Medicinrådet

Baggrund for Medicinrådets anbefaling vedrørende axicabtagene ciloleucel som mulig standardbehandling til diffust storcellet B-celle-lymfom

Versionsnr.: 1.0

Medicinrådet

Om Medicinrådet

Medicinrådet er et uafhængigt råd, som udarbejder anbefalinger og vejledninger om lægemidler til de fem regioner.

Medicinrådet vurderer, om nye lægemidler og nye indikationer kan anbefales som mulig standardbehandling og udarbejder fælles regionale behandlingsvejledninger.

Nye lægemidler vurderes i forhold til effekt, eksisterende behandling og pris. Det skal give lavere priser og lægemidler, der er til størst mulig gavn for patienterne.

De fælles regionale behandlingsvejledninger er vurderinger af, hvilke lægemidler der er mest hensigtsmæssige til behandling af patienter inden for et terapiområde og dermed grundlag for ensartet høj kvalitet for patienterne på tværs af sygehuse og regioner.

Om anbefalingen

Anbefalingen er Medicinrådets vurdering af, om omkostningerne ved behandling lægemidlet er rimelige i forhold til lægemidlets kliniske værdi.

Se Medicinrådets metodehåndbog for yderligere information.

Dokumentoplysninger	
Godkendelsesdato	15. maj 2019
Ikrafttrædelsesdato	15. maj 2019
Dokumentnummer	48426
Versionsnummer	1.0

Medicinrådet, Dampfærgevej 27-29, 3. th., 2100 København Ø
www.medicinraadet.dk
Sprog: dansk
Format: pdf
Udgivet af Medicinrådet, 15. maj 2019

Indhold

1 Lægemiddelinformationer

Handelsnavn	Yescarta®
Generisk navn	Axicabtagene ciloleucel
Firma	Gilead/Kite Pharma EU B.V.
ATC-kode	LO1X
Virkningsmekanisme	Patientens egne T-celler genmodificeres til at udtrykke receptorer (chimeric antigen receptor (CAR)), der genkender den generelle B-cellemarkør, CD19. De modificerede T-celler indgives intravenøst til patienten, hvor de binder sig til B-celler og slår disse ihjel.
Administration/dosis	Administration af én intravenøs infusion af axicabtagene ciloleucel med en target-dosis på 2 x 10^6 CAR T-celler/kg kropsvægt (dag 0). Før transfusion af axicabtagene ciloleucel behandles patienten med lavdosis konditionerende kemoterapi bestående af fludarabinphosphat (30 mg/m^2/d) og cyclophosphamid (500 mg/m^2/d) på dag -5, -4 og -3.
EMA-indikation	Axicabtagene ciloleucel er indiceret til behandling af voksne patienter (≥ 18 år) med relaps eller refraktær diffust storcellet B-celle-lymfom (DLBCL) og primær mediastinal storcellet B-celle-lymfom (PMBCL) efter to eller flere linjer af systemisk behandling.

2 Medicinrådets anbefaling

Medicinrådet **anbefaler ikke** axicabtagene ciloleucel som mulig standardbehandling til voksne patienter med relaps eller refraktær diffust storcellet B-celle-lymfom efter flere systemiske behandlinger.

Det kliniske spørgsmål, som ligger til grund for anbefalingen, er som følger:

Hvilken klinisk merværdi tilbyder axicabtagene ciloleucel sammenlignet med nuværende standardbehandling til voksne patienter (> 18 år) med relaps eller refraktær DLBCL eller PMBCL efter to eller flere linjer af systemisk behandling?

3 Formål

Formålet med baggrund for Medicinrådets anbefaling vedrørende axicabtagene ciloleucel som mulig standardbehandling til diffust storcellet B-celle-lymfom er at skabe gennemsigtighed om det materiale, der ligger til grund for Medicinrådets anbefaling.

4 Baggrund

Diffust storcellet B-celle-lymfom (DLBCL) er en aggressiv kræftform, som diagnosticeres hos ca. 500 patienter årligt i Danmark. Primær mediastinal B-celle-lymfom (PMBCL) er en sjælden DLBCL-undertype. Omkring 100 af disse patienter er refraktære eller oplever recidiv efter to eller flere linjer af systemisk behandling. Heraf forventes ca. 25-50 patienter årligt at være kandidater til axicabtagene ciloleucel, vurderet på baggrund af alder, performancestatus og tidligere behandling.

Denne patientgruppe tilbydes aktuelt den bedste tilgængelige behandling (kemoterapi), da der ikke er evidens for at anbefale et bestemt regime. Hvis sygdommen er kemosensitiv, kan allogen knoglemarvstransplantation anvendes til at konsolidere behandlingen og er potentielt kurativ. Hvis der ikke er mulighed for allogen knoglemarvstransplantation, kan det ikke forventes, at 3. linjebehandling vil være kurativ.

4.1 Sagsbehandlingstid og proces for Medicinrådets vurdering

Medicinrådet modtog den endelige ansøgning den 27. december 2018. Vurderingsrapporten, version 1.0, blev præsenteret og godkendt på rådsmødet den 30. januar 2019. Efter høringssvar blev vurderingsrapporten, version 1.1, offentliggjort den 8. februar 2019 med mindre faktuelle rettelser. Ansøger ønskede clock-stop pr. 5. februar 2019 i forbindelse med prisforhandlingerne. Clock-stoppet blev ophævet den 30. april 2019. Anbefalingen blev behandlet på rådsmødet den 15. maj 2019. Samlet har behandlingstiden varet 7 uger og 6 dage, fraset ansøgers clock-stop.

5 Medicinrådets vurdering af samlet klinisk merværdi

Medicinrådet vurderer, at axicabtagene ciloleucel giver en **ikkedokumenterbar klinisk merværdi** sammenlignet med bedste tilgængelige behandling for voksne patienter med relaps eller refraktær diffust storcellet B-celle-lymfom efter flere systemiske behandlinger. Evidensens kvalitet vurderes at være meget lav.

Medicinrådet mener, at der er behov for et mere solidt evidensgrundlag for at kunne vurdere den kliniske merværdi, sammenlignet med den bedste tilgængelige behandling.

6 Høring

Ansøger har den 5. februar 2019 indsendt et høringssvar, som ikke gav anledning til en ændring af Medicinrådets vurdering af klinisk merværdi. Der er foretaget to faktuelle rettelser som følge af høringssvaret, offentliggjort i version 1.1 af vurderingsrapporten. Høringssvaret er vedlagt som bilag 3.

7 Resumé af økonomisk beslutningsgrundlag

Amgros vurderer, at der ikke er et rimeligt forhold mellem meromkostningerne og den kliniske merværdi for axicabtagene ciloleucel (Yescarta) ved behandling af voksne patienter med relaps eller refraktær diffust storcellet B-celle-lymfom (DLBCL), som efter to eller flere linjer af systemisk behandling vurderes at være kandidater til axicabtagene ciloleucel.

8 Overvejelser omkring alvorlighed/forsigtighed

Medicinrådet har ikke fundet anledning til at inddrage forhold vedrørende alvorlighed eller forsigtighed i anbefalingen.

9 Sammensætning af fagudvalg og kontaktinformation til Medicinrådet

Medicinrådets fagudvalg vedrørende lymfekræft (lymfomer)

Formand	**Indstillet af**
Lars Møller Pedersen Overlæge	Lægevidenskabelige Selskaber og udpeget af Region Hovedstaden
Næstformand	
Paw Jensen Ledende overlæge	Udpeget af Region Nordjylland
Medlemmer	**Udpeget af**
Jakob Madsen Overlæge	Region Nordjylland
Peter Martin Hjørnet Kamper Funktionsledende overlæge	Region Midtjylland
Jacob Haaber Christensen Overlæge	Region Syddanmark
Dorte Maegaard Tholstrup Afdelingslæge	Region Sjælland
Michael Pedersen Overlæge	Region Hovedstaden
Kathrine Bruun Svan Farmaceut	Dansk Selskab for Sygehusapoteksledelse
Kenneth Skov Afdelingslæge	Dansk Selskab for Klinisk Farmakologi
Michael Boe Møller Overlæge	Dansk Patologiselskab
Jørn Søllingvraa Patient/patientrepræsentant	Danske Patienter
En patient/patientrepræsentant	Danske Patienter

Medicinrådets sekretariat

Medicinrådet Dampfærgevej 27-29, 3. th. 2100 København Ø + 45 70 10 36 00 medicinraadet@medicinraadet.dk
Sekretariatets arbejdsgruppe: Louise Klokker Madsen (projekt- og metodeansvarlig) Ditte Marie Irwin-Clugston (sundhedsvidenskabelig konsulent) Jan Odgaard-Jensen (biostatistiker) Diana Odrobináková (biostatistiker) Bettina Fabricius Christensen (informationsspecialist) Anette Pultera Nielsen (fagudvalgskoordinator) Annemette Anker Nielsen (teamleder)

10 Versionslog

Version	Dato	Ændring
1.0	15. maj 2019	Godkendt af Medicinrådet.

11 Bilag

Bilagsliste:

- Amgros' beslutningsgrundlag for axicabtagene ciloleucel (Yescarta)
- Amgros' sundhedsøkonomiske analyse for axicabtagene ciloleucel (Yescarta)
- Høringssvar fra ansøger vedr. axicabtagene ciloleucel (Yescarta)
- Medicinrådets vurdering af klinisk merværdi for axicabtagene ciloleucel til diffust storcellet B-celle-lymfom
- Ansøgers endelige ansøgning vedr. axicabtagene ciloleucel (Yescarta)
- Protokol for Medicinrådets vurdering af den kliniske merværdi for axicabtagene ciloleucel til diffust storcellet B-celle-lymfom

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Beslutningsgrundlag til Medicinrådet

Dette dokument er Amgros' vurdering af axicabtagene ciloleucel (Yescarta) som mulig standardbehandling til patienter med refraktær eller recidiverende diffus storcellet B-celle-lymfom (DLBCL) efter to eller flere linjer af systemisk behandling. Vurderingen er baseret på lægemidlets gennemsnitlige inkrementelle omkostninger (baseret på SAIP) sammenholdt med Medicinrådets vurdering af den kliniske merværdi.

Dato for Medicinrådsbeslutning	15-05-2019
Firma	Gilead Sciences Inc. (ansøger)
Lægemiddel	Axicabtagene ciloleucel (Yescarta)
Indikation	Axicabtagene ciloleucel er indiceret til behandling af voksne patienter (> 18 år) med relaps eller refraktær diffust storcellet B-celle-lymfom (DLBCL) og primær mediastinal storcellet B-celle-lymfom (PMBCL) efter to eller flere linjer af systemisk behandling.

Amgros' vurdering

- Amgros vurderer at der ***ikke*** er et rimeligt forhold mellem meromkostningerne og den kliniske merværdi for axicabtagene ciloleucel (Yescarta) som mulig standardbehandling til patienter med refraktær eller recidiverende diffus storcellet B-celle-lymfom (DLBCL) efter to eller flere linjer af systemisk behandling.

Overordnet konklusion

Medicinrådet har vurderet, at axicabtagene ciloleucel (Yescarta) sammenlignet med bedste tilgængelige behandling giver **ikkedokumenterbar klinisk merværdi.**

Behandling med axicabtagene ciloleucel (Yescarta) er forbundet med meget høje meromkostninger sammenlignet med bedste tilgængelige behandling til nævnte indikation. Amgros vurderer, at der **ikke** er rimeligt forhold mellem den kliniske merværdi for axicabtagene ciloleucel (Yescarta), sammenlignet med bedste tilgængelige behandling. Meromkostningerne drives af prisen på axicabtagene ciloleucel (Yescarta).

Konklusion for populationen

Tabel 1 Merværdi, meromkostninger og Amgros' vurdering (baseret på SAIP)

Population	Komparator	Merværdi	Usikkerhed for klinisk merværdi	Amgros' konklusion om forholdet mellem meromkostninger og merværdi
Axicabtagene ciloleucel er indiceret til behandling af voksne patienter (> 18 år) med relaps eller refraktær diffust storcellet B-celle-lymfom (DLBCL) og primær mediastinal storcellet B-celle-lymfom (PMBCL) efter to eller flere linjer af systemisk behandling.	Bedste tilgængelige behandling	Ikkedokumenterbar klinisk merværdi	Meget lav evidenskvalitet	Ikke rimeligt

Konklusionen er baseret på, at Medicinrådet har valgt forskellige behandlingsregimer og mulig stamcelletransplantation som komparator for patientpopulationen, og vurderingen af meromkostninger og klinisk værdi beror på denne.

Supplerende informationer (resumé af resultaterne fra afrapporteringen)

Konklusion på omkostnings- og budgetkonsekvensanalyserne

Resultatet fra Amgros' afrapportering på omkostningsanalyserne er gengivet i det følgende. For uddybende gennemgang af analyse og resultater henvises til afrapporteringen på http://www.amgros.dk.

Amgros' afrapportering - Inkrementelle omkostninger per patient

Behandling med axicabtagene ciloleucel (Yescarta) er forbundet med meget høje meromkostninger sammenlignet med bedste tilgængelige behandling.

I tabel 2 ses de inkrementelle omkostninger for axicabtagene ciloleucel (Yescarta) og bedste tilgængelige behandling.

Amgros' hovedanalyse resulterer i gennemsnitlige meromkostninger per patient for axicabtagene ciloleucel (Yescarta) sammenlignet med bedste tilgængelige behandling på ca. [redacted] DKK.

Tabel 2: Resultat af Amgros hovedanalyse for axicabtagene ciloleucel (Yescarta) sammenlignet med bedste tilgængelige behandling, DKK, SAIP

Omkostningselement	Axicabtagene ciloleucel (Yescarta)	Bedste tilgængelige behandling	Inkrementelle omkostninger
Procedure/lægemiddel	[redacted]	[redacted]	[redacted]
Administration/Hospitalisering	824.574	200.613	**623.961**
Terminale omkostninger	123.543	170.277	**-46.734**
Bivirkninger	2.775	0	**2.775**
Samlet meromkostninger	[redacted]	[redacted]	[redacted]

Hvis analysen udføres på baggrund af AIP, bliver de inkrementelle omkostninger per patient for axicabtagene ciloleucel (Yescarta) sammenlignet med bedste tilgængelige behandling ca. 3,05 mio. DKK.

Lægemiddelomkostningerne for axicabtagene ciloleucel (Yescarta) er ca. 2,6 mio. DKK og for bedste tilgængelige behandling er lægemiddelomkostningerne ca. 95.000 DKK i AIP.

Amgros' afrapportering – Budgetkonsekvenser

Amgros vurderer, at anbefaling af axicabtagene ciloleucel (Yescarta) som mulig standardbehandling, vil resultere i budgetkonsekvenser på ca. [redacted] DKK per år.

Tabel 3: Amgros' hovedanalyse for totale budgetkonsekvenser, mio. DKK, ikke-diskonterede tal, SAIP.

	År 1	År 2	År 3	År 4	År 5
Anbefales	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anbefales ikke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Samlet budgetkonsekvenser	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Hvis analysen udføres med AIP, vil budgetkonsekvenserne være på ca. 100 mio. DKK per år.

AXICABTAGENE CILOLEUCEL (YESCARTA)

BEHANDLING AF DIFFUS STORCELLET B-CELLE-LYMFOM

AMGROS 30. april 2019

AMGROS

OPSUMMERING

Baggrund

Axicabtagene ciloleucel (Yescarta) er en genetisk modificeret autolog anti-CD19 chimeric antigenreceptor (CAR) T-celleterapi indiceret til behandling af patienter med refraktær eller recidiverende diffus storcellet B-celle-lymfom (DLBCL) efter to eller flere linjer af systemisk behandling. Amgros' vurdering tager udgangspunkt i dokumentationen indsendt af Gilead Science.

[redacted]
Analyse

I analysen af meromkostninger per patient sammenlignes behandling med axicabtagene ciloleucel (Yescarta) med bedste tilgængelige behandling for voksne patienter (> 18 år) med relaps eller refraktær DLBCL efter to eller flere linjer af systemisk behandling. I analysen sammenlignes behandling med axicabtagene ciloleucel (Yescarta) med behandling med komparator bestående af DHAP, GDP og ICE.

[redacted]
Inkrementelle omkostninger og budgetkonsekvenser

Amgros har vurderet de inkrementelle omkostninger per patient ved brug af axicabtagene ciloleucel (Yescarta) sammenlignet med komparator bestående af DHAP, GDP og ICE. De inkrementelle omkostninger er angivet i SAIP.

I scenariet, som Amgros mener er mest sandsynligt, er de gennemsnitlige meromkostninger for axicabtagene ciloleucel (Yescarta) ca. [redacted] per patient sammenlignet med komparator bestående af DHAP, GDP og ICE. Hvis analysen udføres med AIP bliver de inkrementelle omkostninger til sammenligning 3,05 mio. DKK per patient.

Amgros vurderer, at budgetkonsekvenserne for regionerne per år ved anbefaling af axicabtagene ciloleucel (Yescarta) som standardbehandling vil være ca. [redacted] i år 5. Hvis analysen udføres med AIP, er budgetkonsekvenserne ca. 100 mio. DKK i år 5.

[redacted]
Konklusion

Amgros kan konkludere, at behandling med axicabtagene ciloleucel (Yescarta) er forbundet med meget høje inkrementelle omkostninger sammenlignet med behandling med komparator bestående af DHAP, GDP og ICE. De inkrementelle omkostninger drives primært af prisen på axicabtagene ciloleucel (Yescarta).

Liste over forkortelser

AIP	Apotekernes indkøbspris
ALL	Akut lymfatisk Leukæmi
DHAP	Dexamethason, cytarabin og cisplatin
DKK	Danske kroner
DLBCL	Diffus storcellet B-celle-lymfom
DRG	Diagnose Relaterede Grupper
GDP	Gemcitabin, dexamethason og cisplatin
SAIP	Sygehusapotekernes indkøbspris
SoC	Standardbehandling
KOL	Key Opinion Leader
ICE	Ifosphamid, carboplatin og etoposide
IVIG	Immunglobulin indgivet intravenøst

INDHOLD

LOG

Ansøgning	
Lægemiddelfirma:	Gilead Sciences Inc.
Handelsnavn:	Yescarta
Generisk navn:	Axicabtagene ciloleucel
Indikation:	Axicabtagene ciloleucel er indiceret til behandling af voksne patienter (> 18 år) med relaps eller refraktær diffust storcellet B-celle-lymfom (DLBCL) og primær mediastinal storcellet B-celle-lymfom (PMBCL) efter to eller flere linjer af systemisk behandling.
ATC-kode:	L01X

Proces	
Ansøgning modtaget hos Amgros:	09-01-2019
Endelig rapport færdig:	30-04-2019
Sagsbehandlingstid fra endelig ansøgning:	111 dage
Arbejdsgruppe:	**Line Brøns Jensen** **Mark Friborg** Pernille Winther Johansen Louise Greve Dal Lianna Christensen

Priser
Denne rapport bygger på analyser udført på baggrund sygehusapotekernes indkøbspriser (SAIP). Enkelte steder er analysens resultat yderligere angivet på baggrund af listepriser (AIP).

1 BAGGRUND

Axicabtagene ciloleucel (Yescarta) er en genetisk modificeret autolog anti-CD19 chimeric antigenreceptor (CAR) T-celleterapi. Axicabtagene ciloleucel (Yescarta) er indiceret til behandling af patienter med refraktær eller recidiverende diffus storcellet B-celle-lymfom (DLBCL) efter to eller flere linjer af systemisk behandling. Gilead Sciences (herefter omtalt som ansøger) er markedsføringstilladelsesindehaver af axicabtagene ciloleucel (Yescarta) og har den 09.01.2019 indsendt en ansøgning til Medicinrådet om anbefaling af axicabtagene ciloleucel (Yescarta) som standardbehandling på danske sygehuse til den nævnte indikation. Som led i denne ansøgning vurderer Amgros, på vegne af Medicinrådet de økonomiske analyser, ansøger har sendt som en del af den samlede ansøgning til Medicinrådet. Denne rapport er Amgros' vurdering af de fremsendte økonomiske analyser (herefter omtalt som analysen).

1.1 Problemstilling

Formålet med analysen er at estimere meromkostningerne per patient og de samlede budgetkonsekvenser for regionerne ved anbefaling af axicabtagene ciloleucel (Yescarta) som standardbehandling til behandling af patienter med B-celle-lymfom, altså DLBCL, primær mediastinal storcellet B-celle-lymfom (PMBCL) eller transformeret follikulært lymfom (TFL). I analyserne sammenlignes axicabtagene ciloleucel (Yescarta) med bedste tilgængelige behandling. Bedste tilgængelige behandling er kemoterapi bestående af flere præparater, disse er uddybet i afsnit 1.3.1.

1.2 Patientpopulation

DLBCL udgør omkring 40 % af non-Hodgkin lymfom (NHL). I Danmark diagnosticeres ca. 500 patienter årligt med DLBCL. Risikoen for at udvikle DLBCL stiger med alderen, og medianalderen i Danmark ved diagnose er 67 år (1). Det estimeres, at omkring 100 patienter med DLBCL årligt er refraktære eller oplever recidiv efter to eller flere linjer af systemisk behandling. Af disse patienter forventes ca. 25-50 patienter årligt at være kandidater til axicabtagene ciloleucel (Yescarta), vurderet på baggrund af alder, performance status og tidligere behandling (2). Udover denne patientpopulation, inkluderes også PMBCL som er en aggressiv lymfom hvor tilbagefald ofte forekommer inden for de første måneder (3).

1.3 Behandling med axicabtagene ciloleucel (Yescarta)

Indikation

Axicabtagene ciloleucel (Yescarta) er indiceret til behandling af patienter med relaps eller refraktær diffus storcellet B-celle-lymfom (DLBCL) efter to eller flere linjer af systemisk behandling.

Virkningsmekanisme

Patientens perifere blodmononukleære celler opsamles ved brug af leukaferese (stamcellehøst). Herfra isoleres T-cellerne, som modificeres genetisk ved brug af en retroviral vektor, som indsætter CAR i T-cellerne. De CAR-modificerede T-celler ekspanderes og føres tilbage til patienten via blodbanen, hvor de lokaliserer og binder sig til alle CD19-positive B-celler og dræber disse. Inden axicabtagene ciloleucel (Yescarta) kan administreres, skal patienten igennem cellehøst af patientens hvide blodceller, som skal nedfryses, samt en kemoterapicyklus for at "tømme" patienten for lymfocytter (4).

Dosering

Axicabtagene ciloleucel (Yescarta) gives som en enkelt intravenøs infusion, hvorefter cellerne ekspanderes ved celledeling in vivo. Den anbefalede dosis af axicabtagene ciloleucel (Yescarta) er 2 x 10^6 levedygtige CAR T-celler/kg legemsvægt på dag 0. Forud for administration af axicabtagene ciloleucel (dag -5, -4 og -3) behandles patienten med lavdosis kemoterapi bestående af fludarabin (30 mg/m^2/d) og cyclofosfamid (500 mg/m^2/d) (5). Dette skal sikre, at T-cellerne ekspanderer optimalt i patienten og udviser optimal antitumoraktivitet.

1.3.1 Komparator

Medicinrådet har defineret bedste tilgængelige behandling som kan være flere forskellige regimer. Disse regimer er nævnt nedenfor.

- GDP (gemcitabin, dexamethason og cisplatin)
- CEOP (cyclophosphamid, vincristin, epirubicin og prednison)
- CVP (cyclophosphamid, vincristin og prednison)
- GemOx (gemcitabin og oxaliplatin)
- DHAP (cisplatin, cytarabin, dexamethason)
- ICE (ifosfamid, carboplatin, etoposid)

Alternativt kan følgende enkeltstofbehandlinger overvejes:

- Gemcitabin
- Pixantron
- Bendamustin

Ovenstående behandlinger bliver i nogle tilfælde kombineret med rituximab.

Ansøger har valgt at anvende en blandet komparator bestående af DHAP, GDP og ICE. De tre regimer er vægtet, 60 % for DHAP, 15 % for GDP og 25 % for ICE. Derudover har ansøger valgt at antage, at en del af patienterne der modtager denne behandling, også modtager rituximab. Denne blandet komparator sammenlignet med axicabtagene ciloleucel (Yescarta) opfylder protokollens retningslinjer(2).

1.4 Medicinrådets kliniske spørgsmål

Medicinrådet har vurderet den kliniske merværdi af axicabtagene ciloleucel (Yescarta) sammenlignet med nuværende standardbehandling til voksne patienter (>18 år) med relaps eller refraktær DLBCL eller PMBCL efter to eller flere linjer af systemisk behandling.

