in below Table 64.

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Table 64 Indirect treatment comparison of Overall Survival. Final analysis at 60 months

Outcome	Studies included in the analysis	Absolute difference in effect			Relative difference in effect			Method used for quantitative synthesis	Result used in the health economic analysis?
		Difference	CI	*P* value	Difference	CI	*P* value		
Full Analyses Set (Method A)									
Median OS (months)	JULIET CORAL follow-up	[redacted]	NA	NA	[redacted]			Univariable Cox regression	No
Adjusted (Method B)									
Median OS (months)	JULIET CORAL follow-up	[redacted]	NA	NA	[redacted]			Univariable Cox regression Prior to PS weighting	No
Median OS (months)	JULIET CORAL follow-up		NA	NA				Cox regression with fine stratification based on PS	No
Median OS (months)	JULIET CORAL follow-up	[redacted]	NA	NA	[redacted]			Cox regression with SMRW based on PS	Yes
Full Analysis Set (Method A)									

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Outcome	Studies included in the analysis	Absolute difference in effect			Relative difference in effect			Method used for quantitative synthesis	Result used in the health economic analysis?
		Difference	CI	*P* value	Difference	CI	*P* value		
ORR at 60 Months (%)	JULIET CORAL follow-up	[redacted]	NA	NA	[redacted]			Unadjusted line selection Univariable logistic regression	No
Adjusted (Method B)									
ORR at 60 Months (%)	JULIET CORAL follow-up	[redacted]	NA	NA	[redacted]			Prior to PS weighting Univariable logistic regression	No
ORR at 60 Months (%)	JULIET CORAL follow-up	[redacted]	NA	NA	[redacted]			Post PS weighting with fine stratification Logistic regression	No
ORR at 60 Months (%)	JULIET CORAL follow-up	[redacted]	NA	NA	[redacted]			Post PS weighting with SMRW Logistic regression	No

Abbreviations: CI: confidence interval, HR: hazard ratio, NA: not applicable (i.e., available), OS: overall survival, ORR: overall response rate, PS: propensity score , SMRW: standardized mortality ratio weight.

Appendix G

Extrapolation

Figure 14 Parametric curves fitted to the OS KM curve of the JULIET data

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Figure 15 Parametric curves fitted to the OS KM curve of the CORAL follow-up data

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Figure 16 Parametric curves fitted to the PFS KM curve of the JULIET data

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Log cumulative and Schoenfeld residuals plots

Figure 17. Proportional Hazard Plots for Comparison of OS for JULIET vs. CORAL Follow-up (FAS, Method A)

(A) Schoenfeld Residual Plot (unadjusted)

(A) Log Cumulative Hazard Plot (unadjusted)

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Figure 18. Proportional Hazard Plots for Comparison of OS for JULIET vs. CORAL Follow-up (Adjusted, Prior to PS Weighting)

(B) Schoenfeld Residual Plot (FAS, Method B Prior to PS Weighting)

(C) Log Cumulative Hazard Plot (FAS, Method B Prior to PS Weighting)

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Figure 19. Proportional Hazard Plots for Comparison of OS for JULIET vs. CORAL Follow-up (Adjusted, with PS-based Fine Stratification Weight)

(A) Schoenfeld Residual Plot (FAS, Method B with PS-based Fine Stratification Weight)

(B) Log Cumulative Hazard Plot (FAS, Method B with PS-based Fine Stratification Weight)

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Figure 20. Proportional Hazard Plots for Comparison of OS for JULIET vs. CORAL Follow-up (adjusted, with PS-based SMRW)

(A) Schoenfeld Residual Plot (FAS, Method B with PS-based SMRW)

(B) Log Cumulative Hazard Plot (FAS, Method B with PS-based SMRW)

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Table 65 AIC / BIC statistics for extrapolation of the PFS KM data for JULIET

Function	AIC	BIC
Exponential	612,14	614,89
Weibull	527,59	533,08
Gompertz	483,70	489,19
Log-Normal	498,52	504,01
Log-Logistic	502,88	508,37
Gamma	442,34	450,58
Spline with single knot	450,69	458,93
Spline with two knots	**433,48**	**444,46**
Spline with three knots	#N/A	#N/A
Spline with four knots	#N/A	#N/A

Table 66 AIC / BIC statistics for extrapolation of the OS KM data for JULIET

Function	AIC	BIC
Exponential	704,17	706,92
Weibull	671,49	676,98
Gompertz	650,79	656,28
Log-Normal	652,15	657,64
Log-Logistic	657,43	662,92
Gamma	636,81	645,04
Spline with single knot	636,01	**644,24**
Spline with two knots	**634,88**	645,86
Spline with three knots	636,65	650,38
Spline with four knots	638,36	654,83

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Table 67 AIC / BIC statistics for extrapolation of the OS KM data for CORAL follow-up

Function	AIC	BIC
Exponential	692,52	695,49
Weibull	671,87	677,82
Gompertz	647,42	653,37
Log-Normal	644,79	650,74
Log-Logistic	641,55	647,50
Gamma	642,81	651,74
Spline with single knot	**636,40**	**645,33**
Spline with two knots	637,67	649,58
Spline with three knots	638,38	653,26
Spline with four knots	639,30	657,16

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Appendix H

Literature search for HRQoL data

Not enclosed in accordance with dialogue with the secretariat of the Medicines Council.