2 VURDERING AF INDSENDT ØKONOMISK ANALYSE

I den økonomiske analyse sammenlignes axicabtagene ciloleucel (Yescarta) med DHAP, GDP og ICE til behandling af voksne med relaps eller refraktær DLBCL og PMBCL efter to eller flere linjer af systemisk behandling, hvilket er i overensstemmelse med protokollen fra Medicinrådets vurdering af den kliniske merværdi. Derudover har ansøger inkluderet en tredje population bestående af TFL-patienter (6).

Ansøger har valgt ikke at indsende en analyse på subgruppen beskrevet i protokollen der med nuværende behandlingsmuligheder vurderes at kunne behandles med kurativt sigte, dvs. patienter, som er yngre end 65 år, har performancestatus 0-1 og beskeden komorbiditet. Amgros har derfor ikke vurderet de sundhedsøkonomiske omkostninger for denne subgruppepopulation.

2.1 Model, metode og forudsætninger

2.1.1 Modelbeskrivelse

Ansøger har indsendt en partitioned survival model for behandling af patienter i den nævnte population for DLBCL og PMBCL, samt inkluderet en population for TFL. Ansøger har inkluderet omkostninger forbundet med behandlingen jf. Amgros' Metodevejledning, samt kvalitetsjusterede leveår og leveår.

Patienter allokeres til enten axicabtagene ciloleucel (Yescarta) eller et behandlingsmix bestående af de i protokollen nævnte komparatorer. Modellen består af 3 stadier; præ-progression, post-progression og død. Patienter starter i modellen i stadiet præ-progression, hvor de modtager behandling med axicabtagene ciloleucel (Yescarta) eller komparatorer. Herfra kan patienterne opleve sygdomsprogression, hvorfra de vil flytte til stadiet post-progression, eller dø (og flytte til stadiet "Død").

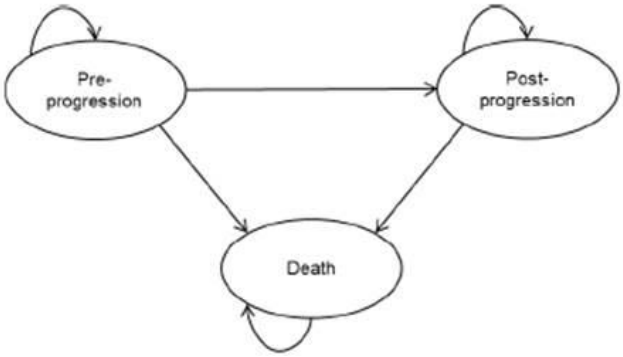
Andelen af patienter i de forskellige stadier bestemmes ud fra overlevelseskurver; overall survival (OS) og progression free survival (PFS). OS er ekstrapoleret via patient level data baseret på en mixture-cure tilgang, mens PFS er ekstrapoleret baseret på en partitioned survival tilgang. I ansøgers model er effektdata fra henholdsvis to kliniske fase 2-studier med DLBCL, PMBCL og TFL-patienter. For SoC er OS estimeret ved brug af patient data fra SCHOLAR-1 studiet(7). For axicabtagene ciloleucel (Yescarta) er der anvendt patient data fra ZUMA-1 studiet (8). Yderligere data, som for eksempel DRG-takster, er danske.

En cyklus på en måned blev anvendt til at estimere proportionen af patienter i hver stadie over tid. Transitionssandsynligheder er estimeret per cyklus for at modellere den behandlingsspecifikke effekt af axicabtagene ciloleucel (Yescarta) og SoC. I hver cyklus bliver patienter redistribueret mellem de tre stadier med død som det absorberende stadie. Derudover har ansøger anvendt half-cycle correction.

ZUMA-1 studiet har en median opfølgningstid på 27,1 måneder (8). SCHOLAR-1 studiet består af fire forskellige studier. SCHOLAR-1 studiet pooler data fra to fase 3 kliniske studier (Lymphoma Academic Research Organization-CORAL og Canadian Cancer Trials Group LY.12) og to kohorte studier (MD Anderson Cancer Center og University of Iowa/Mayo Clinic Lymphoma Specialized Program of Research Excellence). Ud fra disse data estimerer SCHOLAR-1 så responsrater og overlevelsesrater. Tiden som patienter er i studiet, rangerer fra 1 år til 14 år(7).

Modellen består af følgende helbredsstadier:

- Event-free Survival (EFS): Defineret fra start af behandling indtil død, relaps, eller ineffektiv behandling
- Progressive disease (PD): Defineret som tiden i sygdomsprogression. Proportionen af dette stadie er sat til at være lig differencen mellem patienter i EFS og antallet af levende patienter, som er baseret på overlevelseskurven
- Death: Defineret som død. Fungerer som et absorberende stadie i modellen



Figur 1: Modelstruktur (kilde: Gilead Sciences Inc.)

Amgros' vurdering

Amgros vurderer, at den overordnede struktur og opbygning af modellen er rimelig i forhold til beskrivelsen af sygdomsforløbet og omkostningerne forbundet med behandling af DLBCL, PMBCL og TFL.

Ansøgers model anvender ekstrapolering som blandt andet anvender en mixture cure model. En mixture cure model er en type overlevelsesanalysemodel, der er brugbar når der er et klinisk rationale eller antagelse om at en andel af patienterne bliver længerevarende remission, altså kureret. Denne andel af patienterne manifesterer sig ofte som et plateau eller en flad hale på overlevelseskurven, for eksempel på en Kaplan Meier kurve. Mixture cure modellen antager at patientpopulationen kan deles ind i to subpopulationer, en der oplever længerevarende remission og en population der ikke gør.

Amgros accepterer modeltilgangen, men vurderer at resultaterne bør tolkes med forsigtighed, eftersom ZUMA-1 er fase 1/2-studie med en relativ kort opfølgningstid samt det er et single arm, open label studie. Amgros er dog opmærksom på, at den anvendte data er den bedste tilgængelige.

2.1.2 Analyseperspektiv

Analysen har et begrænset samfundsperspektiv og en tidshorisont på livstid som i modellen løber 44 år frem med den sidste patient der forlader modellen efter cirka 40 år. Omkostninger er diskonteret med en faktor på 4%.

Amgros' vurdering

Analysens begrænsede samfundsperspektiv og diskonteringsrate er i tråd med Amgros' retningslinjer og godtages derfor.

Valget af tidshorisont i en økonomisk analyse skal være tilstrækkeligt langt for at opfange betydelige relevante forskelle mellem intervention og komparator i analysen under hensyntagen til det naturlige sygdomsforløb for diagnosen. Langtidseffekten af behandling med axicabtagene ciloleucel (Yescarta) er af gode grunde endnu ikke kendt, da behandlingen er ny og studierne fåtallige, samt kortvarige.

Amgros godtager analysens perspektiv, da den inkluderer patientens fulde potentielle levetid. Denne faktor er usikker men grundet den tilgængelige data eller mangel på bedre, accepterer Amgros i dette konkrete tilfælde ansøgers analyseperspektiv.

2.1.3 Omkostninger

Det følgende afsnit om omkostninger redegør for hvordan og hvilke omkostninger ansøger har inkluderet i analysen.

I modellen gives axicabtagene ciloleucel (Yescarta) i sidste linje, men inden dette kan lade sig gøre skal patienten igennem cellehøst af patientens hvide blodceller, som skal nedfryses, samt en kemoterapicyklus for at "tømme" patienten for lymfocytter. Ansøger har justeret for antallet af patienter der reelt modtager behandling af dem

der modtager leukaferese (cellehøst). Da det kun er 108 af de i alt 119 patienter der modtager axicabtagene ciloleucel (Yescarta) så justeres dette med en faktor 1,102 (119/108 = 1,102) Dette fremgår i tabel 1.

Tabel 1 Omkostning af cellehøst og justering.

Procedure	DKK	Kilde
Leukaferese (cellehøst)	16.003	16MP05 Afareser (Sundhedsdata-styrelsen 2018)
Justering af patientantal	Faktor 1,102	Ansøgers justering (119/108)
Samlet omkostning	**17.633**	

KOL: Key Opinion Leader

Modellen anvender fludarabinphosphat og cyclophosphamid som de to lægemidler der skal administreres før infusion med axicabtagene ciloleucel (Yescarta).

Tabel 2 illustrerer priserne på regimet der bruges i forbindelse med at eliminere patientens lymfocytter. Disse priser er beregnet med SAIP-priser og jævnfør den dosis og protokol, der er brugt i studiet ZUMA-1 (8).

Tabel 2 Kemoterapi før axicabtagene ciloleucel (Yescarta), SAIP (april 2019).

Behandling	DKK (SAIP)	Dosis	Kilde
Fludarabinphosphat	[redacted]	30 mg/m^2/dag	Medicinpriser.dk
Cyclophosphamid	[redacted]	500 mg/m^2/dag	Medicinpriser.dk
Samlet pris	[redacted]		

Tabel 3 viser omkostningerne forbundet med administrationen af kemoterapien. Omkostningerne er baseret på DRG taksten for basis kemoterapi, samt den ambulante takst for administration. Derudover bliver der igen justeret for antallet af patienter der modtager kemoterapi men ikke axicabtagene ciloleucel (Yescarta)(8).

Tabel 3 Omkostningerne forbundet med administration af kemoterapi.

Behandling	DKK	Beregning/Kilde
Ambulant administration	672	Sundhedsdatastyrelsen, 2017 (DAGS: BG50A Ambulant besøg, pat. Mindst 7 år)
Behandling med cytostatika	9.534	Sundhedsdatastyrelsen, 2018 (DRG takst: 2724 Kemoterapi, basis)
Justering af patientantal	Faktor 1,019	Ansøgers justering (110/108)
Samlet pris	**10.400**	

DRG: takst system; DAGS: Ambulant takstsystem.

Amgros' vurdering

Amgros accepterer ansøgers beregninger. Der er dog en potentiel underestimering af administrationen af lægemidlet da dette kræver specialiseret uddannelse og den takst ansøger har anvendt er en generel takst. Hvilke omkostninger det vil medføre er dog stadig ukendt.

Lægemiddelomkostninger

Listeprisen (AIP) på axicabtagene ciloleucel (Yescarta) er 2.440.000 DKK per infusion, standardbehandling er baseret på en fast DRG-takst nævnt i tabel 4.

I modellen tilgår omkostninger primært efter første cyklus for patienter behandlet med axicabtagene ciloleucel (Yescarta), i modsætning til komparator, som gennemgår kemobehandling, der forløber over flere måneder/cyklusser. Tabel 4 viser behandlingsomkostninger for axicabtagene ciloleucel (Yescarta).

Tabel 4 Behandlingsomkostninger for axicabtagene ciloleucel (Yescarta), SAIP (april 2019)

Procedure	Omkostninger DKK	Beregning/Kilde
Lægemiddel/procedure	[redacted]	Ansøger
Administration*	4.325	Sundhedsdatastyrelsen 2018 (DRG: 16PR02 Transfusion af blod, øvrig)
Hospitalisering	7.469	Rigshospitalet 2016 (Heldøgn – ONK, Finsecentret)
Samlet behandlingsomkostninger	[redacted]	

Ansøger har valgt at anvende et mix af de tre anvendte behandlinger DHAP, GDP og ICE. Ansøger har fået dette mix valideret af en dansk klinisk ekspert, samt fordelingen af patienter på disse tre behandlinger. De tre behandlinger er fordelt i ansøgers model som, 60 % DHAP, 15 % GDP og 25 % ICE.

Behandlingskombinationen DHAP indeholder dexamethason, cytarabine, cisplatin og eventuelt rituximab.

Ansøger antager at patienter modtager 3 behandlinger i gennemsnit, baseret på input fra en dansk klinisk ekspert.

Lægemiddelomkostninger for de tre behandlinger kan ses i tabel 5.

Tabel 5 Lægemiddelomkostninger for DHAP, SAIP (april 2019).

Lægemiddel	Mg/dag	Mg/enhed	Pris per enhed DKK	Administration per cyklus
DHAP				
Cisplatin	100 mg/m^2	50 mg 100 mg	[redacted]	1 (dag 1)
Cytarabine	2000 mg/m^2	1000 mg	[redacted]	2 (2 doser dag 2)
Dexamethason	40 mg/dag	20 mg	[redacted]	4 (dag 1-4)
ICE				
Ifosfamid	5000 mg/m^2	1000 mg	[redacted]	1 (dag 2)
Carboplatin	450mg 150 mg	450 mg 150 mg	[redacted]	1 (dag 2)
Etopsid	100 mg/m^2	100 mg	[redacted]	3 (dag 1, 2 og 3)
GDP				
Gemcitabin	1000 mg/m^2	1000 mg	[redacted]	2 (dag 1 and dag 8)
Dexamethason	40 mg/dag	20 mg	[redacted]	4 (dag 1-4)
Cisplatin	100 mg/m^2	50 mg 100 mg	[redacted]	1 (dag 1)

Indlæggelsesomkostninger

Modellen inkluderer omkostninger til indlæggelser, som er beregnet i modellen med estimater ud fra danske kliniske eksperter og danske takster(9). Ansøger har tildelt hvert helbredsstadie en omkostning. Omkostningen for progression-fri stadie er estimeret til DKK 396 og for progression stadiet er det DKK 59.537.

Tabel 6 Hospitaliserings-, ambulante og blodprøve omkostninger.

Procedure	Progressionsfrit stadie	Progression stadie	Enheds-omkostninger	Kilde
Lægebesøg	Hver 3. måned	3 besøg per måned	927	
Sygeplejerske besøg	-	3 besøg per måned	927	Antaget til at være lig lægebesøg
Ambulant besøg	-	7 dage per måned	7.469	Rigshospitalet 2016
Hjemmehjælp	-	-	1.881	Sundhedsdatastyrelsen 2017
Blodprøver	4 per måned	6 per måned	314	Region Sjælland 2018 Region Hovedstaden

Amgros' vurdering

Amgros vurderer, at ansøger overestimerer omkostningerne forbundet med patienter, der dør. Eftersom en større andel af patienterne i komparatorarmen dør, betyder det, at omkostningerne forbundet med behandling med komparatorer overestimeres, og meromkostningerne forbundet med behandling med axicabtagene cilileucel (Yescarta) underestimeres.

Omkostninger til efterfølgende stamcelletransplantation

De estimerede omkostninger til efterfølgende stamcelletransplantation er baseret på et gennemsnit af DRG-takster, input fra en dansk klinisk ekspert indhentet af ansøger, samt tidligere estimater fra tidligere afrapporteringer. Tabel 7 viser omkostningerne for de kirurgiske procedurer inklusiv stamcelletransplantation.

Tabel 7 Anvendte takster for kirurgiske procedurer.

Behandling	Omkostning per enhed (DKK)	Kilde/beregning
Allogen stamcelletransplantation	462.083	DRG takst (26MP24)
Opfølgning omkostninger	43.701	Ansøgers estimat
Samlet omkostning for allogen stamcelletransplantation	**505.784**	
Autolog stamcelletransplantation	208.156	DRG 26MP29
Opfølgning omkostninger	43.701	Ansøgers estimat
Samlet omkostning for autolog stamcelletransplantation	**251.857**	

Stamcelletransplantationsrater for axicabtagene ciloleucel (Yescarta) og komparator er henholdsvis 3% og 29% (7,8). Autologe stamcelletransplantationsrate for axicabtagene ciloleucel (Yescarta) er på 1%. Stamcelletransplantationsrater for komparator fra SCHOLAR-1 differere mellem 0 % og 29 %. Ansøger har valgt at antage, at 29% af patienter i komparatorarmen modtager autolog transplantation, som er den konservative tilgang. Raterne er fra studierne ZUMA-1 og SCHOLAR-1 (7,8).

Ansøger har inkluderet omkostninger forbundet med efterfølgende stamcelletransplantation til patienter, der har fået behandling med axicabtagene ciloleucel (Yescarta). Andelen af patienter, der modtager efterfølgende stamcelletransplantation er fundet i ZUMA-1 studiet (8). Omkostningerne er estimeret baseret på relevante DRG-takster.

Ansøger antager, at ingen patienter i komparator-armen modtager efterfølgende stamcelletransplantation.

Amgros' vurdering

Da nuværende praksis (DHAP, GDP og ICE) har en højere rate af stamcelletransplantationer i forhold til tilsvarende rate for axicabtagene ciloleucel (Yescarta) er omkostningerne forbundet axicabtagene ciloleucel (Yescarta) mindre. I studierne, som ansøger baserer sine antagelser på, er axicabtagene ciloleucel (Yescarta) anvendt som en erstatning til både kemoterapi og transplantation. Derfor transplanteres færre patienter for axicabtagene ciloleucel (Yescarta) i forhold til komparator.

Amgros vurderer, at ansøger foretager et konservativt valg ved at udelade omkostninger til stamcelletransplantation i komparator-armen.

Amgros accepterer den valgte tilgang.

Behandlingsrelaterede bivirkningsomkostninger

Ansøger har inkluderet omkostninger til bivirkninger, cytokin release syndrome (CRS) også kaldet cytokinstorm og B-celle aplasi. Derudover er flere af bivirkningerne inkluderet i hospitalsindlæggelsestakster.

CRS er en formodet nødvendig reaktion på axicabtagene ciloleucel (Yescarta) behandlingen som patienten skal igennem for at opleve effekt af behandlingen. Klinisk manifesterer CRS sig som alt fra relativ milde symptomer som feber, kvalme, opkast og muskelsmerter til mere seriøse symptomer som hypotension, respiratorisk insufficiens, nyre insufficiens og blødningsforstyrrelser. De fleste patienter vil kræve indlæggelse og intensiv behandling.

Tabel 8 Omkostninger for bivirkningen CRS, DKK

Bivirkning	DKK	Beregning/Kilde
Andel der får CRS	13 %	ZUMA-1 (8)
CRS omkostning	21.377	Sundhedsdatastyrelsen, 2018 (DAGS takst: BG50A "Ambulant besøg, pat. mindst 7 år")
Omkostning per patient	**2.779**	

[redacted]

Amgros' vurdering[redacted]

Ansøger har argumenteret omfattende for de inkluderede omkostninger og begrundet antagelserne.

Amgros vurderer, at eksklusion af omkostninger forbundet med IVIG underestimerer omkostningerne forbundet med behandling med axicabtagene ciloleucel (Yescarta). Ifølge ZUMA-1 studiet vil 25% af patienterne 2 år efter behandling stadig have brug for IVIG-behandling (8).

Amgros vurderer, at ansøgers tilgang er forbundet med potentiel underestimering af omkostningerne forbundet med behandlingen, men accepterer ansøgers tilgang.

[redacted]

Patienter og pårørendes tidsforbrug

Terminale omkostninger er også inkluderet i ansøgers model. Ansøger antager 30 dages specialiseret palliativ indsats med taksten "26HJ03 specialiseret palliativ indsats, lille, hjemmebesøg" til DKK 6.080 per dag. Dette resulterer i en omkostning på DKK 182.400 per patient der dør. Ansøger antager, at 51 % af patienterne dør i løbet af de første 5 år for axicabtagene ciloleucel (Yescarta) og 83 % af komparator-patienterne dør i løbet af de første 5 år. Ansøger antager, at den palliative behandling indbefatter 30 dages indlæggelse.

Amgros' vurdering

Ansøger har baseret mange af deres estimater på kliniske studier, deriblandt single arm-studier. Disse studier er på internationale patienter og visse estimater er derfor forbundet med stor usikkerhed. Studier har kort opfølgningstid, dette kan have signifikant betydning for resultatet over tid. Derudover har ansøger også flere estimater der er valideret af danske kliniske eksperter. X

Amgros har gennemgået relevante priser og estimater. Amgros er enige i ansøgers tilgang og modelkonstruktion.

[redacted]

2.2 Følsomhedsanalyser

Ansøger har udarbejdet en række følsomhedsanalyser hvor effekten af variation i forskellige parametre undersøges. Ansøgers følsomhedsanalyser viser at variation i behandlingsomkostningerne har størst indflydelse på resultatet. Variation i andre undersøgte parametre har mindre betydning for resultatet.

Amgros' vurdering

Da analysen hovedsagelig er drevet af lægemiddelomkostninger, vurderes det at denne er særlig vigtig for meromkostningerne. Ansøger har indleveret en grundig følsomhedsanalyse der belyser de fleste parametre af interesse. Dog mangler IVIG behandlingslængde og andel af patienter der modtager IVIG behandling. Amgros vurderer at følsomhedsanalyserne grundlæggende er acceptable.

3 RESULTATER

3.1 Ansøgers hovedanalyse

Ansøgers hovedanalyse resulterer i gennemsnitlige meromkostninger per patient for axicabtagene ciloleucel (Yescarta) sammenlignet med DHAP på ca. [redacted] DKK.

Hvis analysen udføres på baggrund af AIP, bliver lægemiddelomkostningerne for axicabtagene ciloleucel (Yescarta) ca. 2,6 mio. DKK, mens de total inkrementelle omkostninger bliver ca. 3,05 mio. DKK per patient.

Resultaterne fra ansøgers hovedanalyse præsenteres i tabel 9.

Tabel 9 Resultat af ansøgers hovedanalyse, gns. omkostninger per patient, DKK, diskonterede tal, SAIP.

Kategori	Axicabtagene ciloleucel (Yescarta) DKK	Komparator DKK	Inkrementelle omkostninger
Procedure/lægemiddel	[redacted]	[redacted]	[redacted]
Administration/Hospitalisering	824.574	200.613	**623.961**
Terminale omkostninger	123.543	170.277	**-46.734**
Bivirkninger	2.775	0	**2.775**
Samlet meromkostninger	[redacted]	[redacted]	[redacted]

[redacted]

Den største årsag til de inkrementelle omkostninger mellem de to behandlingsalternativer er den store engangsomkostning for axicabtagene ciloleucel (Yescarta). Derudover er der en betydelig omkostning til administration og hospitalisering, særligt for axicabtagene ciloleucel (Yescarta).

Amgros vurderer, at der er usikkerhed forbundet med de estimerede meromkostninger af axicabtagene ciloleucel (Yescarta), eftersom visse parametre er forbundet med stor usikkerhed og kan medføre store ændringer i de inkrementelle omkostninger.

Axicabtagene ciloleucel (Yescarta) er forbundet med høje meromkostninger ved igangsættelse af behandling sammenlignet med komparator.

CAR-T behandling kan dog være forbundet med høje omkostninger mange år frem, hvis IVIG-behandlingslængden viser sig at være mangeårig. Denne behandling er dog kun aktuel for en andel af patienterne, i axicabtagene ciloleucel (Yescarta)s tilfælde, skal 25 % stadig behandles 2 år efter deres infusion.

Amgros' vurdering

Amgros mener, at ansøgers model er en forsimpling af behandlingsforløbet med axicabtagene ciloleucel (Yescarta) og komparatorerne. Amgros accepterer dog ansøgers hovedanalyse, da de antagelser ansøger har valgt er baseret på bedst tilgængelige data. Ansøgers hovedanalyse afspejler derfor Amgros' hovedanalyse.

4 BUDGETKONSEKVENSER

Budgetkonsekvenserne per år er baseret på antagelsen om, at axicabtagene ciloleucel (Yescarta) vil blive anbefalet som standardbehandling. Man ser derfor på to scenarier:

A. Axicabtagene ciloleucel (Yescarta) bliver anbefalet som standardbehandling af Medicinrådet til indikationen, som denne analyse omhandler
B. Axicabtagene ciloleucel (Yescarta) bliver ikke anbefalet som standardbehandling

Budgetkonsekvenserne bliver differencen mellem budgetkonsekvenserne i de to scenarier.

4.1 Ansøgers estimater

4.1.1 Patientpopulation og markedsoptag

Ansøger har antaget, at patientpopulationen er 52 patienter per år, hvilket er baseret på estimater fra forskellige klinikere ud fra de 450 nye DLBCL-patienter per år. Ansøger estimerer selv at patientpopulationen er 52 patienter per år, som stammer fra estimater fra en beregning baseret på estimater på diverse andele af subpopulationer ud fra de 450 patienter per år.

Ansøger antager dog et meget begrænset markedsoptag. Markedsoptaget er beskrevet i tabel 10.

Tabel 10 Markedsoptag for antal patienter per år

Behandling	År 1	År 2	År 3	År 4	År 5
Anbefales					
Axicabtagene ciloleucel (Yescarta)	4	5	9	13	17
Komparatorer	48	47	41	39	35
Anbefales ikke					
Axicabtagene ciloleucel (Yescarta)	0	0	0	0	0
Komparatorer	52	52	52	52	52

Amgros' vurdering

Amgros vurderer, at der er lille usikkerhed forbundet med ansøgers estimater. Amgros har dog valgt at tage et gennemsnit af fagudvalget vedrørende lymfekræft (lymfomer)'s estimat på 25-50 patienter og anvende 38 patienter i budgetkonsekvenserne.

4.1.2 Estimat af budgetkonsekvenser

Ansøger har inkluderet de samme omkostninger i budgetkonsekvensanalysen, som der er inkluderet i omkostningsanalysen.

Med de indlagte antagelser estimerer ansøger, at anvendelse af axicabtagene ciloleucel (Yescarta) vil resultere i budgetkonsekvenser på ca [redacted] DKK det første år og ca. [redacted] DKK i år 5. Ansøger antager derudover at komparator behandler 52 patienter hvert år og axicabtagene ciloleucel (Yescarta) stiger i antal patienter som beskrevet i ovenstående tabel.

Ansøgers estimat af budgetkonsekvenserne fremgår af tabel 11.X

Tabel 11 Ansøgers hovedanalyse for totale budgetkonsekvenser, mio. DKK, ikke-diskonterede tal, SAIP.

	År 1	År 2	År 3	År 4	År 5
Anbefales	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anbefales ikke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Samlet budgetkonsekvenser	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Amgros' vurdering

Amgros mener at ansøgers forskellige estimater på patientpopulation for komparator og axicabtagene ciloleucel (Yescarta), samt det meget begrænsede markedsoptag for axicabtagene ciloleucel (Yescarta) er konservativt.

Amgros anvender det samme patientantal i begge patient populationer for at holde sig indenfor fagudvalget vedrørende lymfekræft (lymfomer) oprindelige estimat på 25-50 patienter om året(6) .X

Ansøgers estimater er i overensstemmelse med Amgros' metodevejledning, samt fagudvalget for lymfekræft's protokol og kan på baggrund heraf accepteres (6)*. Amgros udarbejder egen budgetkonsekvensanalyse, med ændring i at inkluderer 38 patienter og med et 100 % markedsoptag fra år 1. Budgetkonsekvensanalysen er baseret på ansøgers hovedanalyse.*

4.2 Amgros' estimat af budgetkonsekvenser

Amgros har korrigeret følgende estimater i forhold til ansøgers analyse:

- Omkostningerne fra ansøgers hovedanalyse anvendes med undtagelse af diskontering
- Amgros vælger at anvende et gennemsnit på 38 patienter i stedet for ansøgers begrænsede markedsoptag af patienter

Med de indlagte antagelser estimerer Amgros, at anvendelse af axicabtagene ciloleucel (Yescarta) vil resultere i budgetkonsekvenser på ca. [redacted] DKK per år. Budgetkonsekvenserne er usikre og fagudvalget vedrørende lymfekræft (lymfomer) vurderer, at der potentielt er mellem 25-50 patienter, der kan komme i behandling om året. Amgros hovedanalyse for budgetkonsekvenser vil derfor tage udgangspunkt i gennemsnittet på de to tal, altså 38 patienter(1).

Hvis analysen udføres med AIP bliver budgetkonsekvenserne ca. 100 mio. DKK per år.

Amgros' estimat af budgetkonsekvenserne fremgår af tabel 12.

Tabel 12 Amgros' hovedanalyse for totale budgetkonsekvenser, mio. DKK, ikke-diskonterede tal, SAIP.

	År 1	År 2	År 3	År 4	År 5
Anbefales	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anbefales ikke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Samlet budgetkonsekvenser	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

5 DISKUSSION

Amgros vurderer, at behandling med axicabtagene ciloleucel (Yescarta) er forbundet med meget høje meromkostninger sammenlignet med komparator. Meromkostningerne er primært drevet af prisen på axicabtagene ciloleucel (Yescarta).

Amgros identificerede flere usikkerheder og begrænsninger i ansøgers model og indsendte materiale. De kliniske studier af axicabtagene ciloleucel (Yescarta) var single arm-studier med relativt små populationer og kort opfølgningstid. Studierne mangler kontrolarme og derfor er det ikke muligt at sammenligne resultaterne fra disse studier med resultaterne fra komparator studierne uden en betydelig grad af usikkerhed. Patienter, der oplever hypogammaglobulinæmi på grund af B-celle aplasi har en øget risiko for infektioner, der nødsager dem til at modtage behandling med IVIG i et uvist antal år. Andelen af patienter, der kræver IVIG og behandlingslængden af IVIG er ikke kendt, dog må det nævnes at 25 % af patienterne i ZUMA-1 studiet stadig modtog IVIG efter 24 måneder.

Det må dog også nævnes, at patientpopulationens størrelse og alvorligheden af sygdommen vanskeliggør udførelsen af randomiserede kontrollerede studier. Amgros anerkender, at optimale data er begrænsede og at disse begrænsninger har ført til kompromisser.

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Høringssvar fra Gilead i forbindelse med udkast til Medicinrådets vurdering af klinisk merværdi for Yescarta til behandling af diffust storcellet B-celle-lymfom.

Til Medicinrådet 5. februar 2019

I forbindelse med modtagelsen af vurderingsrapporten af 23. januar 2019, vil vi først og fremmest gerne takke for en god og konstruktiv dialog med sekretariatet. Derudover har vi i Gilead en række bemærkninger til vurderingsrapporten. Vi har delt dem op i 3 temaer.

Yescarta tilfører klinisk merværdi

Vi er helt enige med Medicinrådet i at Yescarta tilfører en klinisk merværdi til patienter i Danmark med diagnosen diffust storcellet B-celle-lymfom (DLBCL). Vi noterer os at den kliniske merværdi er opnået på alle Medicinrådets definerede effektmål.

Specielt noterer vi os, at efter 2 års opfølgningstid i ZUMA-1 studiet lever stadig over halvdelen af de patienter som blev behandlet med Yescarta (Estimeret OS 50,5%). To års kliniske data er en væsentlig milepæl indenfor celleterapi.

”Fast track” i EMA fordi patienter ikke kan vente samt valg af komparator

Yescarta blev vurderet så vigtig at det fik ”fast-track” godkendelse i EMA. Dette betyder i sagens natur at Yescarta blev godkendt på fase I/II studier, netop for at nå hurtigt ud til patienter. Patienter som ofte kun har få måneder tilbage at leve (medianoverlevelse på ”standard of care” behandling er 6,3 måneder i SCHOLAR - 1 studiet)

I Gilead er vi uforstående overfor medicinrådets alternative valg af komparator. Vi kan ikke se rationalet i at Medicinrådet fravælger SCHOLAR - 1 som komparator. SCHOLAR - 1 er accepteret af 2 danske eksperter uafhængigt af hinanden, samt godkendt som komparator af EMA samt i både Sverige, Norge og Finland. SCHOLAR - 1 udmærker sig ved at være det største retrospektive observations studie der evaluerer outcome i refraktære NHL pateinter, herunder DLBCL, PMBCL og TFL.

I Gilead anerkender vi og er enige i værdien af CORAL studiepopulationen som komparator. CORAL indgår som én ud af fire populationer i SCHOLAR -1 studiet hvorfor SCHOLAR studiet i sin helhed repræsenter en mere virkelighedsnær og større population. Gilead mener at SCHOLAR -1 populationen udgør det bedste sammenligningsgrundlag for patientpopulationen inkluderet i

ZUMA - 1. Medicinrådets valg af CORAL EXT-1 og CORAL EXT-2 er i vores optik ikke et bedre valg, patienterne i CORAL skal bl.a. være kandidat til ASCT for at komme i betragtning til deltagelse, derudover var en betragtelig del af patienterne i CORAL EXT-2 studiet allerede CR ved opstart, grundet den anvendte definition af "behandlingsfejl". Sammenholdt introducerer disse omstændigheder en kraftig bias i studiet.

I Medicinrådets kliniske vurdering af Yescarta fremgår det på p. 12; "I ZUMA-1 studiet er 2 års overlevelsen estimeret til 50,5% [40,2; 57,7]. Til sammenligning var der efter 2 år ca. 30% der var i live i CORAL EXT-1, og 15,7% i CORAL EXT-2 (ingen konfidensintervaller angivet)." Ligeledes fremgår det igen på p. 12; "De tilgængelige data viser, at axicabtagene ciloleucel har effekt. Fagudvalget har en formodning om, at axicabtagene ciloleucel har en gavnlig effekt i forhold til komparator, men det er ikke muligt at vurdere effektforskellens størrelsesorden."

I Gilead noterer vi os at Yescarta dermed på performance i forhold til komparator/Standard of care kan sidestilles med overlevelsesraten fra evalueringen af Tisagenlecleucel i ALL- indikationen.

Medicinrådet har på p. 12 skrevet at "Fagudvalget bemærker, at der i ZUMA-1 studiet var 101 ud af i alt 119 inkluderede patienter, der reelt modtog infusionen. Blandt de patienter, der ikke modtog infusionen, var der en overvægt af patienter med lav performance og refraktær sygdom forud for inklusionen. Overlevelsesdata skal således tolkes i lyset af en mulig selektionsbias grundet dette frafald".

Gilead vil gerne kommentere dette udsagn. Dels var det 111 og ikke 119 pateinter som blev inkluderet altså 10 pateinter som ikke modtog CAR T celler. Vi understreger at der var forskellige årsager til at infusionen ikke kunne gennemføres samt at information angående disse patienters performance status og refraktær sygdom ikke er tilgængelige. Der var flere forskellige årsager til at pateinterne ikke blev inkluderet. Bl.a. progressiv sygdom, utilsigtet bivirkning samt ikke målbar sygdom. Man kan derfor ikke udlede at disse patienter havde dårligere performance status eller mere refraktær sygdom.

Patientpopulation i Danmark

Med hensyn til den aktuelle patientpopulation i Danmark vurderer Gilead at Medicinrådet overvurderer antallet af patienter som kan have gavn af behandlingen.

Fra Medicinrådets vurdering af Yescarta p. 6, citeres det: "Det estimeres at omkring 100 patienter med DLBCL årligt er refraktære eller oplever recidiv efter to eller flere linjer af systemisk behandling. Af disse patienter forventes ca. 25-50 patienter årligt at være kandidater til axicabtagene ciloleucel, vurderet på baggrund af alder, performance status og tidligere behandling".

Det er Gileads vurdering at dette tal er alt for højt – og dette er understøttet af kliniske eksperter i Danmark.

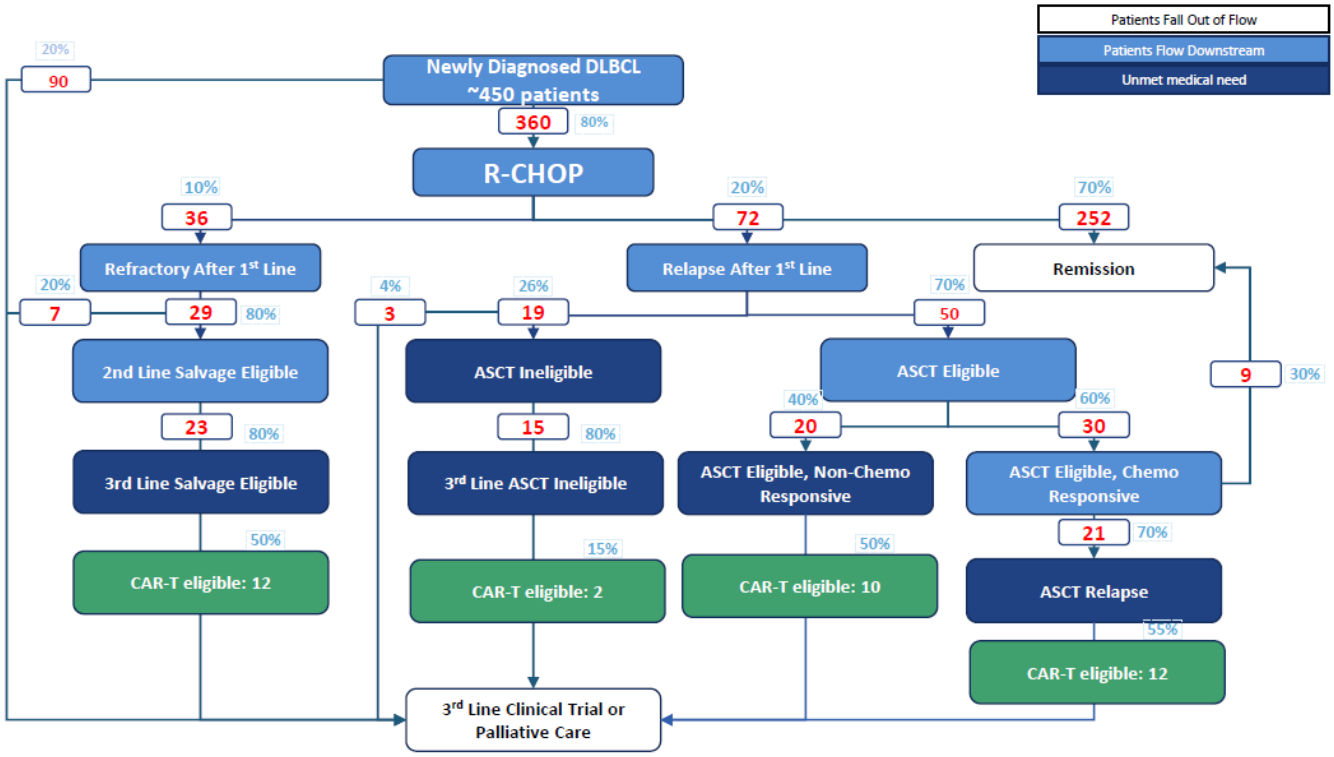
Ved gennemgang af de faglige selskabers data fra de nordiske lande, vurderes incidensen af DLBCL til:

- Sverige 550 patienter pr. år
- Norge 350 patienter pr. år
- Finland 500 patienter pr. år
- Danmark 450 patienter pr. år

Specialisterne kan ikke redegøre for forskellen i incidens mellem de nordiske lande.

I Danmark diagnosticeres ca. 450 individer årligt med DLBCL. Dette gør DLBCL til den hyppigst forekommende lymfom undergruppe.

I figuren herunder vises i flowchart behandlingsvejen i Danmark for DLBCL patienter. Behandlingsvej og patientdata er verificeret af bl.a. danske specialister.



Ca. 450 patienter diagnosticeres årligt i Danmark med DLBCL. Under det nuværende behandlingsparadigme vil ca. 36 patienter (summen af de grønne felter) ikke respondere eller relapse på behandlingen. Af disse ca. 36 patienter vurderer specialister at 15-20 patienter kan være kandidater til CAR-T behandling i Danmark pr. år.

På denne baggrund skal Gilead anmode Medicinrådet om at genoverveje sin vurdering af klinisk merværdi for Yescarta.

Med venlig hilsen

Flemming Axelsen
Sundhedsøkonom

Rikke Lyngaa
Medical advisor

Medicinrådet

Medicinrådets vurdering af klinisk merværdi for axicabtagene ciloleucel til behandling af diffust storcellet B-celle-lymfom

Versionsnr.: 1.1

Medicinrådet

Om Medicinrådet

Medicinrådet er et uafhængigt råd, som udarbejder anbefalinger og vejledninger om lægemidler til de fem regioner.

Medicinrådet vurderer, om nye lægemidler og nye indikationer kan anbefales som standardbehandling og udarbejder fælles regionale behandlingsvejledninger.

Nye lægemidler vurderes i forhold til effekt, eksisterende behandling og pris. Det skal give lavere priser og lægemidler, der er til størst mulig gavn for patienterne.

De fælles regionale behandlingsvejledninger er vurderinger af, hvilke lægemidler der er mest hensigtsmæssige til behandling af patienter inden for et terapiområde og dermed grundlag for ensartet høj kvalitet for patienterne på tværs af sygehuse og regioner.

Om vurderingen af klinisk merværdi

Vurderingen af klinisk merværdi er Medicinrådets vurdering af, hvor effektiv og sikkert lægemidlet er i forhold til andre lægemidler til den samme gruppe patienter.

Vurderingen af klinisk merværdi indgår, når Medicinrådet skal beslutte, om lægemidlet anbefales som mulig standardbehandling.

Se Medicinrådets metodehåndbog for yderligere information.

Dokumentoplysninger	
Godkendelsesdato	30. januar 2019
Ikrafttrædelsesdato	8. februar 2019
Dokumentnummer	40737
Versionsnummer	1.1

Medicinrådet, Dampfærgevej 27-29, 3. th., 2100 København Ø
www.medicinraadet.dk
Sprog: dansk
Format: pdf
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Indhold

1 Lægemiddelinformationer

Handelsnavn	Yescarta®
Generisk navn	Axicabtagene ciloleucel
Firma	Gilead/Kite Pharma EU B.V.
ATC-kode	LO1X
Virkningsmekanisme	Patientens egne T-celler genmodificeres til at udtrykke receptorer (chimeric antigen receptor (CAR)), der genkender den generelle B-celle-markør, CD19. De modificerede T-celler indgives intravenøst til patienten, hvor de binder sig til B-celler og slår disse ihjel.
Administration/dosis	Administration af én intravenøs infusion af axicabtagene ciloleucel med en target dosis på 2 x 10^6 CAR T-celler/kg kropsvægt (dag 0). Før transfusion af axicabtagene ciloleucel behandles patienten med lavdosis konditionerende kemoterapi bestående af fludarabinphosphat (30 mg/m^2/d) og cyclophosphamid (500 mg/m^2/d) på dag -5, -4 og -3.
EMA-indikation	Axicabtagene ciloleucel er indiceret til behandling af voksne patienter ($\geq$ 18 år) med relaps eller refraktær diffust storcellet B-celle-lymfom (DLBCL) og primær mediastinal storcellet B-celle-lymfom (PMBCL) efter to eller flere linjer af systemisk behandling.

2 Medicinrådets konklusion vedrørende klinisk merværdi

Medicinrådet vurderer, at axicabtagene ciloleucel giver en **ikkedokumenterbar klinisk merværdi** sammenlignet med bedste tilgængelige behandling, for voksne patienter med relaps eller refraktær diffust storcellet B-celle-lymfom efter flere systemiske behandlinger. Evidensens kvalitet vurderes at være meget lav.

Medicinrådet er enig med fagudvalget i, at der er behov for et mere solidt evidensgrundlag.

Medicinrådet kategoriserer lægemidlers kliniske merværdi i en af følgende kategorier:

Kategori 1. Stor merværdi: Vedvarende og stor forbedring i effektforhold der ikke tidligere er opnået med et relevant behandlingsalternativ. Eksempler herpå er sygdomsremission, markant stigning i overlevelsestid, langvarigt fravær af alvorlige sygdomssymptomer eller udtalt fravær af alvorlige bivirkninger.

Kategori 2. Vigtig merværdi: Markant forbedring, eksempelvis lindring af sygdomstilstand, moderat stigning i overlevelsestid, lindring af alvorlige symptomer, fravær af alvorlige bivirkninger og væsentligt fravær af andre bivirkninger.

Kategori 3. Lille merværdi: Moderat forbedring, f.eks. reduktion i ikkealvorlige sygdomssymptomer eller fravær af bivirkninger.

Kategori 4. Ingen merværdi: Ingen merværdi sammenlignet med standardbehandling/andre behandlinger.

Kategori 5. Negativ merværdi: Negativ merværdi sammenlignet med standardbehandling/andre behandlinger.

Kategori 6. Ikkedokumenterbar merværdi: Ikkedokumenterbar merværdi sammenlignet med standardbehandling/ andre behandlinger. Effektforskellen kan ikke kvantificeres ud fra det videnskabelige datagrundlag.

3 Forkortelser

CAR:	*Chimeric antigen receptor*
CHOP:	Cyclophosphamid, doxorubicin, vincristin og prednison
CNS:	Centralnervesystem
CRS:	*Cytokine release syndrome*
CVP:	Cyclophosphamid, vincristin og prednison
DHAP:	Cisplatin, cytarabin, dexamethason
DLBCL:	Diffust storcellet B-celle-lymfom
EMA:	*European Medicines Agency*
EPAR:	*European public assessment reports*
GDP:	Gemcitabin, dexamethason og cisplatin
GemOx:	Gemcitabin og oxaliplatin)
ICE:	Ifosfamid, carboplatin, etoposid
IPI:	*International Prognostic Score*
NHL:	Non-Hodgkins lymfom
OS:	Samlet overlevelse
PBMC:	Perifær blodmononukleær celle
PFS:	Progressionsfri overlevelse
PMBCL:	Primært mediastinal B-celle-lymfom
SAE:	*Serious adverse events*
TFL:	Transformeret follikulært lymfom

4 Formål

Formålet med Medicinrådets vurdering af klinisk merværdi af axicabtagene ciloleucel til diffust storcellet B-celle lymfom er at vurdere den kliniske merværdi i forhold til et eller flere lægemidler til samme patientgruppe (komparator).

Med udgangspunkt i den kliniske merværdi og en omkostningsanalyse udarbejdet af Amgros vurderer Medicinrådet, om axicabtagene ciloleucel anbefales som mulig standardbehandling.

5 Baggrund

Diffust storcellet B-celle-lymfom (DLBCL) er en aggressiv undertype af Non-Hodgkin lymfom (NHL). DLBCL udgør omkring 40 % af NHL. I Danmark diagnosticeres ca. 500 patienter årligt med DLBCL [1,2]. Risikoen for at udvikle DLBCL stiger med alderen, og medianalderen i Danmark ved diagnose er 67 år [2]. Prognosen er forholdsvis god med en 5-årsoverlevelse på 65-90 % afhængigt af risikoprofil (IPI). Patienter med DLBCL har typisk med en eller flere hurtigt voksende lymfeknuder, ofte lokaliseret på hals, i mediastinum og/eller i abdomen. Hos 40 % af patienterne præsenterer sygdommen sig dog med ekstranodal involvering af for eksempel mave-tarm-kanalen og det centrale nervesystem (CNS) [1,2]. Flere ekstranodale manifestationer er forbundet med dårlig prognose, og visse lokalisationer er forbundet med øget risiko for CNS-recidiv.

Det estimeres, at omkring 100 patienter med DLBCL årligt er refraktære eller oplever recidiv efter to eller flere linjer af systemisk behandling. Af disse patienter forventes ca. 25-50 patienter årligt at være kandidater til axicabtagene ciloleucel, vurderet på baggrund af alder, performancestatus og tidligere behandling.

Nuværende behandling

I henhold til de nuværende retningslinjer findes der ikke evidens for at anbefale et bestemt regime til 3. linjebehandling af patienter med refraktær eller recidiverende DLBCL [2,3]. Denne patientgruppe tilbydes den bedste tilgængelige behandling. Hvis sygdommen er kemosensitiv, kan allogen knoglemarvstransplantation anvendes til at konsolidere behandlingen og er potentielt kurativ. Hvis der ikke er mulighed for allogen knoglemarvstransplantation, kan det ikke forventes, at 3. linjebehandling vil være kurativ. Det anbefales at overveje eksperimentel behandling, når denne er tilgængelig. Behandlingsregimerne har forskellig intensitet og bivirkningsprofil. Valget af behandling vurderes for den enkelte patient og afhænger blandt andet af muligheden for allogen stamcelletransplantation, performancestatus, komorbiditet, tidligere behandlinger og alder. Følgende regimer kan overvejes med eventuelt tillæg af CD20-antistof (rituximab), såfremt det vurderes, at patienten kan tolerere behandlingen:

- GDP (gemcitabin, dexamethason og cisplatin)
- CHOP (cyclophosphamid, vincristin, doxorubicin og prednison)
- CVP (cyclophosphamid, vincristin og prednison)
- GemOx (gemcitabin og oxaliplatin)
- DHAP (cisplatin, cytarabin, dexamethason)
- ICE (ifosfamid, carboplatin, etoposid)

Alternativt kan følgende enkeltstofbehandlinger overvejes:

- Gemcitabin
- Pixantrone
- Bendamustin

Anvendelse af det nye lægemiddel
Axicabtagene ciloleucel er en autolog anti-CD19 chimeric antigen receptor (CAR) T-celleterapi [4] indiceret til 3. linjebehandling af patienter med refraktær eller recidiverende DLBCL.

En del af patientens hvide blodlegemer (perifere, mononukleære celler) opsamles ved brug af leukaferese. Herfra isoleres T-cellerne, som modificeres genetisk ved brug af en retroviral vektor, som indsætter CAR i T-cellerne. De CAR-modificerede T-celler ekspanderes og føres tilbage til patienten via blodbanen, hvor de lokaliserer og binder sig til alle CD19-positive B-celler og dræber disse [4].