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Appendix I

Mapping of HRQoL data

Described in the application.

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Appendix J

Probabilistic sensitivity analyses

Table 68 Probabilistic sensitivity analysis

Category	Description	Expected value	Standard error	Probability distribution	Parameter distribution (Name: Value)	Parameter distribution (Name: Value)	Reason / Rationale / Source	Refers to cell (in the Excel model)
Hazard ratio for CTL020	MAIC hazard ratio for CTL019 (OS from infusion) vs. Salvage chemotherapy (CORAL)	[redacted]					Overall effect of intervention	raw_os_hr_tx4
CTL019 infusion rate	CTL019 infusion rate	0,69	0,04				In real life, more patients receive Tisagenlecleucel than in the study	prop_infused
Utility for health states	PFS utility	0.84	0.02	Beta	16	0	Parameter uncertinaty and imnpact on spread of results	utility_PFS
	Progressive disease utility	0.73	0.04	Gamma	281	53,6	Parameter uncertinaty and imnpact on spread of results	Utility_PD
Treatment disutility	CTL019 CRS disutility	0.00	0.00	Gamma	89	32,99	Parameter uncertinaty	AE_disu_tx4
	CTL019 ICU disutility	0.00	0.00	Gamma	100	192 066.22	Parameter uncertinaty	AE_disu_tx4_v2
		0.00	0.00	Gamma	100	47 940.09	Parameter uncertinaty	AE_disu_tx5
	CTL019 (vs. CORAL) treatment disutility	0.01	0.00	Gamma	0	0	Parameter uncertinaty	Disutility_tx4
	Salvage Chemotherapy (CORAL) treatment disutility	0.01	0.00	Gamma	99	8 524.10	Parameter uncertinaty	Disutility_tx5
Subsequent ST	CTL019 (vs. CORAL) subsequent ASCT rate	0.87%	0.87%	Beta	16	7 456	SCTs carries significant costs and can have impact on results	Sub_autoSCT_rate_tx4

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Category	Description	Expected value	Standard error	Probability distribution	Parameter distribution (Name: Value)	Parameter distribution (Name: Value)	Reason / Rationale / Source	Refers to cell (in the Excel model)
	CTL019 (vs. CORAL) subsequent allo-SCT rate	6.09%	2.23%	Beta	1	113.01	SCTs carries significant costs and can have impact on results	Sub_alloSCT_rate_tx4
	Salvage Chemotherapy (CORAL) subsequent ASCT rate	21.22%	5.31%	Gamma	7	107.06	SCTs carries significant costs and can have impact on results	Sub_autoSCT_rate_tx5
	Salvage Chemotherapy (CORAL) subsequent allo-SCT rate	7.55%	1.89%	Gamma	12	45.10	SCTs carries significant costs and can have impact on results	Sub_alloSCT_rate_tx5
	Subsequent ASCT cost	152 421	38 105	Gamma	15	180.09	SCTs carries significant costs and can have impact on results	sub_autoSCT_cost
	Subsequent allo-SCT cost	818 117	204 529	Gamma	16	9 526	SCTs carries significant costs and can have impact on results	sub_alloSCT_cost
	Subsequent allo-SCT disutility	0.03	0.00	Gamma	16	51 132	SCTs carries significant costs and can have impact on results	sub_alloSCT_disutil
	Subsequent ASCT disutility	0.03	0.00	Gamma	97	3 801.53	SCTs carries significant costs and can have impact on results	sub_autoSCT_disutil
AE cost	CTL019 IVIG cost	32 493	8 123	Gamma	97	3 801.53	AEs change in the real life treatment setting	BCell_cost_tx4
	CTL019 (vs. CORAL) AE cost	24 079	6 020	Gamma	16	2 031	AEs change in the real life treatment setting	AE_cost_tx4
	CTL019 CRS cost	14 097	3 524	Gamma	16	1 505	AEs change in the real life treatment setting	CRS_cost

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Category	Description	Expected value	Standard error	Probability distribution	Parameter distribution (Name: Value)	Parameter distribution (Name: Value)	Reason / Rationale / Source	Refers to cell (in the Excel model)
	CTL019 neurotoxicity cost	0.00	0.00	Gamma	16	881	AEs change in the real life treatment setting	neuro_cost_tx4
	Salvage Chemotherapy (CORAL) AE cost	14 980	3 745	Beta	0	0	AEs change in the real life treatment setting	AE_cost_tx5
SMR for long-term DLBCL survivors	SMR for long-term survivors	1.09	0.24	Beta	16	936	Long term survival can have an impact on the final result	smr
Patient characteristics	Age	56.00	1.197	Beta			The age of the patients will in real life treatment setting	age
	Weight	78.51	1.906	Beta			The weight of the patient will vary in the real life treatment setting	weight
	Gender	37%	4%	Gamma	62	104.37	The gender might be different in a Danish treatment setting	female
	BSA	1.91	0.03	Gamma			The body weigh of patients vary in a real life treatment setting	bsa

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