Axicabtagene ciloleucel gives som en enkelt intravenøs infusion i en dosis på 2 x 10^6 CAR T-celler/kg legemsvægt (dag 0). Forud for administration af axicabtagene ciloleucel (dag -5, -4 og -3) behandles patienten med lavdosis kemoterapi bestående af fludarabin (30 mg/m^2/d) og cyclofosfamid (500 mg/m^2/d) [5]. Dette skal sikre, at T-cellerne ekspanderer optimalt i patienten og udviser optimal antitumoraktivitet.

6 Metode

Ansøgningen er valideret af Medicinrådet. Ansøger har anvendt og fulgt den præspecificerede metode, jf. protokol, som er udarbejdet af fagudvalget vedrørende lymfekræft og godkendt i Medicinrådet den 20. september 2018.

I protokollen stillede fagudvalget ét klinisk spørgsmål for at belyse effekten af axicabtagene ciloleucel sammenlignet med bedste tilgængelige behandling til voksne patienter med relaps eller refraktær DLBCL eller PMBCL efter to eller flere linjer af systemisk behandling.

Det kliniske studie omhandlende axicabtagene ciloleucel er enarmet, det vil sige, at det ikke er et randomiseret kontrolleret studie. Derfor er det ikke muligt at lave direkte sammenlignende analyser af effekten i forhold til en komparator.

Ansøger har leveret resultater for henholdsvis axicabtagene ciloleucel og komparator fra separate studier. Ingen af studierne er randomiserede kontrollerede studier, og ingen statistiske analyser er foretaget. Derfor er der for alle effektmål foretaget en naiv indirekte sammenligning.

Fra evidens til kategori. Medicinrådet vurderer den kliniske merværdi af et lægemiddel ud fra den indsendte endelige ansøgning, evt. suppleret med andet materiale. I protokollen blev effektmålene angivet som "kritiske", "vigtige" og "mindre vigtige". I vurderingen af klinisk merværdi vægter de kritiske højest, de vigtige næsthøjest og de mindre vigtige indgår ikke.

Den kliniske merværdi kategoriseres først enkeltvis pr. effektmål, hvorefter der foretages en vurdering af den samlede kategori for lægemidlet på tværs af effektmålene. Kategoriseringen pr. effektmål foretages på baggrund af absolutte og relative værdier for det enkelte effektmål. Den relative effekt beskrives med et estimat og et konfidensinterval, der sammenholdes med generiske væsentlighedskriterier. Den absolutte effekt sammenholdes med den i protokollen beskrevne "mindste klinisk relevante forskel". Den endelige kategorisering af lægemidlets kliniske merværdi er en delvis kvalitativ proces, hvor der foretages en vurdering af det samlede datagrundlag på tværs af effektmålene.

Vurdering af evidensens kvalitet foretages med udgangspunkt i GRADE og udtrykker tiltroen til evidensgrundlaget for de enkelte effektstørrelser og den endelige kategori for klinisk merværdi. Evidensens kvalitet inddeles i fire niveauer: høj, moderat, lav og meget lav. GRADE-metoden er et internationalt anerkendt redskab til systematisk vurdering af evidens og udarbejdelse af anbefalinger. I denne vurdering er metoden anvendt til at vurdere evidensens kvalitet.

7 Litteratursøgning

Ansøger har søgt litteratur som beskrevet i protokollen. Ansøgers PRISMA-diagram og litteraturgennemgang fremgår af ansøgningen. EMAs EPAR for axicabtagene ciloleucel er blevet konsulteret i udarbejdelsen af vurderingen [6]. Ansøger har identificeret fem datakilder, som er anvendt til at besvare det kliniske spørgsmål i ansøgningen (tabel 1). Fra disse kilder findes data vedrørende effekten af henholdsvis axicabtagene ciloleucel og den bedste tilgængelige behandling (kemoterapi og stamcelletransplantation).

Tabel 1: Datakilder identificeret af ansøger ved litteratursøgning til besvarelse af det kliniske spørgsmål samt Medicinrådets anvendelse i vurderingen af klinisk merværdi.

	Datakilde	Klinisk studie	N	Effektmål	Analyse i ansøgning	Anvendt i Medicinrådets vurdering
Komparator	Outcomes in refractory diffuse large B-cell lymphoma: results from the international SCHOLAR-1 study. *Crump et al. Blood. 2017* [4]	SCHOLAR-1 (relevant data fra fire observationelle studier: to kohortestudier (MDACCa [10] og IA/MCb [11,12]) samt opfølgningsdata fra to ublindede randomiserede fase 3-studier (LY.12 study [13]) og (CORAL study [14, 15].	636	OS Uønskede hændelser Responsrate PFS	*Naiv indirekte sammenligning*	*Nej (se afsnit 8)*
Axicabtagene ciloleucel	Axicabtagene Ciloleucel CAR T-Cell Therapy in Refractory Large B-Cell Lymphoma. *Neelapu et al. Engl J Med, 2017* [1]	ZUMA-1	7	OS Uønskede hændelser Responsrate PFS	*Naiv indirekte sammenligning*	*Kun data uønskede hændelser anvendes (se afsnit 8)*
	Phase 1 Results of ZUMA-1: A Multicenter Study of KTE-C19 Anti-CD19 CAR T Cell Therapy in Refractory Aggressive Lymphoma. *Locke et al. Mol Ther. 2017* [2]	ZUMA-1	101	OS Uønskede hændelser Responsrate PFS	*Naiv indirekte sammenligning*	*Nej (se afsnit 8)*
	Long-term safety and activity of axicabtagene ciloleucel in refractory large B-cell lymphoma (ZUMA-1): a single-arm, multicentre, phase 1-2 trial. *Locke et al. Lancet Oncol. 2018* [7][e]	ZUMA-1	101	OS Responsrate PFS	*Naiv indirekte sammenligning*	*Ja*
	Data on file (ZUMA-1-studiet)	ZUMA-1	33	Livskvalitet		*Nej (se afsnit 8)*
	European public assessment reports Yescarta 2018	EPAR		Uønskede hændelser (serious adverse reactions angivet)	*Naiv indirekte sammenligning*	*Ja*

[a]*MD Anderson Cancer Center*
[b]*the Molecular Epidemiology Resource of the University of Iowa/Mayo Clinic Lymphoma Specialized Program of Research Excellence*
[c]*Canadian Cancer Trials Group study*
[d]*Lymphoma Academic Research Organization (LYSARC) Collaborative Trial in Relapsed Aggres- sive Lymphoma*
[e]*Note fra ansøger: "After completion of the literature search, long-term safety and activity data of YESCARTA® (Axicabtagene Ciloleucel) in the ZUMA-1 study were published, and the article was therefore included."*

Fagudvalget har inddraget to datakilder, som vurderes at udgøre et bedre sammenligningsgrundlag for effekten af axicabtagene ciloleucel. Datakilderne fremgår af tabel 2.

Tabel 2: Datakilder identificeret af fagudvalget til besvarelse af det kliniske spørgsmål samt Medicinrådets anvendelse i vurderingen af klinisk merværdi.

	Datakilde	Klinisk studie	N	Effektmål	Analyse i ansøgning	Anvendt i Medicinrådets vurdering
Komparator	Outcomes of diffuse large B-cell lymphoma patients relapsing after autologous stem cell transplantation: an analysis of patients included in the CORAL study, *Van Den Neste, Bone Marrow Transplantation, 2017*	CORAL EXT-1 NCT00137995 [8]	75	OS Responsrate	-	*Data anvendt i naiv indirekte sammenligning*
	Outcome of patients with relapsed diffuse large B-cell lymphoma who fail second-line salvage regimens in the International CORAL study. *Van Den Neste, Bone Marrow Transplantation, 2016*	CORAL EXT-2 NCT00137995 [9]	203			

8 Databehandling

Medicinrådets fagudvalg vurderer, at ZUMA-1 kan anvendes til vurdering af den kliniske merværdi af axicabtagene ciloleucel. Som defineret i protokollen anvendes data med længst mulig opfølgningstid, derfor vil resultaterne fra ZUMA-1 2018-publikationen indgå i vurderingen. For effektmålet uønskede hændelser anvendes data fra ZUMA-1 2017-publikationen, idet opgørelsen herfra stemmer bedst overens med det i protokollen efterspurgte.

Fagudvalget vurderer, at SCHOLAR-1 ikke er den bedst tilgængelige datakilde til sammenligningen med komparator, idet det er uklart, hvordan patienterne i SCHOLAR er udvalgt, og hvilken behandling de har fået. Fagudvalget har derfor valgt at inddrage data fra to observationelle opfølgningsstudier fra CORAL-studiet (NCT00137995): CORAL EXT-1 [8] og CORAL EXT-2 [9], idet studiepopulationerne herfra er mere sammenlignelige med den i protokollen definerede population. Dog påpeger fagudvalget, at data skal tolkes med forbehold, idet populationerne ikke er direkte sammenlignelige, og på grund af de generelle metodiske forbehold ved sammenligning med observationelle data. Det generelle evidensgrundlag for behandling i 3. linje er sparsomt, hvilket yderligere vanskeliggør en sammenligning.

Ansøger har indsendt upublicerede data for livskvalitet for 33 patienter inkluderet i ZUMA-1-studiet. Det fremgår ikke, hvorvidt dette er en præspecificeret analyse, hvorfor der kun er data for 33 patienter, og hvorvidt disse patienter adskiller sig fra den øvrige studiepopulation. De upublicerede data for livskvalitet indgår ikke i vurderingen.

For alvorlige uønskede hændelser er der ikke data for alvorlige uønskede hændelser fra CORAL EXT-1 og EXT-2. Derfor er vurderingen af dette effektmål baseret på data fra ZUMA-1-studiet og fagudvalgets kliniske erfaringer.

For alle øvrige effektmål er der foretaget naive indirekte sammenligninger, idet det ikke er muligt at foretage statistiske sammenligninger med de tilgængelige data.

Data indsendt af ansøger kan ses i bilag 1.

9 Klinisk merværdi

9.1 Konklusion klinisk spørgsmål

Hvilken klinisk merværdi tilbyder axicabtagene ciloleucel sammenlignet med nuværende standardbehandling til voksne patienter (>18 år) med relaps eller refraktær DLBCL eller PMBCL efter to eller flere linjer af systemisk behandling?

Fagudvalget vurderer, axicabtagene ciloleucel til patienter med diffust storcellet B-celle-lymfom giver en **udokumenterbar klinisk merværdi** sammenlignet med bedste tilgængelige behandling. Evidensens kvalitet vurderes at være meget lav.

9.1.1 Gennemgang af studier

ZUMA-1 studiet er ublindet og ikke-kontrolleret, det vil sige, alle de inkluderede patienter, der kunne, blev behandlet med axicabtagene ciloleucel.

CORAL EXT-1 og EXT-2 er observationelle opfølgningsstudier af et ublindet, randomiseret studie, som sammenligner de to kemoterapiregimer R-DHAP (rituximab, dexamethason, cytarabin, cisplatinum) og R-ICE (rituximab, ifosfamid, carboplatinum, etoposid). CORAL EXT-1 omfatter patienter, der fik relaps efter stamcelletransplantation, og CORAL EXT-2 omhandler patienter, der ikke var kandidater til stamcelletransplantation efter to tidligere behandlinger. Begge patientpopulationer ville være kandidater til behandling med axicabtagene ciloleucel.

Karakteristika

Tabel 3: Studie- og baselinekarakteristika for studierne der ligger til grund for Medicinrådets vurdering af klinisk merværdi

	ZUMA-1 (fase 2 data fra august 2018)	CORAL EXT-1	CORAL EXT-2
Design	Enarmet, ublindet, multicenter, internationalt registerstudie	Ublindet, randomiseret fase 3 studie (subgruppe som fik relaps efter stamcelletransplantation)	Ublindet, randomiseret fase 3 studie (subgruppe som ikke responderede på induktionsbehandlingen før stamcelletransplantation, og dermed var kandidater til 3. linje)
Antal deltagere	101 modtog infusion, ud af 111 inkluderede	75	203
Median opfølgning, mdr. (min.-maks.)	27,1	32,8	30,1
Intervention	Én dosis a 2 x 10^6 anti-CD19 CAR-T-celler/kg	R-DHAP (rituximab, dexamethason, cytarabin, cisplatinum) +/- vedligeholdelsesbehandling (rituximab)	R-DHAP (rituximab, dexamethason, cytarabin, cisplatinum) +/- vedligeholdelsesbehandling (rituximab)
Komparator	Ingen	R-ICE (rituximab, ifosfamid, carboplatinum, etoposid)	R-ICE (rituximab, ifosfamid, carboplatinum, etoposid)
Analysepopulation	Efficacy: *Activity analyses excluded patients from phase 1* Safety: *all patients who received axicabtagene ciloleucel in both phases 1 and 2*	*"All patients with survival data"*	*"All patients with survival data"*

Population[a]	≥ 18 år, refraktær B-celle-lymfom (inklusiv DLBCL, PMBCL og TFL)[b] relaps efter sidste behandlingslinje, ECOG[c] performance status: 0-1	18-65 år, CD20-positiv DLBCL, relaps efter to tidligere kemoterapier, ECOG^ performance status på 0-2.	18-65 år, CD20-positiv DLBCL, relaps efter to tidligere kemoterapier, ikke kandidat til stamcelletransplantation, ECOG^ performance status på 0-2.
Median alder, år (min.-maks.)	58 (IQR 51-64)	56,1 (20,9-67,7)	55 (19-65)
Alder ≥ 65 år	24 %	-	-
Andel mænd	67 %	68 %	61 %
Primær diagnose			
DLBCL (%)	76	100	
PMBCL (%)	8	0	
TFL (%)	16	0	
Tidligere kemoterapi/ASCT			
1	3	28	
2	28	-	
2-3	-	46	
≥3	69	-	
≥4	-	0	
ECOG performance status	0: 42 % 1: 58 %	-	-
IPI status	≤2: 54 % >2: 46 %	0-2: 72 % >2: 28 %	<2: 30 % ≥2: 70 %

IQR: interquatile range, ECOG: Eastern Cooperative Oncology Group (performance status 0 = fuld funktionsdygtighed), IPI: international prognostic index (0 = bedste prognose).
[a] fyldestgørende beskrivelse af in- og eksklusionskriterier fremgår af ansøgningen.
[b] 2008 WHO-klassifikation

Population

Fagudvalget vurderer, at populationen i ZUMA-1 studiet og den poolede population i komparatorstudierne ikke er direkte sammenlignelig, men er det bedste tilgængelige data for sammenligning.

Fagudvalget vurderer, at populationerne i studierne overordnet set er sammenlignelige med den danske population, og at behandlingsregimerne anvendt i komparatorstudiet CORAL svarer til de, der anvendes i Danmark. Den population, som er defineret i protokollen, er patienter, som ikke længere har mulighed for kurativ behandling, fraset en mindre del som ville kunne få allogen knoglemarvs transplantation. Det stemmer overens med CORAL-studiet, hvor 17 % bliver transplanteret.

Fagudvalget vurderer, at effekterne påvist i studierne kan overføres til danske forhold. Fagudvalget bemærker dog, at studiepopulationerne udgør en selekteret undergruppe af den totale patientpopulation og er typisk yngre og med bedre funktionsniveau. Derfor er der i den kliniske virkelighed fortsat en patientgruppe med højere alder, større grad af komorbiditet og dårligere funktionsniveau, som ikke har nogen behandlingsmuligheder, og hvor effekten af axicabtagene ciloleucel ikke er undersøgt.

9.1.2 Resultater og vurdering

Resultater og vurdering af de effektmål, som fagudvalget har præspecificeret som hhv. kritiske og vigtige, følger nedenfor. Som beskrevet i afsnit 8 er det ikke muligt at sammenligne axicabtagene ciloleucel direkte med komparator. Derfor er den kliniske merværdi for OS baseret på naive indirekte sammenligninger.

Samlet overlevelse (overall survival, OS, kritisk)
Jævnfør protokollen er OS opgjort som andel, der opnår 2-årsoverlevelse. I ZUMA-1-studiet defineres OS som tiden fra axicabtagene ciloleucel-infusion til død uanset årsag. CORAL-EXT-1 definerer OS som tiden fra relaps efter stamcelletransplantation til død uanset årsag. CORAL-EXT-2 definerer OS som tiden fra *'failure'* på induktionsbehandling til død uanset årsag.

I ZUMA-1 studiet er 2-årsoverlevelsen estimeret til 50,5 % [40,2; 59,7]. Til sammenligning var der efter 2 år ca. 30 %, der var i live i CORAL EXT-1, og 15,7 % i CORAL EXT-2 (ingen konfidensintervaller angivet).

Der var 50 patienter, der døde i fase 2 af ZUMA-1-studiet, heraf 47 på grund af sygdomsprogression og 3 på grund af uønskede hændelser (data taget fra ZUMA-1 2018 appendix).

Fagudvalget bemærker, at der i ZUMA-1-studiet var 101 ud af i alt 111 inkluderede patienter, der reelt modtog infusionen. Overlevelsesdata skal således tolkes i lyset af en mulig selektionsbias grundet dette frafald.

De tilgængelige data viser, at axicabtagene ciloleucel har effekt. Fagudvalget har en formodning om, at axicabtagene ciloleucel har en gavnlig effekt i forhold til komparator, men det er ikke muligt at vurdere effektforskellens størrelsesorden. Fagudvalget kan derfor ikke på baggrund af disse data vurdere den kliniske merværdi af axicabtagene ciloleucel for effektmålet samlet overlevelse. Den kliniske merværdi er dermed **ikkedokumenterbar**.

Uønskede hændelser (vigtig)
Uønskede hændelser er et effektmål, der har til formål at belyse sikkerheden af axicabtagene ciloleucel og inkluderer bivirkninger, som kan have betydning for patientens livskvalitet. Jævnfør protokollen skulle uønskede hændelser opgøres som:

- andel af patienter, der oplever ≥ 1 alvorlig uønsket hændelse (*serious adverse event, SAE*), herunder en opgørelse af alvorlige bivirkninger (grad 3, 4 og 5)
- en beskrivelse af *cytokin release syndrom* (CRS)
- en beskrivelse af neurologiske bivirkninger.

Andel af patienter der oplever ≥ 1 alvorlig uønsket hændelse (SAE)
Som beskrevet i afsnit 8 er der ikke grundlag for at sammenligne alvorlige bivirkninger ved axicabtagene ciloleucel med komparator. Forskellen kan derfor ikke kvantificeres ud fra det videnskabelige datagrundlag, og en sammenligning af bivirkningsfrekvens mellem axicabtagene ciloleucel og komparator kan ikke foretages. Fagudvalget bemærker, at det er forventeligt, at axicabtagene ciloleucel giver andre bivirkninger end kemoterapi. Ansøger har angivet andele, der oplever mindst én alvorlig uønsket reaktion, det vil sige uønskede hændelser, som vurderes at være relateret til behandlingen.

Data er opgjort for både fase 1 og 2 i ZUMA-1-studiet, hvor 55 % af patienterne oplevede alvorlige uønskede reaktioner. De hyppigst forekommende alvorlige uønskede reaktioner var påvirket hjernefunktion (18 %), lungeinfektion (7 %), feber (7 %), lungebetændelse (6 %) (data taget fra ZUMA-1 2017).

De hyppigst forekommende grad uønskede hændelser ≥ 3 var lavt antal hvide blodlegemer (78 %), blodmangel (43 %) and lavt antal blodplader (38 %) (data taget fra ZUMA-1 2017).

Der var tre dødsfald på grund af uønskede hændelser, heraf 2 på grund af CRS efter infusion med axicabtagene ciloleucel og 1 på grund af blodprop i lungen (data taget fra ZUMA-1 2018 appendix).

Der er således en stor andel, der oplever alvorlige uønskede hændelser efter behandling med axicabtagene ciloleucel. Der er tale om en væsentligt anderledes bivirkningsprofil i forhold til komparator, derfor er det

ikke direkte sammenligneligt. Idet komparator er kemoterapi med betydelige bivirkninger, mener fagudvalget, at der også for axicabtagene ciloleucel kan accepteres væsentlige bivirkninger. Bivirkningerne er håndterbare, men der var to dødsfald relateret til de uønskede hændelser efter behandlingen.

Cytokin release syndrom (CRS)
CRS begynder typisk med forholdsvis milde symptomer som feber, muskelsmerter, svimmelhed og opkastning, men kan udvikle sig til mere alvorlige symptomer med stigende feber, lavt blodtryk, åndedrætsbesvær, ændringer i blodets evne til at størkne og nyresvigt.

Jævnfør protokollen lagde fagudvalget vægt på at vurdere alvorlighed, hyppighed og håndterbarhed af CRS.

I fase 2 af ZUMA-1-studiet var 94 ud af de 101 patienter, der fik axicabtagene ciloleucel (93 %), som oplevede CRS (alle grader) og 12 (13 %), som oplevede alvorlig CRS (grad 3 og 4). Symptomer ved CRS $\geq$ 3 var feber (11 %), lavt blodtryk (9 %), iltmangel (9 %) og for hurtig hjerterytme (1 %). Den mediane tid, før CRS satte ind, var 2 dage (fra 1 til 12 dage), og den mediane varighed var 8 dage (data taget fra ZUMA-1 2017).

Fagudvalget lægger vægt på den meget høje frekvens af CRS. I forhold til komparator med en helt anden bivirkningsprofil er det ikke relevant at sammenligne, men der er tale om en hyppig og ofte alvorlig bivirkning med potentiel dødelig udgang. I ZUMA-1-studiet var der således to dødsfald, som formodes at være relateret til CRS. Disse to tilfælde er forklaret ved udvikling af hæmofagocytose respektiv hjertestop.

Neurologiske bivirkninger
Jævnfør protokollen lagde fagudvalget vægt på at vurdere alvorlighed, hyppighed og håndterbarhed af neurologiske bivirkninger.

Ansøger beskriver, at der i fase 2 af ZUMA-1-studiet var 65 ud af de 101 patienter, der fik axicabtagene ciloleucel (65 %), som oplevede neurologiske bivirkninger, heraf var 28 % grad $\geq$ 3. De hyppigst forekommende neurologiske bivirkninger $\geq$ 3 var påvirket hjernefunktion (21 %), forvirring (9 %) talebesvær (7 %) og søvnløshed (7 %) (data taget fra ZUMA-1 2017).

Den mediane tid, før de neurologiske bivirkninger satte ind, var 5 dage (fra 1 til 17 dage), og den mediane varighed var 17 dage. I fire tilfælde varede bivirkningerne ved, til patienten døde (to på grund af sygdomsforværring og to på grund af uønskede hændelser, der ikke var relaterede til de neurologiske bivirkninger) (data taget fra ZUMA-1 2017).

Fagudvalget bemærker, at en bekymrende høj andel af patienterne oplever alvorlige neurologiske bivirkninger, og at bivirkningerne hos nogle patienter var til stede frem til patientens død.

Håndtering af CRS og neurologiske bivirkninger
I ZUMA-1-studiet var der 43 %, der blev behandlet med tocilizumab (et lægemiddel som er målrettet interleukin-6 (IL-6), og som sædvanligvis hjælper hurtigt på patientens tilstand) og 27 %, der blev behandlet med binyrebarkhormon på grund af CRS eller neurologiske bivirkninger. Ansøger beskriver, at dette tilsyneladende ikke påvirkede responsraterne (data taget fra ZUMA-1 2017).

I løbet af studiet faldt andelen af patienter, der oplevede CRS eller alvorlige neurologiske bivirkninger. Ansøger bemærker, at det kan skyldes den øgede erfaring med at håndtere bivirkningerne, og at en protokolændring tillod tidligere behandling i tilfælde af bivirkninger.

Samlet vurdering af uønskede hændelser
Fagudvalgets samlede vurdering er, at både axicabtagene ciloleucel og den nuværende bedste tilgængelige behandling er associeret med høj toksicitet, som er en belastning for patienterne. Bivirkningsprofilen er

væsentlig anderledes for axicabtagene ciloleucel, idet den langt hyppigste bivirkning er CRS og neurologiske bivirkninger, som ikke ses ved nuværende bedste tilgængelige behandling.

Fagudvalget vurderer samlet set, at bivirkningsprofilen for axicabtagene ciloleucel ikke er værre end for komparator, og at den overordnet set er acceptabel taget patienternes prognose i betragtning. Desuden bemærker fagudvalget, at bivirkningerne er håndterbare og for de fleste forbigående. Fagudvalget bemærker dog, at der var to dødsfald i det kliniske studie ZUMA-1.

Fagudvalget opfordrer til, at der indsamles omfattende data for CRS og neurologiske bivirkninger relateret til behandling med axicabtagene ciloleucel, som kan være alvorlige og varige.

På baggrund af tilgængelige data vurderer fagudvalget, at for effektmålet uønskede hændelser har axicabtagene ciloleucel en **ikkedokumenterbar klinisk merværdi**.

Helbredsrelateret livskvalitet (vigtig)
Der findes ikke publicerede data for effekten af behandling med axicabtagene ciloleucel på patienternes livskvalitet. Derfor er den kliniske merværdi i forhold til livskvalitet **ikkedokumenterbar**.

Responsrate (vigtig)
Jævnfør protokollen er responsrate opgjort som andel patienter, der fortsat er i komplet remission efter 1 år.

I ZUMA-1-studiet var der efter 1 år 35 %, der fortsat var i komplet remission, vurderet af en uafhængig central komité. Til sammenligning var der efter 1 år ca. 32 %, der var i komplet remission i CORAL EXT-1, og 27,1 % i CORAL EXT-2 (ingen konfidensintervaller angivet).

Fagudvalget vurderer, at en andel på 35 % i fortsat komplet remission efter ét år er en god effekt for patienter, sammenlignet med nuværende behandlingsmuligheder uden kurativt potentiale. Det er ikke muligt at vurdere effektforskellen i forhold til komparator. Fagudvalget kan derfor ikke på baggrund af disse data vurdere den kliniske merværdi af axicabtagene ciloleucel for effektmålet responsrate. Den kliniske merværdi er dermed **ikkedokumenterbar**.

Progressionsfri overlevelse, PFS (vigtig)
Jævnfør protokollen er progressionsfri overlevelse opgjort som median PFS. Dog findes kun data for patienter, der blev behandlet med axicabtagene ciloleucel fra ZUMA-1-studiet, som havde en median PFS på 5,9 mdr. [95 % CI 3,3; 15]. Der var ingen data for komparator at sammenligne med. Derfor kan den kliniske merværdi i forhold til PFS ikke dokumenteres.

Fagudvalget bemærker, at den mediane PFS er 5,9 måneder, hvilket er udtryk for, at mindst halvdelen har sygdomsprogression inden for det første halve år. Det betyder, at en stor, men ukendt, andel af patienterne ikke har gavn af behandlingen. Til gengæld er der stor effekt for de patienter, som har gavn af behandlingen, hvilket ses af effekten på overlevelse.

På baggrund af tilgængelige data vurderer fagudvalget, at for effektmålet PFS har axicabtagene ciloleucel **ikkedokumenterbar** klinisk merværdi.

9.1.3 Evidensens kvalitet

Evidensens kvalitet for vurderingen af axicabtagene ciloleucel er samlet set vurderet som værende **meget lav**.

Der findes ikke velvaliderede værktøjer til at vurdere evidensens kvalitet for ikkekomparative studier. Der foreligger derfor ikke en stringent vurdering af Risk of Bias eller en GRADE-profil. Evidensens kvalitet er beskrevet med inspiration fra de gængse værktøjer.

ZUMA-1 er et ikkekontrolleret studie, hvilket giver risiko for systematiske fejl (bias), idet man ikke har mulighed for at vide, hvordan det ville være gået patienterne, hvis de havde fået en anden behandling. Det medfører også en risiko for bias, at en del medforfattere har økonomiske interessekonflikter. CORAL EXT-1 og EXT-2 er begge observationelle studier af hver sin subgruppe, som har indgået i et randomiseret studie. Det giver risiko for bias, idet randomiseringen ikke længere er gældende. Alle tre studier er ublindede, hvilket giver risiko for bias, idet forventninger til behandlingernes effekt kan påvirke nogle af resultater. Alle studierne vurderes derfor at have høj risiko for bias, hvilket påvirker evidensens kvalitet negativt. Evidensgrundlaget er meget sparsomt, derfor vurderes det, at resultaterne er meget usikre. Da der ikke er nogen direkte sammenligninger i studierne, er evidensen indirekte, hvilket påvirker evidensens kvalitet negativt. Evidensen er desuden indirekte, fordi studiepopulationerne er en selekteret gruppe af de patienter, der behandles i praksis på grund af eksklusionskriterier i forhold til funktionsniveau, komorbiditet og alder.

Fagudvalget anser manglen på et randomiseret studie med en direkte sammenligning mellem axicabtagene ciloleucel og bedst tilgængelige standardbehandling som den væsentligste faktor i vurderingen af evidensens kvalitet.

9.1.4 Konklusion for det kliniske spørgsmål

For alle effektmål vurderer fagudvalget, at axicabtagene ciloleucel giver en **ikkedokumenterbar klinisk merværdi** sammenlignet med bedste tilgængelige behandling for voksne patienter med diffust storcellet B-celle-lymfom efter flere systemiske behandlinger. Evidensens kvalitet vurderes at være meget lav.

Det har ikke været muligt at udføre statistisk forsvarlige komparative analyser mellem axicabtagene ciloleucel og bedste tilgængelige behandling på baggrund af tilgængelige data. Der findes derfor ikke relative effektforskelle, som den kliniske merværdi kan vurderes ud fra, og i stedet er der udført en naiv indirekte sammenligning. Der er ikke data, som underbygger effekten af axicabtagene ciloleucel i forhold til komparator for nogen effektmål, og fagudvalget vurderer derfor, at den kliniske merværdi i forhold til komparator er ikkedokumenterbar.

Fagudvalget antager ud fra tilgængelige data, at axicabtagene ciloleucel har en bedre klinisk effekt end komparator. Fagudvalget bemærker desuden, at bivirkningsprofilen – til trods for at være væsentlig forskellig fra – ikke er mere toksisk end bedste tilgængelige behandling. Overordnet finder fagudvalget, at bivirkningsprofilen for axicabtagene ciloleucel er acceptabel, når patienternes prognose tages i betragtning.

Fagudvalget anser derfor axicabtagene ciloleucel som et muligt behandlingsalternativ for patienter, som ikke længere har et reelt kurativt behandlingstilbud, bortset fra enkelte patienter, som kan få allogen knoglemarvstransplantation. Det er ikke muligt at forudsige, hvilke af disse patienter der vil have effekt af behandlingen.

Fagudvalget efterspørger derfor et mere solidt evidensgrundlag med længere opfølgningstid og en direkte sammenligning med aktuel standardbehandling i et randomiseret design. Fagudvalget opfordrer til, at såfremt axicabtagene ciloleucel tages i brug, bør data indsamles systematisk, således det kan indgå i en fremtidig revurdering af den kliniske merværdi. Da det tyder på, at ikke alle patienter har samme gavnlige effekt af axicabtagene ciloleucel, efterspørger fagudvalget herunder viden om, hvilke subgrupper der har gavn af behandlingen.

10 Andre overvejelser

CAR-T er en ny behandlingsform i Danmark, og fagudvalget bemærker følgende i forhold til dette:

Behandlingen kræver særlige ressourcer og tilladelser. Leukaferesen skal udføres af vævscentre godkendt af Styrelsen for Patientsikkerhed. Produktet er et lægemiddel, hvor apoteket har tilladelse fra Lægemiddelstyrelsen til opbevaring og udlevering.

Fagudvalget påpeger, at selv om CRS er håndterbart kræver det for en stor del af de behandlede patienter indlæggelse på intensiv afdeling.

Sikkerhed for patienter: På grund af risikoen for udvikling af CRS skal der være min. 4 doser tocilizumab tilgængelige før infusion. Der er ingen kendte risikofaktorer for udvikling af CRS hos voksne patienter med DLBCL. Der skal sørges for forebyggende og terapeutisk behandling af infektioner, og der må ikke være infektion forud for infusion. På grund af risikoen for CRS skal patienten efter infusion være indlagt til observation/indlæggelse i 10 dage. Desuden skal patienten være i nærheden af behandlingsstedet i min. 4 uger efter infusion.

Spild: Det er vigtigt, at optøningen af axicabtagene ciloleucel planlægges nøje, da lægemidlet skal administreres indenfor 30 min. Efter optøning. Der er risiko for udsættelse eller aflysning af behandlingen, hvis patienten har for højt niveau af hvide blodceller eller har alvorlige bivirkninger efter kemoterapi, som påvirker lunger eller hjerte. Hvis optøningen af lægemidlet er påbegyndt, kan lægemidlet ikke genfryses, og behandlingen vil være spildt.

11 Fagudvalgets vurdering af samlet klinisk merværdi og samlet evidensniveau

Fagudvalget vurderer, at axicabtagene ciloleucel giver en **ikkedokumenterbar klinisk merværdi** sammenlignet med bedste tilgængelige behandling for voksne patienter med relaps eller refraktær diffust storcellet B-celle-lymfom efter flere systemiske behandlinger. Evidensens kvalitet vurderes at være meget lav.

Der er ikke data, som direkte underbygger effekten af axicabtagene ciloleucel i forhold til bedste tilgængelige behandling, derfor er den kliniske merværdi i forhold til komparator ikkedokumenterbar, jævnfør de præspecificerede kategorier.

Fagudvalget formoder dog på baggrund af det foreliggende evidensgrundlag, at axicabtagene ciloleucel har en bedre klinisk effekt end komparator og en acceptabel bivirkningsprofil for nogle af de patienter, som ikke længere har et reelt kurativt behandlingstilbud, fraset enkelte patienter som kan få allogen knoglemarvstransplantation. Det er ikke muligt at forudsige, hvilke af disse patienter der vil have effekt af behandlingen.

Fagudvalget efterspørger et mere solidt evidensgrundlag med længere opfølgningstid og en direkte sammenligning med aktuel standardbehandling i et randomiseret design, herunder viden om prognostiske markører. Såfremt axicabtagene ciloleucel tages i brug, bør data indsamles systematisk og indgå i evidensgrundlaget for en fremtidig revurdering af den kliniske merværdi.

12 Rådets vurdering af samlet klinisk merværdi og samlet evidensniveau

Medicinrådet tilslutter sig fagudvalgets vurdering.

13 Relation til eksisterende behandlingsvejledning

Der er ingen eksisterende behandlingsvejledninger på området.

14 Referencer

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15 Sammensætning af fagudvalg og kontaktinformation til Medicinrådet

Medicinrådets fagudvalg vedrørende lymfekræft (lymfomer)

Formand	***Indstillet af***
Lars Møller Pedersen *Overlæge*	Lægevidenskabelige Selskaber og udpeget af Region Hovedstaden
Næstformand	
Paw Jensen *Ledende overlæge*	Udpeget af Region Nordjylland
Medlemmer	***Udpeget af***
Jakob Madsen *Overlæge*	Region Nordjylland
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Jacob Haaber Christensen *Overlæge*	Region Syddanmark
Dorte Maegaard Tholstrup *Afdelingslæge*	Region Sjælland
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Kathrine Bruun Svan *Farmaceut*	Dansk Selskab for Sygehusapoteksledelse
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Michael Boe Møller *Overlæge*	Dansk Patologiselskab
Jørn Søllingvraa *Patient/patientrepræsentant*	Danske Patienter
En patient/patientrepræsentant	Danske Patienter

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16 Versionslog

Version	Dato	Ændring
1.1	08.02.2019	**Tabel 3, s. 10**: antal inkluderede patienter i ZUMA-studiet er ændret til 111 i stedet for 119. **s. 12**, under afsnit om samlet overlevelse er antal inkluderede ligeledes rettet fra 19 til 111. Desuden er følgende sætning slettet: ”Blandt de patienter, der ikke modtog infusionen, var der en overvægt af patienter med lav performance og refraktær sygdom forud for inklusionen.”
1.0	30.01.2019	Godkendt af Medicinrådet.

17 Bilag 1: Data indsendt af ansøger

Resultater for overlevelse fra ZUMA-1 og SCHOLAR-1 studierne.

	ZUMA-1 (2018)	SCHOLAR-1				
		MDACC	IA/MC	LY.12	CORAL	Pooled
Andel der opnår 2-årsoverlevelse	estimeret 50,5 % [40,2; 59,7]	17	10	23	22	20 % [16-23]

Resultater for uønskede hændelser fra ZUMA-1 og SCHOLAR-1 studierne.

	ZUMA-1 (fase 1- og 2-data)	SCHOLAR-1				
		MDACC	IA/MC	LY.12	CORAL	Pooled
Andel der oplever ≥ 1 alvorlig uønsket hændelse	55 %	-	-	-	29 % i R-ICE-gruppen 35 % i R-DHAP-gruppen	-

Resultater for responsrate fra ZUMA-1- og SCHOLAR-1-studierne.

	ZUMA-1 (2018)	SCHOLAR-1				
		MDACC	IA/MC	LY.12	CORAL	Pooled
Andel der fortsat er i komplet remission efter 1 år	35 %	-	-	-	-	10 % [5; 20]*

**ikke klart defineret om det er opnået eller opnået og fastholdt.*

Resultater for progressionsfri overlevelse fra ZUMA-1- og SCHOLAR-1-studierne.

	ZUMA-1 (fase 2 data fra august 2018)	SCHOLAR-1				
		MDACC	IA/MC	LY.12	CORAL	Pooled
PFS, mdr.	5,9 mdr. [3,3; 15]	2,8 mdr. [2,4; 3,3]	-	-	-	-

i.n.: ikke nået

Application for the assessment of clinically added value of YESCARTA® (Axicabtagene Ciloleucel) for treatment of diffuse large B-cell lymphoma

Contents

1 Basic information

TABLE 1-1 CONTACT INFORMATION

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TABLE 1-2 OVERVIEW OF THE PHARMACEUTICAL

Proprietary name	YESCARTA®
Generic name	Axicabtagene Ciloleucel
Marketing authorization holder in Denmark	Kite Pharma EU B.V. Science Park 408 1098 XH Amsterdam The Netherland
ATC code	LO1X
Pharmacotherapeutic group	Other antineoplastic agents
Active substance	Axicabtagene Ciloleucel (YESCARTA®) is an engineered autologous T-cell immunotherapy product whereby a patient's own T-cells are harvested and genetically modified ex vivo by retroviral transduction using an MSCV-based retroviral vector to express a CAR comprising an anti-CD19 single chain variable fragment linked to CD28 and CD3-zeta co-stimulatory domains. CD19 is expressed as a surface antigen in DLBCL and other aggressive B cell lymphomas. The transduced anti-CD19 CAR T cells are expanded ex vivo and infused back into the patient, where they can recognize and eliminate CD19 expressing target cells.
Pharmaceutical form	Dispersion for infusion. A clear to opaque, white to red dispersion.
Mechanism of action	YESCARTA® (Axicabtagene Ciloleucel) binds to CD19 expressing cancer cells and normal B cells. Following anti-CD19 CAR T cell engagement with CD19 expressing target cells, the CD28 and CD3-zeta co-stimulatory domains activate downstream signalling cascades that lead to T-cell activation, proliferation, acquisition of effector functions and secretion of inflammatory cytokines and chemokines. This sequence of events leads to apoptosis and necrosis of CD19 expressing target cells.
Dosage regimen	Administration of a single dose of YESCARTA® (Axicabtagene Ciloleucel) with a target dose of 2 x 106 CAR-positive viable T-cells per kg of body weight (or maximum of 2 x 108 CAR-positive viable T cells for patients 100 kg and above) in approximately 68 mL dispersion in an infusion bag. As pre-treatment, a lymphodepleting chemotherapy regimen consisting of cyclophosphamide 500

	mg/m^2 intravenous and fludarabine 30 mg/m^2 intravenous should be administered on the 5^{th}, 4^{th}, and 3^{rd} day before infusion of YESCARTA® (Axicabtagene Ciloleucel).
Therapeutic indication relevant for assessment (as defined by the European Medicines Agency, EMA)	YESCARTA® (Axicabtagene Ciloleucel) is indicated for the treatment of adult patients with relapsed or refractory DLBCL and PMBCL, after two or more lines of systemic therapy
Other approved therapeutic indications	None
Will dispensing be restricted to hospitals?	Yes, it will be restricted to qualified hospitals. Expected 1-2 centres in Denmark.
Combination therapy and/or co-medication	No, single therapy but with pre-medication of cyclophosphamide and fludarabine
Packaging – types, sizes/number of units, and concentrations	Each patient specific single infusion bag of YESCARTA® (Axicabtagene Ciloleucel) contains a dispersion of anti-CD19 CAR T cells in approximately 68 mL for a target dose of 2 x 10^6 anti-CD19 CAR-positive viable T-cells/kg body weight (range: 1 x 10^6 – 2 x 10^6 cells/kg), with a maximum of 2 x 10^8 anti-CD19 CAR T cells.
Orphan drug designation	Yes

2 Abbreviations

AE	Adverse event
AR	Adverse reaction
ASCT	Autologous stem-cell transplantation
CAR	Chimeric antigen receptor
CI	Confidence interval
CHOP	Cyclophosphamide, hydroxydaunorubicin, oncovin and prednisone
CR	Complete remission/ complete response
CRS	Cytokine release syndrome
DHAP	Cisplatin, cytarabine and dexamethasone
DLBCL	Diffuse large B-cell lymphoma
DMC	Danish Medicines Council
ECOG PS	Eastern Cooperative Oncology Group performance status
EQ-5D-3L	EuroQol 5-dimension 3-level
EQ-5D-5L	EuroQol 5-dimension 5-level
FACT-Lym	Functional assessment of cancer therapy – lymphoma
FL	Follicular lymphoma
G-CSF	Granulocyte colony stimulating factor
GDP	Gemcitabine, dexamethasone and cisplatin
HRQL	Health-related quality of life
Hyper-CVAD	Cyclophosphamide, vincristine, doxorubicin, dexamethasone, methotrexate and cytarabine
IA/MC	Iowa/Mayo Clinic Lymphoma Specialized Program of Research Excellence
ICE	Ifosfamide, carboplatin and etoposide
ITT	Intention-to-treat
IQR	interquartile range
IV	Intravenous(ly)
LOCF	Last observation carried forward
MCID	Minimal clinically important difference
MDACC	MD Anderson Cancer Center
MSCV	Murine Stem Cell Virus
NHL	Non-Hodgkin lymphoma
OS	Overall survival
PD	Progressive disease
PFS	Progression free survival
PMBCL	Primary mediastinal B-cell lymphoma
PR	Partial response
R-DHAP	Rituximab+DHAP
R-ICE	Rituximab+ICE
SAE	Serious adverse event
SAR	Serious adverse reaction
SD	Standard deviation
SF-36	36 item short form survey
TFL	Transformed follicular lymphoma
Vs	Versus
YESCARTA®	Axicabtagene Ciloleucel

3 Summary

YESCARTA® (Axicabtagene Ciloleucel) is an engineered autologous T-cell immunotherapy product whereby a patient's own T-cells are harvested and genetically modified ex vivo by retroviral transduction using an MSCV-based retroviral vector to express a CAR comprising an anti-CD19 single chain variable fragment linked to CD28 and CD3-zeta co-stimulatory domains. CD19 is expressed as a surface antigen in DLBCL and other aggressive B cell lymphomas. The transduced anti-CD19 CAR T-cells are expanded ex vivo and infused back into the patient, where they can recognize and eliminate CD19 expressing target cells.

YESCARTA® (Axicabtagene Ciloleucel) was approved by EMA 22 June 2018 with an indication for the treatment of adult patients with relapsed or refractory DLBCL and PMBCL, after two or more lines of systemic therapy. The clinical efficacy assessment was based on a comparison between the ZUMA-1 and SCHOLAR-1 study.

The ZUMA-1 study was a single arm, open-label, multi-centre, phase 1/2 clinical study in patients with relapsed or refractory DLBCL, PMBCL or TFL. 64% of the patients came with a history of 3 or more prior lines of treatment. In ZUMA-1, the initial phase 1 part enrolled and treated 7 patients and confirmed that YESCARTA® (Axicabtagene Ciloleucel) could be centrally manufactured and safely administered after which a phase 2 part was initiated. The phase 2 part enrolled 111 patients of which YESCARTA® (Axicabtagene Ciloleucel) was successfully manufactured for 110 (99%) and administered to 101 (91%).

The provided results stem partly from an updated analysis of the phase 1 and phase 2 part of the ZUMA-1 study including a total of 108 treated patients (mITT population) who had been followed for a minimum of 12 months from YESCARTA® (Axicabtagene Ciloleucel) infusion (median follow-up of 15.4 months) and partly from recently published long-term follow-up data to the phase 2 part where the 101 treated patients had been followed for a median of 27·1 months. In addition, long-term follow-up data are provided for patients treated at the National Cancer Institute with an anti CD19 CAR T construct identical to YESCARTA® (Axicabtagene Ciloleucel).

The literature search did not provide any direct comparator matches to the patient and intervention criteria for the clinical question. Therefore, the SCHOLAR-1 study was used as comparator to ZUMA-1 as done in the EPAR. The SCHOLAR-1 study retrospectively evaluated response rates and OS in 636 patients with relapsed or refractory DLBCL, PMBCL or TFL, to provide a benchmark for future clinical trials in this under-studied population.

The SCHOLAR-1 study also does not fully comply with the patient and intervention criteria as it includes patients with a broader range of indications and treatment backgrounds, but it is currently the best available approximation of real-world data for DLBCL and PMBCL patients with refractory disease on their 3rd or greater line of treatment. Danish clinical experts have confirmed that the survival data are representative of the survival they see in these patient groups.

As the two studies were single arm studies no calculations have been performed for relative or absolute differences. Instead a narrative comparison is provided.

In ZUMA-1, the median overall survival was not reached (95% CI 12.8–not estimable). The estimated 24-month survival proportion was 50.5% compared with a 2-year rate of OS of 17% in SCHOLAR-1 with no overlap in the 95%CIs of the two treatment results and clearly exceeding the 10%-point MCID. In further support of a high long-term median OS with YESCARTA® (Axicabtagene Ciloleucel) treatment, the OS for

22 patients (19 with DLBCL) treated with an anti CD19 CAR T construct identical to YESCARTA® (Axicabtagene Ciloleucel) was approximately 40% at 32 months.

The proportion of patients with ≥1 SAE was higher with YESCARTA® (Axicabtagene Ciloleucel) treatment than with R-ICE and R-DHAP treatment. It is, however, important to note that the patient population treated with R-ICE and R-DHAP were poorly matched to the ZUMA-1 population. It should also be noted that the CRS and neurologic events reported with YESCARTA® (Axicabtagene Ciloleucel) were generally reversible with no clinical sequelae and that the incidence of the CRS and neurologic events of grade 3 or higher decreased over the course of the ZUMA-1 study.

As different assessments of HRQL data were available for ZUMA-1 and SCHOLAR-1 no comparison could be done between YESCARTA® (Axicabtagene Ciloleucel) and standard treatment for this outcome, but patient health related quality of life was shown to be improved back to beyond their original levels by YESCARTA® (Axicabtagene Ciloleucel) therapy.

In addition to the higher OS rate, the proportion of patients who achieved and remained in CR when treated with YESCARTA® (Axicabtagene Ciloleucel), after a median follow-up of 15.4 months, was more than double the CR rate obtained in patients treated with standard treatment in the pooled patient analysis with 40% compared to 10% (again exceeding the 10%-point MCID). Additionally, the median duration of PFS was also higher than observed in the MDACC observational study with 5.8 months versus 2.8 months (meeting the MCID of 3 months).

In further support of the durable effect of anti-CD19 CAR T-cell therapy, OS at 32 months was 40% in 22 DLBCL patients treated with anti-CD19 CAR T-cell therapy identical to YESCARTA® (Axicabtagene Ciloleucel) and durable CRs were reported in 4 of 7 DLBCL patients treated with same anti-CD19 CAR T-cell therapy with duration of response ranging from 38-56 months.

The scarcity of relevant references for DLBCL or PMBCL patients with a history of two or more lines of therapy provides a grim indication of the poor survival chances of these patients with the current available standard treatment. The SCHOLAR-1 study is currently the best available approximation of real-world data for DLBCL and PMBCL patients with refractory disease on their 3rd or greater line of treatment. Danish clinical experts have confirmed that this survival is representative of the survival they see in these patient groups and clearly indicates a need for more effective treatment to improve CR and OS for these patients. With one YESCARTA® (Axicabtagene Ciloleucel) treatment a clinically relevant prolonged overall survival and durable CR can be obtained for a large proportion of these patients.

4 Literature search

A systematic literature search was performed in PubMed and in the Cochrane Library by two independent researchers. The inclusion and exclusion criteria for the search and selection are provided in Table 7-1 and the databases and search strategy are summarized in Table 7-2. In addition, the SCHOLAR-1 study was selected as a comparator to ZUMA-1 as done in the EPAR. Scholar-1 was developed as a companion study to ZUMA-1 to provide context for interpreting the ZUMA-1 results. The analysis included patients with DLBCL, PMBCL and TFL, with refractory defined as progressive disease or stable disease < 6 months as best response to last line of chemotherapy (≥ 4 cycles of first-line or 2 cycles of later-line therapy) or relapse ≤ 12 months after ASCT [5].

Altogether, 182 references were found. Of these, 77 were excluded as a consequence of being abstracts, duplicates, review articles or from non-EU/US journals. An additional 95 references were excluded at the title or abstract level based on the inclusion and exclusion criteria (Table 7-1). A total of 10 references were evaluated by reading the full text. Of these, 7 were excluded because the outcomes were from patients undergoing 2nd line treatment, only a minority of the patients had undergone 2 or more lines of treatment or there was no information on the number of previous treatment lines (Table 7-5). One of the studies (the LY.12 study[13]) was, however, included as one of the four studies providing patient data for the SCHOLAR-1 study (roughly 1/3 of the patients enrolled in the LY.12 study fitted the inclusion criteria for SCHOLAR-1 [4,13]).

The remaining three references, including the pooled multicohort retrospective SCHOLAR-1 study, were used for the narrative comparisons between YESCARTA® (Axicabtagene Ciloleucel) and the three comparator combinations: GDP, DHAP and ICE. In cases, where the outcomes were available in one or more of the individual studies from SCHOLAR-1 but not presented in SCHOLAR-1, data from the individual studies have been extracted but should be assessed with caution as the full study populations of those studies included patients who did not fulfil the criteria for refractory DLBCL. See section 5.2.1 for further details.

In addition, two references that did not otherwise fulfil the search criteria were included to provide the longest follow-up data available for treatment with the same CAR construct as YESCARTA® (Axicabtagene Ciloleucel), see section 5.2.2.

After completion of the literature search (Table 7-2), long-term safety and activity data of YESCARTA® (Axicabtagene Ciloleucel) in the ZUMA-1 study were published [3], and the article was therefore included in section 4.1 and 5.2.

4.1 Relevant studies

The relevant studies included in this application for the assessment of each clinical question, as defined in the assessment protocol, are listed in Table 4-1.

TABLE 4-1 RELEVANT STUDIES INCLUDED IN THE ASSESSMENT

Reference (title, author, journal, year)	Trial name/official title	NCT number	Dates of study (start and expected completion date)	Relevant for clinical question (main or subgroup)
YESCARTA® (Axicabtagene Ciloleucel) relevance				
Axicabtagene Ciloleucel CAR T-Cell Therapy in Refractory Large B-Cell Lymphoma. Neelapu, S. S. Locke, F. L., Bartlett, N. L., Lekakis, L. J., Miklos, D. B., Jacobson, C. A., Braunschweig, I., Oluwole, O. O., Siddiqi, T., Lin, Y., Timmerman, J. M., Stiff, P. J., Friedberg, J. W., Flinn, I. W., Goy, A., Hill, B. T., Smith, M. R., Deol, A., Farooq, U., McSweeney, P., Munoz, J., Avivi, I., Castro, J. E., Westin, J. R., Chavez, J. C., Ghobadi, A., Komanduri, K. V., Levy, R., Jacobsen, E. D. ,Witzig, T. E., Reagan, P., Bot, A. ,Rossi, J., Navale, L., Jiang, Y., Aycock, J. ,Elias, M. ,Chang, D. ,Wiezorek, J. Go, W. Y. N Engl J Med, 2017 [1]	ZUMA-1	NCT02348216	January 2015 - March 2032	Main and subgroup question
Phase 1 Results of ZUMA-1: A Multicenter Study of KTE-C19 Anti-CD19 CAR T Cell Therapy in Refractory Aggressive Lymphoma. Locke FL, Neelapu SS, Bartlett NL, Siddiqi T, Chavez JC, Hosing CM, Ghobadi A, Budde LE, Bot A, Rossi JM, Jiang Y, Xue AX, Elias M, Aycock J, Wiezorek J, Go WY. Mol Ther. 2017 [2]	ZUMA-1	NCT02348216	January 2015 - March 2032	Forms the background of the updated analysis presented in [1]
Long-term safety and activity of axicabtagene ciloleucel in refractory large B-cell lymphoma (ZUMA-1): a single-arm, multicentre, phase 1-2 trial. Locke FL, Ghobadi A, Jacobson CA, Miklos DB, Lekakis LJ, Oluwole OO, Lin Y, Braunschweig I, Hill BT, Timmerman JM, Deol A, Reagan PM, Stiff P, Flinn IW, Farooq U, Goy A, McSweeney PA, Munoz J, Siddiqi T, Chavez JC, Herrera AF, Bartlett NL, Wiezorek JS, Navale L, Xue A, Jiang Y, Bot A, Rossi JM, Kim JJ, Go WY, Neelapu SS. Lancet Oncol. 2018 [3][a]	ZUMA-1	NCT02348216	January 2015 - March 2032	Main and subgroup question

Reference (title, author, journal, year)	Trial name/official title	NCT number	Dates of study (start and expected completion date)	Relevant for clinical question (main or subgroup)
ICE, DHAP or GDP +/- R relevance but also including other chemotherapy agents (antracyclin based, HyperCVAD and ESHAP among the most frequent)				
Outcomes in refractory diffuse large B-cell lymphoma: results from the international SCHOLAR-1 study. Crump M, Neelapu SS, Farooq U, Van Den Neste E, Kuruvilla J, Westin J, Link BK, Hay A, Cerhan JR, Zhu L, Boussetta S, Feng L, Maurer MJ, Navale L, Wiezorek J, Go WY, Gisselbrecht C. Blood. 2017 [4]	SCHOLAR-1	Not provided	Data collection from 4 studies	Main

[a] After completion of the literature search, long-term safety and activity data of YESCARTA® (Axicabtagene Ciloleucel) in the ZUMA-1 study were published, and the article was therefore included in section 4.1 and 5.2

4.2 Main characteristics of included studies

The included studies were the ZUMA-1 study, which included a phase 1 and phase 2 part of a single-arm study in patients with refractory DLBCL, PMBCL or TFL treated with YESCARTA® (Axicabtagene Ciloleucel), and the SCHOLAR-1 study which provided a patient-level pooled analysis of OS and CR in patients with refractory DLBCL, including TFL and PMBCL, who went on to receive subsequent therapy with the selected comparators, among other treatments (see section 5.2.1 for further details).
The main characteristics of each of the studies are summarised in appendix 7.2. The following summary tables are provided for the main studies:

Table 7-6 Main study characteristics – ZUMA-1 study
Table 7-7 Main study characteristics – SCHOLAR-1 study

In the cases were outcomes were not reported as part of the SCHOLAR-1 study but were available in the individual studies included in SCHOLAR-1, data are presented from these instead although the full study populations in the original publications also included patients who did not meet the criteria for refractory DLBCL applied in SCHOLAR-1 (see section 5.2.1 for further details). Main study characteristics are therefore also shown for CORAL in Table 7-8 and for LY.12 in Table 7-9.

5 Clinical questions

Section 5.1 summarises the outcomes and assessments performed. The 2 clinical questions included in the assessment protocol are answered separately in sections 5.2 and 5.3.

5.1 Outcomes and assessments

The 7 outcomes to be evaluated for each clinical question, according to the assessment protocol for YESCARTA® (Axicabtagene Ciloleucel) from the DMC, are shown in Table 5-1 together with the pre-defined MCID for each outcome.

TABLE 5-1 OUTCOMES AND MCIDS DEFINED IN THE ASSESSMENT PROTOCOL FOR YESCARTA® (AXICABTAGENE CILOLEUCEL)

Outcome	Importance	Definition and unit	MCID between groups
OS	Critical	Proportion of patients who survives 2 years	10%-points
AE	Important	Proportion of patients who experience ≥1 serious adverse event	10%-points
		A narrative description of cytokine release syndrome adverse reactions (ARs) and neurological ARs. In addition, a detailed presentation of grade 3, 4 and 5 ARs	-
Health-related quality of life	Important	A difference in SF-36: Change from baseline to 1 year after the end of treatment.	0.5 SD of the pooled baseline score
		A difference in FACT-Lym: Change from baseline to 1 year after the end of treatment.	4 points
Response-rate	Important	Proportion of patients who achieve and remain in complete remission (CR) by 1 year	10%-points
PFS	Important	Median PFS	3 months

SF-36: 36-item Short Form Health Survey, FACT-Lym: Functional Assessment of Cancer Therapy - Lymphoma

5.2 Clinical question 3 (full population)

What added clinical value does YESCARTA® (Axicabtagene Ciloleucel) offer compared to the current standard treatment for adult patients (>18 years) with relapsed or refractory DLBCL and PMBCL, after two or more lines of systemic therapy?

Population

Adult patients (>18 years) with aggressive relapsed or refractory DLBCL or PMBCL after two or more lines of systemic therapy who are assessed to be candidates for YESCARTA® (Axicabtagene Ciloleucel).

Intervention

YESCARTA® (Axicabtagene Ciloleucel)

Comparator

As no standard treatment as such exists for the defined population in Denmark, the chosen comparator is the best available treatment. Patients who are candidates for treatment with the intervention will typically be selected based on age, performance status and former treatments. For this group, a combination therapy would typically be offered and the following combinations have been chosen as comparators:

GDP: gemcitabine, dexamethasone and cisplatin +/- rituximab
DHAP: cisplatin, cytarabine and dexamethasone +/- rituximab
ICE: ifosfamide, carboplatin and etoposide +/- rituximab

Outcomes

See Table 5-1 for the selected outcomes.

5.2.1 Presentation of relevant studies

Intervention: ZUMA-1

The ZUMA-1 study was a single arm, open-label, multi-centre, phase 1/2 clinical study in which the initial phase 1 part enrolled 7 patients and confirmed YESCARTA® (Axicabtagene Ciloleucel) could be centrally manufactured and safely administered after which a phase 2 part was initiated. The phase 2 part enrolled 111 patients of which 101 were administered YESCARTA® (Axicabtagene Ciloleucel). The provided results below primarily stem from an updated analysis of the phase 1 and phase 2 part of the ZUMA-1 study including the 108 treated patients and is based on the publication by Neelapu et al., 2017[1] and the EPAR assessment report[5] unless specified otherwise. The data cut-off for the updated analysis was 11 Aug 2017 at which time all patients had been followed for a minimum of 12 months from YESCARTA® (Axicabtagene Ciloleucel) infusion (median follow-up 15.4 months). In addition, a newly published article on long-term safety and activity of YESCARTA® (Axicabtagene Ciloleucel) for ZUMA-1 provided 2-year survival data for the phase 2 patients: At the cut-off date of Aug 11, 2018, 101 patients treated patients from the phase 2 part were followed up for a median of 27·1 months (IQR 25·7–28·8).[3]

The patients had DLBCL, PMBCL or TFL and all had relapsed or refractory disease. 64% of the patients had a history of 3 or more prior lines of treatment.

Additional details of the baseline characteristics in ZUMA-1 are provided in Table 7-6.

To provide further long-term efficacy and safety data for YESCARTA® (Axicabtagene Ciloleucel), outcome results from two single-institution studies (National Cancer Institute) of treatment with an anti CD19 CAR T construct identical to YESCARTA® (Axicabtagene Ciloleucel) are also presented where available:

- The “CAR T-Cell Receptor Immunotherapy for Patients With B-cell Lymphoma” study, reported by Kochenderfer et al., 2017 [6]. The study was a single-arm, open-label, single centre, phase 1/2 clinical study in which 22 patients were treated with CAR T-Cell Receptor Immunotherapy. Out of the treated patients, 19 had DLBCL, two patients had follicular lymphoma, and one patient had mantle cell lymphoma. Eleven of the 19 patients with DLBCL had chemotherapy-refractory lymphoma. Five patients with DLBCL had lymphoma that had relapsed 10 months or less after ASCT as their last treatment prior to protocol enrolment. The median number of unique lymphoma therapies received before protocol enrolment was four (range, one to seven). Two-year OS and PFS provided.
- Long-term follow-up results on durable CRs are provided for seven patients with subtypes of DLBCL, also reported by Kochenderfer et al., 2017 [7]. Individual patient follow-up up to as much as 4.7 years.

Comparators: SCHOLAR-1

The literature search did not provide any direct matches to the PICO for the clinical question for the comparator: None of the publications were based solely on patients with DLBCL or PMBCL with a history of 2 or more lines of chemotherapy and presented the relevant outcomes based on treated with GDP, DHAP or ICE (+/- R) (section 7.1). In the YESCARTA® (Axicabtagene Ciloleucel) EPAR [5], the clinical efficacy assessment was based on a comparison between the ZUMA-1 and SCHOLAR-1 studies. SCHOLAR-1 was undertaken in order to understand the expected response and OS rates with currently available therapies in a refractory NHL patient population to establish a benchmark for future studies and included 636 patients with refractory DLBCL. Although the SCHOLAR-1 study also does not fully comply with the PICO, it is currently the best available approximation of real-world data for patients on their 3 or later line of treatment and Danish clinical experts support that the pooled patient data in SCHOLAR-1 are similar to

what is seen for Danish patients with the current standard treatments used [8,9]. Therefore, SCHOLAR-1 was included as comparator in the present application.

The SCHOLAR-1 study was an international, multicohort retrospective NHL research study, which represents the largest patient-level pooled analysis to evaluate responses and OS rates in patients with refractory NHL, including DLBCL, TFL and PMBCL. For SCHOLAR-1, patient-level data were collected for patients with refractory DLBCL from 4 sources: observational cohorts from MDACC [10] and IA/MC [11,12] and follow-up of 2 large phase 3 randomized controlled trials, the LY.12 study [13] and the CORAL study [14, 15].

ALL PATIENTS FROM EACH DATA SOURCE WHO MET CRITERIA FOR REFRACTORY DLBCL, INCLUDING TFL AND PMBCL, WHO WENT ON TO RECEIVE SUBSEQUENT THERAPY, WERE CONSIDERED FOR ANALYSIS (

Figure 5-1). Refractory DLBCL, and subtypes PMBCL and TFL, was defined as progressive disease or stable disease as best response to chemotherapy (received ≥4 cycles of first-line therapy or two cycles of later line therapy, respectively) or relapse ≤12 months post-ASCT.

FIGURE 5-1 PATIENT INCLUSION AND SEARCH CRITERIA IN SCHOLAR-1

Reffering to Figure 1. In “Outcomes in refractory diffuse large B-cell lymphoma: results from the

international SCHOLAR-1 study” Crump et al. 2018

Diagram of (A) patients with refractory DLBCL included in the SCHOLAR-1 analysis and (B) search criteria for refractory DLBCL included in SCHOLAR1. CCTG, Canadian Cancer Trials Group; PD, progressive disease; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; SD, stable disease.
Source: Figure 1 [4]

Out of the patients selected from the individual studies by use of the refractory DLBCL criteria, 49% had a history of two or more lines of chemotherapy and ASCT at baseline (see Table 7-7 for baseline characteristics and additional details for SCHOLAR-1).

Briefly, the treatment history of the patients in SCHOLAR-1 were as outlined below. The treatments indicated in the DMC protocol (GDP, ICE and DHAP) were the most commonly used treatments in these studies.

MDACC database study: Second line rituximab-containing salvage therapies included: HyperCVAD (17%), ICE (15%), DHAP (14%), ESHAP (12%), Gem-Ox (9%) and methotrexate-cytarabine (4%), other chemotherapies (14%) and therapies on clinical trials (15%) [10].

IA/MC database study: anthracycline-based immunotherapy as initial treatment

LY.12 study: GDP or DHAP as second line treatment

CORAL study: ICE or DHAP in addition to rituximab

In the cases were outcomes were not reported as part of the SCHOLAR-1 study but were available in the individual studies, data are presented from these instead although the full study populations in the original publications also included patients who did not meet the criteria for refractory DLBCL applied in SCHOLAR-1. Furthermore, the majority of patients were in first relapse or refractory after first-line therapy in the

CORAL study [14] and had other indications than DLBCL such as peripheral T-cell lymphoma and anaplastic large-cell lymphoma in the LY.12 study [13]. Main study characteristics are shown for CORAL in Table 7-8 and for LY.12 in Table 7-9.

5.2.2 Results per study (ZUMA-1)

As the ZUMA-1 study was a single arm study no calculations have been performed for relative or absolute differences. The available results have been extracted from the two articles[1 and 3], and the EPAR[5] where relevant. An overview of the results is provided in Table 5-2 and detailed descriptions of the individual outcomes are provided in the below subsections.
A narrative comparison with the SCHOLAR-1 study is provided in section 5.2.4.

TABLE 5-2 SUMMARY OF TREATMENT EFFECT FOR YESCARTA® (AXICABTAGENE CILOLEUCEL), CLINICAL QUESTION 3.1 (ZUMA-1 STUDY)

Outcome	Available results
OS at 2 years	The median overall survival was not reached (95% CI 12.8–not estimable). The estimated 24-month survival proportion was 50.5% (95% CI 40.2–59.7).[3]
Proportion of patients with ≥1 SAE	59 out of 108 patients: 55% of the patients treated with YESCARTA® (Axicabtagene Ciloleucel) [5]
Narrative description of CRS and neurological adverse reactions	See the relevant subsections in the section Serious adverse events
Quality of life SF-36 and FACT-Lym	Published data for SF-36 and FACT-Lym were not available for ZUMA-1 but EQ-5D-3L are presented which are available on file. Patients experienced a decrease in utility scores from screening (0.739) to Week 4 (0.675), most likely because of a disutility associated with the timing of the transient toxicities associated with CAR T therapy. By Month 3 and Month 6, the patient utilities had increased back to beyond their original levels (0.756 and 0.758, respectively), showing that patient HRQL was improved by YESCARTA® (Axicabtagene Ciloleucel) therapy. See the section Health-related quality of life.
CR	After a median follow-up of 15,4 months, 40% remained in CR. [1]
PFS	Median duration of PFS at follow-up of minimum 12 months was 5.8 months (95%CI: 3.3 to could not be estimated) [1]

Overall survival – 2-year survival

At the data-cut-off for the long-term follow-up of ZUMA-1 (Aug 11, 2018)[3], 101 patients assessable for activity in phase 2 were followed up for a median of 27.1 months (IQR 25.7–28.8). The median overall survival was not reached (95% CI 12.8–not estimable; Figure 5-2). The estimated 24-month survival proportion was 50.5% (95% CI 40.2–59.7). No patients were lost to follow-up.[3]

FIGURE 5-2 KAPLAN-MEIER ESTIMATES OF OVERALL SURVIVAL (ZUMA-1, TREATED PHASE 1 + PHASE 2 PATIENTS)

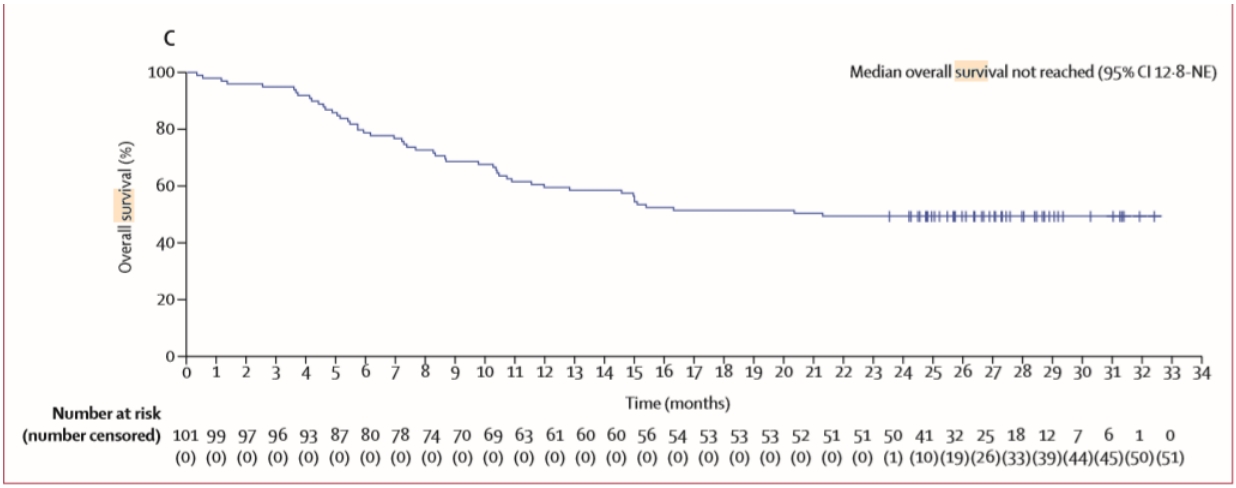


Figure 1: **Kaplan-Meier estimates of investigator-assessed duration of response (A), progression-free survival (B), and overall survival (C)**
All 101 patients assessable for activity in phase 2 are shown. The x-axis shows time since infusion of chimeric antigen receptor T cells. NE=not estimable.

Source: Figure 1, C [3]

In further support of a high long-term median OS with YESCARTA® (Axicabtagene Ciloleucel) treatment, the OS for 22 patients (19 with DLBCL) treated at the National Cancer Institute with an anti CD19 CAR T construct identical to YESCARTA® (Axicabtagene Ciloleucel) was approximately 40% at 32 months (Figure 5-3).

FIGURE 5-3 KAPLAN-MEIER ESTIMATES OF OVERALL SURVIVAL FROM SAME CAR CONSTRUCT AS YESCARTA® (AXICABTAGENE CILOLEUCEL)

Reffering to Supplemental figure 2 in “Lymphoma Remissions Caused by Anti-CD19 Chimeric Antigen Receptor T Cells Are Associated With High Serum Interleukin-15 Levels”. Kochenderfer et al. 2017 [6]

Serious adverse events

Proportion of patients experiencing ≥ 1 SAE

The proportion of patients from the combined phase 1 and 2 parts of the ZUMA-1 trial who had at least 1 SAE during the trial was 55% [Table 5-3].

TABLE 5-3 SAEs IN > 1 PATIENT IN ZUMA-1

MedDRA Preferred Term	Phase 1 and 2 Combined (N = 108) n (%)
Subjects with any Serious TE Adverse Event	59 (55)
Encephalopathy	19 (18)
Lung infection	8 (7)
Pyrexia	8 (7)
Pneumonia	6 (6)
Confusional state	5 (5)
Febrile neutropenia	5 (5)
Aphasia	4 (4)
Atrial fibrillation	4 (4)
B-cell lymphoma	4 (4)
Cardiac arrest	4 (4)
Urinary tract infection	4 (4)
Acute kidney injury	3 (3)
Agitation	3 (3)
Ejection fraction decreased	3 (3)
Hypotension	3 (3)
Hypoxia	3 (3)
Neutropenia	3 (3)
Somnolence	3 (3)
Atrial flutter	2 (2)
Delirium	2 (2)

Note: Preferred terms are sorted in descending order of total frequency count.
Adverse events are coded using MedDRA Version 19.0 and graded per CTCAE 4.03.
Percentages are calculated using N in each column as the denominator.

Source: Table 34 [5]

The most common SAEs occurring in >1 patient included encephalopathy (18%), lung infection (7%) and pyrexia (7%) (Table 5-3). 44 patients died from causes that included disease progression (37 patients), AEs (3 patients of which 2 patients died from YESCARTA® (Axicabtagene Ciloleucel) related events associated with CRS and 1 from pulmonary embolism unrelated to YESCARTA® (Axicabtagene Ciloleucel)) and other causes (4 patients) after disease progression and subsequent therapies that were not related to YESCARTA® (Axicabtagene Ciloleucel) [1].

The most common grade ≥3 AE in the 108 patients were neutropenia (78%), anaemia (43%) and thrombocytopenia (38%) [1].

Cytokine release syndrome

It is important to underline that CRS is an expected risk associated with the mode of action of CAR T cells.

Phase 1

CRS was reported in six of the 7 patients treated with YESCARTA® (Axicabtagene Ciloleucel) [2]. Five patients experienced grade ≤2 CRS and 1 patient experienced grade 4 CRS. The most common CRS related symptoms were pyrexia (71%), hypotension (43%) and tachycardia (29%). All grade 3 and 4 CRS related events, except for one grade 3 pyrexia and one grade 3 hypoxia, occurred in the one patient with a dose-

limiting toxicity [2]. Except for the patient experiencing the dose-limiting toxicity, the CRS were found to be self-limiting and reversible.

Phase 2

When considering the 101 patients treated in the phase 2 part of ZUMA-1, CRS occurred in 94 of the patients and the most frequently reported events of CRS were pyrexia, hypotension and hypoxia (Table 5-4). The median time after infusion until the onset of the CRS was 2 days (range, 1 to 12), and the median time until resolution was 8 days [1]. All the events associated with the CRS resolved except for one event of grade 5 hemophagocytic lymphohistiocytosis. Another event of grade 5 cardiac arrest occurred in a patient with CRS. It is important to note that the rate of the CRS decreased over the course of the study as seen by comparing the first 62 patients at an interim analysis versus all 101 treated patients in the phase 2 part (Table 5-5).

TABLE 5-4 OVERVIEW OF CYTOKINE RELEASE SYNDROME EVENTS BY CTCAE GRADE (ZUMA-1)

Event	Any Grade	Grade 1 or 2	Grade ≥3
		number of patients (percent)	
Adverse event			
Any	101 (100)	5 (5)	96 (95)
Cytokine release syndrome			
Any	94 (93)	81 (80)	13 (13)
Pyrexia	77 (76)	66 (65)	11 (11)
Hypotension	41 (41)	32 (32)	9 (9)
Hypoxia	22 (22)	13 (13)	9 (9)
Tachycardia	21 (21)	20 (20)	1 (1)
Chills	20 (20)	20 (20)	0
Sinus tachycardia	8 (8)	8 (8)	0
Headache	5 (5)	5 (5)	0

Source: Modified from Table 2 [1]

TABLE 5-5 ADVERSE EVENT RATES AT INTERIM AND PRIMARY ANALYSES FOR THE MODIFIED INTENT-TO-TREAT (MITT) POPULATION OF THE PHASE 2 PART OF ZUMA-1.

Adverse event — no. (%)	Interim Analysis (N = 62)	mITT Analysis (N = 101)
Grade ≥3 AE	59 (95)	96 (95)
Grade ≥3 CRS	11 (18)	13 (13)
Grade ≥3 NE	21 (34)	28 (28)

Source: Table S5 [1]

Updated analysis – combined phase 1 and 2 with median follow-up of 15.4 months

There were no new events associated with the CRS.

Neurologic events

Phase 1

All seven patients experienced at least one neurotoxicity event of any grade with three having a maximum grade 3 event and one having a maximum grade 4 event (the patient with the dose-limiting toxicity) (Table 5-6). Except for the patient experiencing the dose-limiting toxicity, the neurotoxicity events were found to be self-limiting and reversible.

TABLE 5-6 GRADE 3 OR HIGHER TREATMENT EMERGENT AES

Neurotoxicity, Specific Symptoms			
Encephalopathy	5 (71)	2 (29)	1 (14)[c]
Tremor	4 (57)	1 (14)	0
Somnolence	2 (29)	1 (14)	0
Agitation	1 (14)	1 (14)	0
Aphasia	1 (14)	0	0
Delirium	1 (14)	1 (14)	0
Dizziness	1 (14)	0	0
Dyskinesia	1 (14)	0	0
Hallucination	1 (14)	0	0
Restlessness	1 (14)	1 (14)	0

Source: Modified from Table 2 [2]

Phase 2

When considering only the 101 patients treated in the phase 2 part of ZUMA-1 [1], neurologic events occurred in 65 patients; 28% experiencing a grade 3 or higher event (Table 5-7). The most common neurologic events of grade 3 or higher were encephalopathy (in 21% of the patients), confusional state (in 9%), aphasia (in 7%), and somnolence (in 7%). Early neurologic signs included word-finding difficulties (dysphasia), attention or calculation defects (counting backward by serial 7s), and difficulty executing complex commands (handwriting). The median onset of neurologic events occurred on day 5 (range, 1 to 17), with median resolution on day 17 after infusion. Rates of the neurologic events decreased over the course of the study. One patient had ongoing grade 1 memory impairment that resolved after the data cut-off for the primary analysis. All the other neurologic events resolved except for four events, which were ongoing at the time of death (two deaths from progressive disease and two from adverse events unrelated to neurologic events).

TABLE 5-7 OVERVIEW OF NEUROLOGIC EVENTS BY NCCTC GRADE (ZUMA-1)

Table 2. (Continued.)

Event	Any Grade	Grade 1 or 2	Grade ≥3
		number of patients (percent)	
Neurologic event			
Any	65 (64)	37 (37)	28 (28)
Encephalopathy	34 (34)	13 (13)	21 (21)
Confusional state	29 (29)	20 (20)	9 (9)
Tremor	29 (29)	28 (28)	1 (1)
Aphasia	18 (18)	11 (11)	7 (7)
Somnolence	15 (15)	8 (8)	7 (7)
Agitation	9 (9)	5 (5)	4 (4)
Memory impairment	7 (7)	6 (6)	1 (1)
Mental-status change	6 (6)	4 (4)	2 (2)

Source: Modified from Table 2 [1]

Updated analysis – combined phase 1 and 2 with median follow-up of 15.4 months

There were no new events associated with neurologic events related to YESCARTA® (Axicabtagene Ciloleucel) treatment in the updated analysis [1].

Conclusion on CRS and neurologic events

Forty-three percent of patients received tocilizumab and 27% received glucocorticoids for the management of the CRS, neurologic events, or both, with no apparent effect on overall or ongoing response rates.

The incidence of the CRS and neurologic events of grade 3 or higher decreased over the course of the study, possibly because of increased experience at the study centers and a protocol amendment allowing for earlier administration of tocilizumab or glucocorticoids. The CRS and neurologic events were generally reversible with no clinical sequelae. With extended follow-up, there were no new onset of the CRS or neurologic events related to CAR T cells. Furthermore, the 3% rate of death during treatment compares favourably with rates observed during ASCT [1,24].

Health-related quality of life

At present, no HRQL data in relation to treatment with YESCARTA® (Axicabtagene Ciloleucel) have been published. However, HRQL data was collected in a cohort of 33 patients in ZUMA-1 (the safety management cohort) using the EQ-5D-5L at screening, Week 4, Month 3 and Month 6 post YESCARTA® (Axicabtagene Ciloleucel) infusion, as well as results by response category and for progression-free and progressed patients. The EQ-5D-5L were subsequently converted to EQ-5D-3L by use of a crosswalk algorithm and the EQ-5D-3L descriptive scores were converted to the EQ-5D-3L index with UK population-based health utility values by a UK valuation algorithm.

EQ-5D-3L

Patients experienced a decrease in utility scores from screening (0.739) to Week 4 (0.675) (Table 5-8), most likely because of a disutility associated with the timing of the transient toxicities associated with CAR T

therapy. By Month 3 and Month 6, the patient utilities had increased back to beyond their original levels (0.756 and 0.758, respectively), showing that patient HRQL was improved by YESCARTA® (Axicabtagene Ciloleucel) therapy. This was particularly evident when the results were broken down by response category and by health state, with patients in response experiencing much higher HRQL (0.743 and 0.788 for CR and PR, respectively) than patients who had not responded to treatment (0.636 and 0.647 for stable disease and PD, respectively) and patients with PFS experiencing much higher HRQL (0.722) than patients with progressed disease (0.647).

TABLE 5-8 EQ-5D-3L UTILITY SCORES FROM THE ZUMA-1 SAFETY MANAGEMENT COHORT

Results by time point, mean (SD)	N	EQ-5D-3L index score
Screening	33	0.739 (0.257)
Week 4	27	0.675 (0.198)
Month 3	20	0.756 (0.183)
Month 6	7	0.758 (0.317)
Total	87	0.724 (0.228)
Results by response category		
CR	25	0.743 (0.177)
PR	11	0.788 (0.237)
Stable disease	13	0.636 (0.256)
PD	5	0.647 (0.136)
Total	54	0.715 (0.210)
Results by health state		
Progression-free survival	49	0.722 (0.216)
Progressed disease	5	0.647 (0.136)
Key: CR, complete response; EQ-5D-3L, EuroQol 5-dimension 3-level; N, number of patients; PD, progressive disease; PR, partial response; SD, standard deviation. Source: Analysis of ZUMA-1 data performed to inform the economic model.		

Source: Data on file

Other oncology treatments, such as current chemotherapies and even newer immunotherapies, involve long-term, multiple and regular clinical visits. The potential for patients receiving YESCARTA® (Axicabtagene Ciloleucel) to achieve long-term, durable response and potentially be cured avoids multiple future hospital visits for additional treatments and disease-related monitoring. Therefore, YESCARTA® (Axicabtagene Ciloleucel) treatment visits will have less impact on patients HRQL, and given that the treatment is intended for patients who would otherwise be considered as being at end-of-life, anything that reduces their time in hospital or their number of clinic visits can be considered to be a massive benefit to the patients [22, 23].

Complete remission

In the 108 patients in the combined phase 1 and 2 parts of the ZUMA-1 study, after a median follow-up of 15.4 months, the rate of achieved CR was 58% and 40% remained in CR at the data cut-off [1]. Of the 7 patients in the phase 1 part of the study, 3 had an ongoing CR at 24 months.

In line with this, 7 patients with DLBCL treated with a CAR construct identical to YESCARTA® (Axicabtagene Ciloleucel), reported durable CRs in 4 of the 7 patients with duration of response ranging from 38-56 months (Table 5-9).

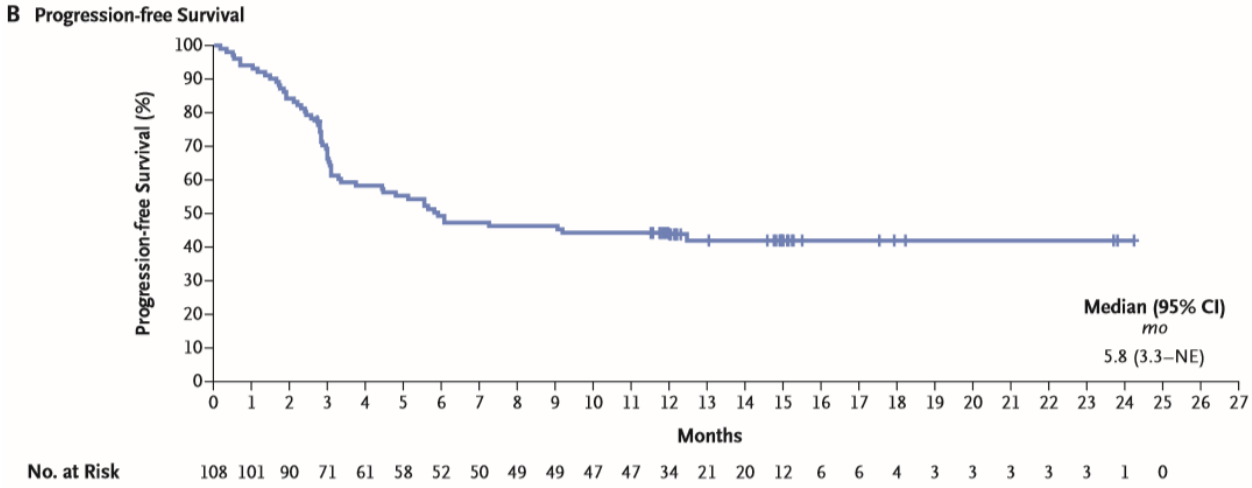
TABLE 5-9 PATIENT CHARACTERISTICS AND RESPONSE FORM 7 PATIENTS WITH LONG-TERM FOLLOW-UP

Reffering to Table 1. In “Axicabtagene Ciloleucel CAR T-Cell Therapy in Refractory Large B-Cell Lymphoma” Neelapu et al. 2017 [7]

Progression-free survival

When considering the 108 combined phase 1 and 2 patients, after a median follow-up pf 15.4 months, the median duration of PFS was 5.8 months (95%CI: 3.3 to could not be estimated) (Figure 5-4) with PFS rates of 44% (95%CI: 34 to 53) at 12 months and 41% (95%CI: 31 to 50) at 15 months [1].

FIGURE 5-4 PROGRESSION-FREE SURVIVAL



Source: Figure 2B [1]

Out of the 22 patients (19 with DLBCL) treated at the National Cancer Institute with an anti CD19 CAR T construct identical to YESCARTA® (Axicabtagene Ciloleucel), approximately 35% of the subjects were still in PFS at 24 months (Figure 5-5).

FIGURE 5-5 PROGRESSION-FREE SURVIVAL FROM CAR CONSTRUCT IDENTICAL TO YESCARTA® (AXICABTAGENE CILOLEUCEL)

Reffering to Figure 2B in "Lymphoma Remissions Caused by Anti-CD19 Chimeric Antigen Receptor T Cells Are Associated With High Serum Interleukin-15 Levels" Kochenderfer et al. 2017 [6]

Red marks indicate censored patients with ongoing CRs at the time of last follow-up with one exception: the red mark at 4 months after CAR T-cell infusion indicates the time point when patient 40 underwent ASCT while in partial remission. Two patients were censored at the 13-month time point and three patients were censored at the 14-month time point, but there is only one red mark on the graph for each of these time points

5.2.3 Results per study (SCHOLAR-1)

No comparator arm is provided in the SCHOLAR-1 study. Therefore, no calculations have been performed for relative or absolute differences.
A narrative comparison with the ZUMA-1 study is provided in section 5.2.4.

An overview of the results from SCHOLAR-1 is provided in Table 5-10 and detailed descriptions of the individual outcomes are provided in the below subsections.

In the cases were outcomes were not reported as part of the SCHOLAR-1 study but were available in one or more of the 4 individual studies, data are presented from these instead although, as described in section 5.2.1, the full study populations in the original publications also included patients who did not meet the criteria for refractory DLBCL applied in SCHOLAR-1. Furthermore, the majority of patients were in first relapse or refractory after first-line therapy in the CORAL study [14] and had other indications than DLBCL such as peripheral T-cell lymphoma and anaplastic large-cell lymphoma in the LY.12 study [13]. Main study characteristics of SCHOLAR-1 are available in Table 7-7, for CORAL in Table 7-8 and for LY.12 in Table 7-9.

TABLE 5-10 SUMMARY OF TREATMENT EFFECT FOR COMPARATOR COMBINATIONS, CLINICAL QUESTION 3.1 (SCHOLAR-1 STUDY)

Outcome	Available results based on the pooled patient analysis
OS at 2 years[1]	2-year survival rate: 17% (95%CI: 13-22) [4]
Proportion of patients with ≥1 SAE	Not available in pooled patient analysis • In the CORAL study, 29% of the patients in the R-ICE arm (58 out of 202 patients), and 35% of the patients in the R-DHAP arm (68 out of 194) experienced at least 1 SAE [14].
Narrative description of CRS and neurological adverse reactions	Not available in pooled patient analysis • In the CORAL study the most common SAE was infections. Similar rates of infection as a result of neutropenia were seen for the two treatment arms: 16% in both the R-ICE and R-DHAP arm [14]
Quality of life SF-36 and FACT-Lym	No data available in pooled patient analysis • In the LY.12 study, FACT-Total scores are presented (Figure 5-7) QoL assessment, using FACT-Total scores, showed that, compared with baseline status, there was less deterioration among patients who were allocated to GDP compared with patients allocated to DHAP, with significant differences observed at the end of the first cycle of treatment and at the midpoint of treatment cycle 2. At the midpoint of cycle 2, more patients receiving GDP had an improved clinically meaningful change score and fewer had a worse clinically meaningful change score compared with those treated with DHAP. The score did not return to baseline levels.
CR[1]	Not clearly defined if only achieved or achieved and remained: 10% (95%CI: 5-20) [4]
PFS	No data available in pooled analysis • In the MDACC database study, a PFS of 2.8 months was reported [10]

[1] In patients refractory to second-line or later-line therapy

Overall survival – 2-year survival

Based on the pooled patient analysis, survival from the start of salvage therapy for refractory disease was consistently poor in patients with refractory DLBLC. The 2-year survival rate among patients who were refractory to second-line (or more) therapy was 17% (95%CI: 13-22) [4]. Similar median OS was seen for patients who were refractory to second-line (or greater) therapy and those who were relapsed ≤12 months after ASCT (Figure 5-6).

FIGURE 5-6 OVERALL SURVIVAL FROM COMMENCEMENT OF SALVAGE THERAPY BY REFRACTORY SUBGROUPS IN SCHOLAR-1

Referring to figure 3.B in “Outcomes in refractory diffuse large B-cell lymphoma: results from the international SCHOLAR-1 study”. Crump et al 2018.

Source: Figure 3,B [4]

Serious adverse events

The SCHOLAR-1 patient analysis did not provide safety information, nor was safety information presented in the papers based on the observational cohorts. Therefore, the below information is based on the follow-up of the 2 large phase 3 randomised controlled trials LY.12 and CORAL in the available form. The results from the individual studies should, however, be interpreted with care as the original studies also included patients who did not meet the criteria for refractory DLBCL applied in SCHOLAR-1. Furthermore, the majority of patients were in first relapse or refractory after first-line therapy in the CORAL study [14] and had other indications than DLBCL such as peripheral T-cell lymphoma and anaplastic large-cell lymphoma in the LY.12 study [13].

Proportion of patients experiencing ≥ 1 SAE

In the CORAL study, 29% of the patients in the R-ICE arm (58 out of 202 patients), and 35% of the patients in the R-DHAP arm (68 out of 194) experienced at least 1 SAE [14]. 90 SAEs were reported in the R-ICE arm and 120 SAEs in the R-DHAP arm.

In the LY.12 study, the total number of patients experiencing one or more SAEs was not provided, instead a table showing the most frequently reported SAEs occurring in more than 5% of the patients was presented (see Table 5-11). In the table, 47% of the patients in the GDP arm and 61% of the patients in the DHAP arm were included in the category “worst overall” SAE.

However, as described above and in section 5.2.1, the full patient populations from CORAL and LY.12 did not match the SCHOLAR-1 refractory DLBCL criteria, many of the patients were enrolled with a history of only 1 treatment regimen and some had other indications than DLBCL.

TABLE 5-11 MOST FREQUENTLY REPORTED SAES IN THE LY.12 STUDY

Referring to table 3. In “Randomized Comparison of Gemcitabine, Dexamethasone,and Cisplatin Versus Dexamethasone, Cytarabine, andCisplatin Chemotherapy Before Autologous Stem-CellTransplantation for Relapsed and Refractory AggressiveLymphomas: NCIC-CTG LY.12”. Crump et al. 2014

Source: Table 3,[13]

Cytokine release syndrome and neurologic events

In the CORAL study, in both the R-ICE and the R-DHAP arm, the most common SAEs were infections, with a similar rate of infection as a result of neutropenia (16%) in both arms. Grade 3 to 4 nonhematologic toxicities were more severe in the R-DHAP arm and included grade 4 renal toxicity in 11 patients [14].

In the LY.12 study, 8 patients died as a result of protocol treatment–related complications: two during treatment with GDP and six after receiving DHAP [13]. During the first two cycles of chemotherapy episodes of febrile neutropenia were reported by 9% in the GDP group and 23% in the DHAP group (Table 5-11).

Health-related quality of life

The SCHOLAR-1 patient analysis did not provide information on health-related quality of life. Data were only available in the LY.12 publication but on the FACT-Total scores, not the SF-36 or FACT-Lym.

In the LY.12 study the following was reported: QoL assessment, using FACT-Total scores, showed that, compared with baseline status, there was less deterioration among patients who were allocated to GDP compared with patients allocated to DHAP, with significant differences observed at the end of the first cycle of treatment and at the midpoint of treatment cycle 2 (Figure 5-7, A).At the midpoint of cycle 2, more patients receiving GDP had an improved clinically meaningful change score (18% v 11%) and fewer had a worse clinically meaningful change score (33% v 41%; P = 0.04; Figure 5-7, B) compared with those treated with DHAP. The score did not return to baseline levels (Figure 5-7, A).

FIGURE 5-7 TOTAL FUNCTIONAL ASSESSMENT OF CANCER THERAPY–GENERAL (FACT-G) SCORES IN THE LY.12 STUDY

Referring to figure 3 in "Randomized Comparison of Gemcitabine, Dexamethasone,and Cisplatin Versus Dexamethasone, Cytarabine, andCisplatin Chemotherapy Before Autologous Stem-CellTransplantation for Relapsed and Refractory AggressiveLymphomas: NCIC-CTG LY.12". Crump et al. 2014

A) Mean change in total Functional Assessment of Cancer Therapy–General (FACT-G) scores; significant differences were seen at the end of cycle 1 (End 1), the middle of cycle 2 (Mid 2), and the end of cycle 2 (End 2). (B) Percentage of patients reporting a minimally important difference in FACT-G total score of 10% or more, assessed at midpoint of cycle 2: more patients who received gemcitabine, dexamethasone, and cisplatin (GDP) experienced improvement in and fewer experienced deterioration in quality of life than those treated with dexamethasone, cytarabine, and cisplatin (DHAP). ASCT, autologous stem-cell transplantation.

Source: Figure 3, [13]

Complete remission

Based on the pooled patient analysis, the CR rate among patients who were refractory to second-line (or more) therapy was 10% (Table 5-12). It was not clearly defined if the percentage for CR was for proportion of patients who had achieved CR or for those who had achieved and remained in CR.

TABLE 5-12 RATE OF RESPONSE TO CHEMOTHERAPY AFTER REFRACTORY DISEASE IN SCHOLAR-1

Referring to Table 2 "Rate of response to chemotherapy after refractory disease" in "Outcomes in refractory diffuse large B-cell lymphoma: results from the international SCHOLAR-1 study".Crump et al. 2017

Source: Table 2, [4]

Progression-free survival

The SCHOLAR-1 patient analysis did not provide data for PFS but PFS data were provided for the MDACC observation cohort in which the majority of the patients had received 2 or more lines of chemotherapy and ASCT at baseline.

In the MDACC cohort the median PFS was 2.8 months (95%CI: 2.4-3.3) [10].

5.2.4 Narrative comparison between YESCARTA® (Axicabtagene Ciloleucel) and standard treatment based on SCHOLAR-1

An overview of the outcomes of treatments with YESCARTA® (Axicabtagene Ciloleucel) versus standard treatment (including R-ICE, R-DHAP, DHAP and GDP but also including other treatment backgrounds (see Table 7-7)) is provided in Table 5-13 and a brief narrative comparison provided below.

TABLE 5-13 OVERVIEW OF OUTCOME COMPARISONS BETWEEN YESCARTA® (AXICABTAGENE CILOLEUCEL) AND COMPARATOR TREATMENTS

Outcome	Available results for YESCARTA® (Axicabtagene Ciloleucel) (ZUMA-1)	Available results for comparator treatment (SCHOLAR-1 or sub-studies)
OS at 2 years	The median overall survival was not reached (95% CI 12.8–not estimable). The estimated 24-month survival proportion was 50.5% (95% CI 40.2–59.7).3]	2-year survival rate: 17% (95%CI: 13-22) [SCHOLAR-1, 4]
Proportion of patients with ≥1 SAE	55% of the patients (3rd line treatment) [5]	29% of the patients in the R-ICE arm and 35% of the patients in the R-DHAP arm (majority 2nd line treatment) [CORAL, 14].
Narrative description of CRS and neurological adverse reactions	See the relevant subsections in the section Serious adverse events	Not available in pooled patient analysis and only limited information in the individual papers. See section Serious adverse events.
Quality of life SF-36 and FACT-Lym	Published data for SF-36 and FACT-Lym were not available for ZUMA-1 but EQ-5D-3L are presented which are available on file. • Patients experienced a decrease in utility scores from screening (0.739) to Week 4 (0.675), most likely because of a disutility associated with the timing of the transient toxicities associated with CAR T therapy. By Month 3 and Month 6, the patient utilities had increased back to beyond their original levels (0.756 and 0.758, respectively), showing that patient HRQL was improved by YESCARTA® (Axicabtagene Ciloleucel) therapy	No data available in pooled patient analysis • In the LY.12 study, FACT-Total scores are presented (Figure 5-7). QoL assessment, using FACT-Total scores, showed that, compared with baseline status, there was less deterioration among patients who were allocated to GDP compared with patients allocated to DHAP, with significant differences observed at the end of the first cycle of treatment and at the midpoint of treatment cycle 2. At the midpoint of cycle 2, more patients receiving GDP had an improved clinically meaningful change score and fewer had a worse clinically meaningful change score compared with those treated with DHAP. The score did not return to baseline levels.
CR	At data cut-off for the updated analysis, 40% remained in CR.[1]	Not clearly defined if only achieved or achieved and remained: 10% (95%CI: 5-20) [4]
PFS	5.8 months (95%CI: 3.3 to could not be estimated) [1]	No data available in pooled patient analysis 2.8 months (95%CI: 2.4-3.3) in MDACC [10]

In ZUMA-1, the OS rate after treatment with YESCARTA® (Axicabtagene Ciloleucel) was more than double the rate obtained in the pooled patient analysis in SCHOLAR-1 (and clearly exceeding the 10%-point MCID) with no overlap in the 95%CIs of the two treatment results (Table 5-13). In further support of a high long-term median OS with YESCARTA® (Axicabtagene Ciloleucel) treatment, the OS for 22 patients (19 with

DLBCL) treated with anti-CD19 CAR T-cell therapy identical to YESCARTA® (Axicabtagene Ciloleucel) treatment was approximately 40% at 32 months (Figure 5-3).

In addition, a 77% reduction in the overall risk of death for subjects in ZUMA-1 relative to SCHOLAR-1 were reported in the EPAR (p 78) [5].

Only limited information on the SAE profiles were available for comparison between the treatments, but the proportion of patients with ≥1 SAE was higher with YESCARTA® (Axicabtagene Ciloleucel) treatment than with R-ICE and R-DHAP treatment. It is, however, important to note that, as described in section 5.2.1, the full patient populations from CORAL and LY.12 did not match the SCHOLAR-1 refractory DLBCL criteria, many of the patients were enrolled with a history of only 1 treatment regimen and some had other indications than DLBCL. The full patient populations are thus poorly matched to the ZUMA-1 population. It should also be noted that the CRS and neurologic events reported with YESCARTA® (Axicabtagene Ciloleucel) were generally reversible with no clinical sequelae and that the incidence of the CRS and neurologic events of grade 3 or higher decreased over the course of the ZUMA-1 study. With extended follow-up, there were no new unexpected SAEs and no new onset of the CRS or neurologic events related to CAR T cells.

As different assessments of HRQL data were available for ZUMA-1 and SCHOLAR-1 no comparison could be done between YESCARTA® (Axicabtagene Ciloleucel) and standard treatment for this outcome, but patient health related quality of life was shown to be improved back to beyond their original levels by YESCARTA® (Axicabtagene Ciloleucel) therapy. This was not observed for GDP and DHAP where the score did not return to baseline levels.

In addition to the higher OS rate, the proportion of patients who achieved and remained in CR when treated with YESCARTA® (Axicabtagene Ciloleucel), after a median follow-up of 15.4 months, was more than double the CR rate obtained in patients treated with standard treatment in the pooled patient analysis (again exceeding the 10%-point MCID). Additionally, the median duration of PFS was also higher than observed in the MDACC observational study (meeting the MCID of 3 months).

The scarcity of relevant references for DLBCL or PMBCL patients with a history of 2 or more lines of therapy provides a grim indication of the poor survival chances of these patients with the current available standard treatment. The SCHOLAR-1 study provides a good estimate of real-world data for current standard treatment according to Danish experts and clearly indicates a need for more effective treatment to improve CR and OS for these patients. With a single YESCARTA® (Axicabtagene Ciloleucel) treatment a large proportion of this patient group can obtain a clinically relevant prolonged overall survival and durable CRs.

5.3 Clinical question 3, subgroup

What added clinical value does YESCARTA® (Axicabtagene Ciloleucel) offer compared to the current standard treatment after two or more lines of systemic therapy for adult patients (>18 but <65 years) with relapsed or refractory DLBCL or PMBCL, who are candidates for curative treatment?

Population

Adult patients (>18 but <65 years) with aggressive relapsed or refractory DLBCL or PMBCL after two or more lines of systemic therapy who are assessed to be candidates for curative treatment, i.e. patients who have performance status 0-1 and limited comorbidity.

Intervention

YESCARTA® (Axicabtagene Ciloleucel)

Comparator
GDP: gemcitabine, dexamethasone and cisplatin +/- rituximab
DHAP: cisplatin, cytarabine and dexamethasone +/- rituximab
ICE: ifosfamide, carboplatin and etoposide +/- rituximab

Outcomes
See Table 5-1 for the selected outcomes.

5.3.1 Results per study (ZUMA-1)

In ZUMA-1, 81 out of the 111 patients (combined phase 1 and 2 patients) were below 65 years of age [5]. The inclusion criteria of the study dictated that eligible patients

- had an ECOG performance status of 0-1
- Serum ALT/AST ≤2.5 ULN
- Total bilirubin ≤1.5 mg/dl, except in subjects with Gilbert's syndrome.
- Cardiac ejection fraction ≥ 50%, no evidence of pericardial effusion as determined by an ECHO, and no clinically significant ECG findings

With the exception of the broader age range, the full study population in ZUMA-1 consisted of candidates for curative treatment based on ECOG performance status and liver ad heart condition. See Table 7-6 for additional details of the main study characteristics. Thus, the outcomes presented for the study for the full population in section 5.2.1 should also be applicable for the subgroup of patients who are assessed to be candidates for curative treatment.

The SCHOLAR-1 population was too broad to fit the subgroup criteria and none of the four individual studies provided results for this specific subgroup. Thus, specific comparator outcomes for this patient subgroup could not be provided.

5.4 Additional information

5.4.1 Pharmacology

In the DMC protocol, when discussing the outcome CR, the following statement was made (p 7): "Farmakodynamikken omkring opnåelse af response er ukendt, men fagudvalget antager at response formentlig kommer langsommere end ved kemoterapi".

In the ZUMA-1 study, phase 2 part, the median time to response was 1 month; range 0.8 to 6.0 [1].

DATA PRESENTED AT ASCO 2018 ON TIME TO OBJECTIVE RESPONSE AND COMPLETE RESPONSE SUPPORTS THE RESPONSE TIME AT 1 MONTH (FIGURE 5-8) AND FURTHERMORE SHOW THAT PATIENTS IN RESPONSE AT MONTH 3 HAVE NEARLY AN 80% LIKELIHOOD OF MAINTAINING RESPONSE AT MONTH 12 (

Figure 5-9). Response to YESCARTA® (Axicabtagene Ciloleucel), either PR or CR, by 3 months may be prognostic for long-term remission.

FIGURE 5-8 TIME TO OBJECTIVE RESPONSE AND COMPLETE RESPONSE

Referring to ASCO 2018 oral presentation, presenting 2 year follow up data on ZUMA 1 study. Locke 2018
Source: [25]

FIGURE 5-9 PROGRESSION-FREE SURVIVAL BY RESPONSE AT MONTH 3

Referring to ASCO 2018 oral presentation, presenting 2 year follow up data on ZUMA 1 study. Locke 2018
Source: [25]

Furthermore, to provide as much information as possible for the assessment of YESCARTA® (Axicabtagene Ciloleucel), the below text has been extracted from the Discussion on clinical pharmacology (EPAR [5], p 45):

Results from the NCI 09-C-0082 and ZUMA-1 showed that peak levels of anti-CD19 CAR T cells occurred within the first 7-14 days after YESCARTA® (Axicabtagene Ciloleucel) infusion. In the primary analysis of ZUMA-1 Phase 2, the median peak level of anti-CD19 CAR T cells in the blood (C_{max}) were 41.9 cells/µL (range: 0.8 - 1513.7 cells/µL), which decreased to a median of 2.1 cells/µL by 1 month (range 0 - 167.4 cells/µL) and to a median of 0.4 cells/µL by 3 months (range 0 - 15.8 cells/µL) after YESCARTA® (Axicabtagene Ciloleucel) infusion.

The number of anti-CD19 CAR T cells in blood was positively associated with objective response (CR or PR) based on the central assessment and the 12-month update. The median anti-CD19 CAR T cell C_{max} levels in responders (n=73) were 205% higher compared to the corresponding level in non-responders (n=23) (43.6 cells/µL vs 21.2 cells/µL). Median $AUC_{Day\ 0-28}$ in responding patients (n=73) was 251% of the corresponding level in non-responders (n=23) (557.1 days × cells/µL vs. 222.0 days × cells/µL).

Patients who had co-medication with steroids (n=26) and tocilizumab (n=43) showed increased C_{max} and AUC-level. For the other covariates such as gender, age, race and tumour burden no significant impact on the pharmacokinetics became evident.

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7 Appendices

7.1 Literature search

TABLE 7-1 INCLUSION AND EXCLUSION CRITERIA FOR SCREENING AND ASSESSMENT

Inclusion criteria	**Population:** Adult patients (>18 years) with aggressive relapsed or refractory DLBCL or PMBCL after two or more lines of systemic therapy who are assessed to be candidates for YESCARTA® (Axicabtagene ciloleucel). **Interventions:** YESCARTA® (Axicabtagene ciloleucel) **Comparators:** GDP +/- rituximab; DHAP +/- rituximab or ICE +/- rituximab **Outcomes:** OS, SAEs, SF-36 and FACT-Lym data, CR, PFS **Settings (if applicable):** Not defined **Study design:** Both single and multiple arm studies **Language restrictions:** English **Other search limits or restrictions applied:** Trials only
Exclusion criteria	**Population:** Patients with aggressive relapsed or refractory DLBCL or PMBCL younger than 18 years or elderly or patients who are newly diagnosed/treatment naïve **Interventions:** N/A **Comparators:** other combinations than defined in the inclusion criteria **Outcomes:** If none of the outcomes defined as inclusion criteria are available **Settings (if applicable):** Studies performed exclusively outside of Europe or USA/Canada **Study design:** None **Language restrictions:** Not English **Other search limits or restrictions applied:** abstracts with no full text, clinicaltrials.gov registrations, non-EU/US journals

TABLE 7-2 DATABASES AND SEARCH STRATEGY

Database	Date of search	Time period covered	Number of search results	Applied search strings
PubMed via https://www.ncbi.nlm.nih.gov/pubmed/advanced	22 October 2018	No limits applied	100 hits, 96 full text	See Table 7-3
Cochrane Library via http://cochranelibrary-wiley.com/cochranelibrary/search/advanced	22 October 2018	No limits applied	92, 85 trials	See Table 7-4

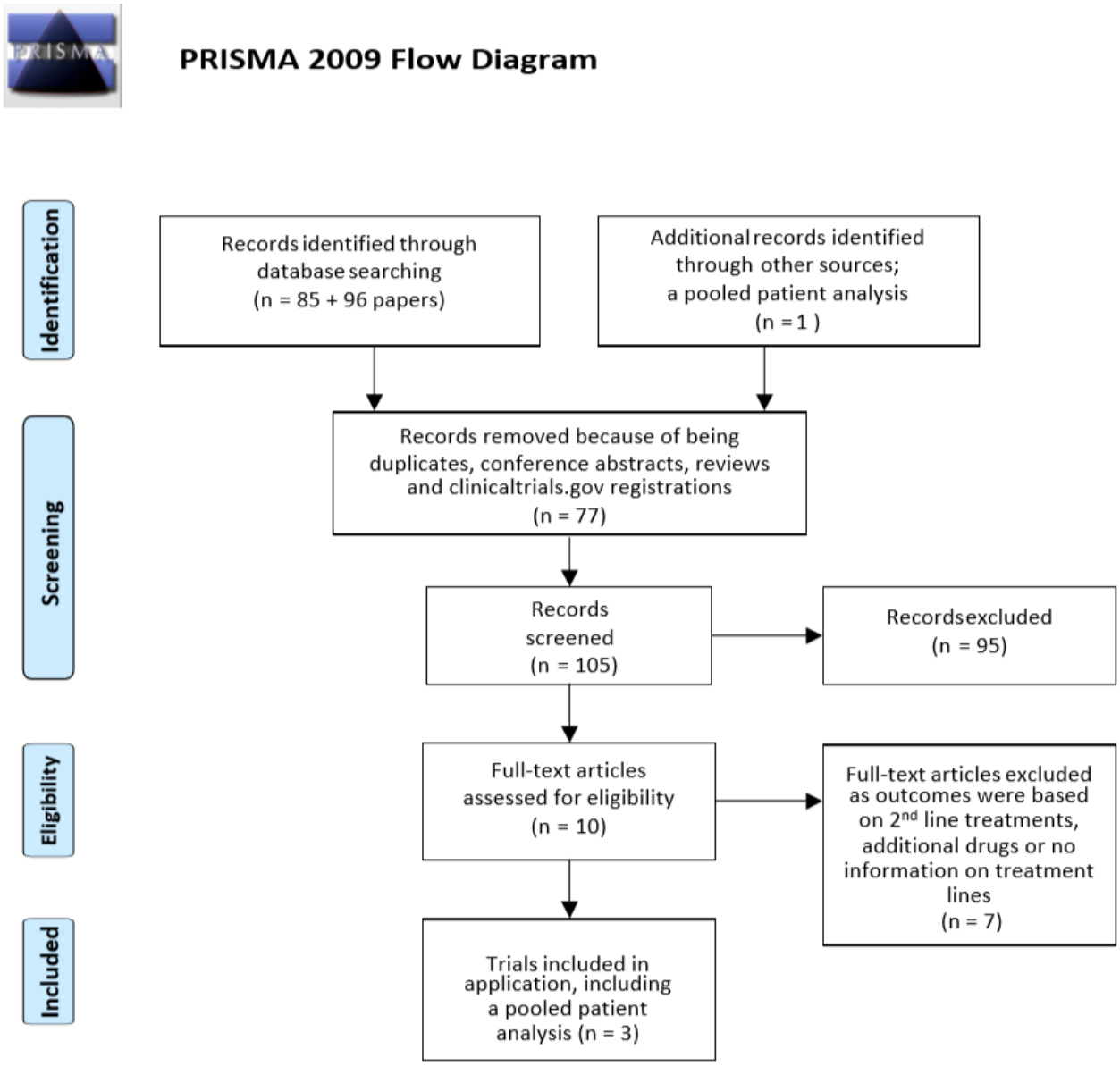
TABLE 7-3 PUBMED SERACH STRING

Search	Add to builder	Query	Items found
#21	Add	Search (#19) AND #20	100
#20	Add	Search (#8) OR (#12 OR #14 OR #18)	1058
#19	Add	Search (((((((diffuse large cell lymphoma[MeSH Terms]) OR diffuse large cell lymphomas[MeSH Terms]) OR lymphoma, diffuse large cell[MeSH Terms]) OR lymphomas, diffuse large cell[MeSH Terms]) OR Diffuse large B-cell lymphoma[Title/Abstract]) OR (DLBCL[Title/Abstract] OR DLBL [Title/Abstract])) OR Diffuse large B-cell lymphoma)) OR (Primary mediastinal B-cell lymphoma or PMBL or PMBCL)	24721
#18	Add	Search ((#15) AND #16) AND #17	810
#17	Add	Search ((Etoposide or Etopophos or toposar or vepesid or eposin)) OR etoposide[MeSH Terms]	24172
#16	Add	Search ((Carboplatin or Carboplatin Fresenius Kabi or Carboplatin accord or paraplatin)) OR carboplatin[MeSH Terms]	16232
#15	Add	Search ((Ifosfamide or IFO or Ifex or mitoxana)) OR ifosfamide[MeSH Terms]	8583
#14	Add	Search ((#11) AND #13) AND #10	183
#13	Add	Search ((Cytarabine or cytosine arabinoside or ara-C or cytosar-U or arabinosylcytosine or depocyt)) OR cytarabine[MeSH Terms]	19030
#12	Add	Search ((#9) AND #10) AND #11	62
#11	Add	Search ((Cisplatin or Platinol or Platinol-AQ or cddp or cisplatin ebewe or Cisplatin "Accord" or cisplatinum or cis-diamminedichloroplatinum (II))) OR cisplatin[MeSH Terms]	52879
#10	Add	Search ((Dexamethasone or Decadron or Dexasone or Diodex or Hexadrol or Maxidex or Dexamethasone Intensol or Solurex or Baycadron)) OR dexamethasone[MeSH Terms]	67597
#9	Add	Search ((Gemcitabine OR gemzar OR Gemcitabine Hcl or Gemcitabine hydrochloride)) OR gemcitabine[MeSH Terms]	15104
#8	Add	Search (Axicabtagene ciloleucel or KTE-C19 or Axi-cel or Yescarta)	26

TABLE 7-4 COCHRANE SEARCH STRING

#1	Axicabtagene ciloleucel or KTE-C19 or Axi-cel or Yescarta		24
#2	Gemcitabine OR gemzar OR Gemcitabine Hcl or Gemcitabine hydrochloride		3923
#3	Dexamethasone or Decadron or Dexasone or Diodex or Hexadrol or Maxidex or Dexamethasone Intensol or Solurex or Baycadron		8919
#4	MeSH descriptor: [Dexamethasone] explode all trees	MeSH	3775
#5	#3 OR #4		8937
#6	Cisplatin or Platinol or Platinol-AQ or cddp or cisplatin ebewe or Cisplatin "Accord" or cisplatinum or cis-diamminedichloroplatinum (II)		0
#7	MeSH descriptor: [Cisplatin] explode all trees	MeSH	4382
#8	#6 OR #7		1297206
#9	#2 AND #5 AND #8		119
#10	Cytarabine or cytosine arabinoside or ara-C or cytosar-U or arabinosylcytosine or depocyt		2913
#11	MeSH descriptor: [Cytarabine] explode all trees	MeSH	1166
#12	#10 or #11		2913
#13	#8 and #5 and #12		340
#14	Ifosfamide or IFO or Ifex or mitoxana		1291
#15	MeSH descriptor: [Ifosfamide] explode all trees	MeSH	511
#16	#14 OR #15		1291
#17	Carboplatin or Carboplatin Fresenius Kabi or Carboplatin accord or paraplatin		4989
#18	MeSH descriptor: [Carboplatin] explode all trees	MeSH	1877
#19	#17 OR #18		4989
#20	Etoposide or Etopophos or toposar or vepesid or eposin		3568
#21	MeSH descriptor: [Etoposide] explode all trees	MeSH	1584
#22	#20 OR #21		3568
#23	#16 and #19 and #22		229
#24	#9 or #13 or #23		640
#25	MeSH descriptor: [Lymphoma, Large B-Cell, Diffuse] explode all trees	MeSH	327
#26	("diffuse large B cell lymphomata" or Diffuse large B-cell lymphoma or DLBCL or DLBL):ti,ab,kw	S	1123
#27	(Primary mediastinal B-cell lymphoma or PMBL or PMBCL):ti,ab,kw	S	91
#28	large B-cell lymphoma		1259
#29	Primary mediastinal B-cell lymphoma or PMBL or PMBCL		96
#30	#25 or #26 or #27 or #28 or #29		1314
#31	#1 or #24 and #30		92

FIGURE 7-1 PRISMA FLOW CHART FOR LITERATURE SEARCH



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit www.prisma-statement.org.

TABLE 7-5 EXCLUDED LITERATURE

Official title (clinicaltrials.gov)/title of article	NCT number	Reason for exclusion
Randomized comparison of gemcitabine, dexamethasone, and cisplatin versus dexamethasone, cytarabine, and cisplatin chemotherapy before autologous stem-cell transplantation for relapsed and refractory aggressive lymphomas: NCIC-CTG LY.12 [13]	NCT00078949	Patients with more than 1 line of treatment included but not clear from publication how many. Trial designed to compare GDP and DHAP as 2nd line treatment. The trial is however included in the SCHOLAR-1 study, where additional information has been provided [4].
Rituximab in combination with platinum-containing chemotherapy in patients with relapsed or primary refractory diffuse large B-cell lymphoma [16]	Not provided	Number of previous lines of treatment not provided
Gemcitabine, dexamethasone, and cisplatin in patients with recurrent or refractory aggressive histology B-cell non-Hodgkin lymphoma: a Phase II study by the National Cancer Institute of Canada Clinical Trials Group (NCIC-CTG) [17]	Not provided	2nd line treatment
Dexamethasone, high-dose cytarabine, and cisplatin in combination with rituximab as salvage treatment for patients with relapsed or refractory aggressive non-Hodgkin's lymphoma [18]	Not provided	10 patients out of 53 had received 2 or more lines of chemotherapy. Results were not split to allow separation between these and patients with first relapse
Gemcitabine, dexamethasone, and cisplatin (GDP) is an effective and well-tolerated salvage therapy for relapsed/refractory diffuse large B-cell lymphoma and Hodgkin lymphoma [19]	Not provided	2nd line treatment
Outpatient-based ifosfamide, carboplatin and etoposide (ICE) chemotherapy in transplant-eligible patients with non-Hodgkin's lymphoma and Hodgkin's disease [20]	Not provided	Patients with both DLBCL and FL included and mostly only 1 previous line of treatment. The results were not split to allow distinction.
Rituximab, gemcitabine, cisplatin, and dexamethasone in patients with refractory or relapsed aggressive B-cell lymphoma [21]	Not provided	All patients were administered premedication with acetaminophen and chlorpheniramine and some later received G-CSF. Only some of patients had the relevant indication and only some had a history of more than 2 lines of treatment. The results were not split to allow distinction.

7.2 Main study characteristics of included studies

7.2.1 ZUMA-1 study

TABLE 7-6 MAIN STUDY CHARACTERISTICS – ZUMA-1 STUDY

Trial name (official title from clinicaltrials.gov)	A Phase 1/2 Multicenter Study Evaluating the Safety and Efficacy of KTE-C19 in Subjects With Refractory Aggressive Non-Hodgkin Lymphoma (ZUMA-1)
NCT number	NCT02348216
Objective	To determine the safety and efficacy of KTE-C19, an autologous anti-CD19 chimeric antigen receptor (CAR)-positive T cell therapy, in refractory aggressive Non-Hodgkin Lymphoma (NHL)
Publications – title, author, journal, year	Axicabtagene Ciloleucel CAR T-Cell Therapy in Refractory Large B-Cell Lymphoma. Neelapu SS, Locke FL, Bartlett NL, Lekakis LJ, Miklos DB, Jacobson CA, Braunschweig I, Oluwole OO, Siddiqi T, Lin Y, Timmerman JM, Stiff PJ, Friedberg JW, Flinn IW, Goy A, Hill BT, Smith MR, Deol A, Farooq U, McSweeney P, Munoz J, Avivi I, Castro JE, Westin JR, Chavez JC, Ghobadi A, Komanduri KV, Levy R, Jacobsen ED, Witzig TE, Reagan P, Bot A, Rossi J, Navale L, Jiang Y, Aycock J, Elias M, Chang D, Wiezorek J, Go WY. N Engl J Med. 2017 [1] Phase 1 Results of ZUMA-1: A Multicenter Study of KTE-C19 Anti-CD19 CAR T Cell Therapy in Refractory Aggressive Lymphoma. Locke FL, Neelapu SS, Bartlett NL, Siddiqi T, Chavez JC, Hosing CM, Ghobadi A, Budde LE, Bot A, Rossi JM, Jiang Y, Xue AX, Elias M, Aycock J, Wiezorek J, Go WY. Mol Ther. 2017 [2] Long-term safety and activity of axicabtagene ciloleucel in refractory large B-cell lymphoma (ZUMA-1): a single-arm, multicentre, phase 1-2 trial. Locke FL, Ghobadi A, Jacobson CA, Miklos DB, Lekakis LJ, Oluwole OO, Lin Y, Braunschweig I, Hill BT, Timmerman JM, Deol A, Reagan PM, Stiff P, Flinn IW, Farooq U, Goy A, McSweeney PA, Munoz J, Siddiqi T, Chavez JC, Herrera AF, Bartlett NL, Wiezorek JS, Navale L, Xue A, Jiang Y, Bot A, Rossi JM, Kim JJ, Go WY, Neelapu SS. Lancet Oncol. 2018 [3]
Study type and design	A single arm, open-label, multi-center, phase 1/2 clinical trial.
Follow-up time	An updated analysis was performed when the 108 patients in the phase 1 and 2 portions of ZUMA-1 had been followed for a minimum of 1 year (medium follow-up time 15,4 months). Furthermore, in the published study on long-term safety, 101 patients assessable for activity in phase 2 were followed up for a median of 27·1 months (IQR 25·7–28·8).
Population (inclusion and exclusion criteria) (from clinicaltrials.gov)	*Key Inclusion Criteria* 1. Histologically confirmed: • Diffuse Large B Cell Lymphoma (DLBCL) • Primary Mediastinal Large B Cell Lymphoma (PMBCL) • Transformation Follicular Lymphoma (TFL) • High grade B-cell lymphoma (HGBCL) 2. Chemotherapy-refractory disease, defined as one of more of the following: • No response to last line of therapy i. PD as best response to most recent therapy regimen ii. SD as best response to most recent therapy with duration no longer than 6 month from last dose of therapy OR • Refractory post-ASCT i. Disease progression or relapsed less than or equal to 12 months of ASCT (must have biopsy proven recurrence in relapsed subjects) ii. If salvage therapy is given post-ASCT, the subject must have had no response to or relapsed after the last line of therapy

	3. Subjects must have received adequate prior therapy including at a minimum: • anti-CD20 monoclonal antibody unless investigator determines that tumor is CD20-negative and • an anthracycline containing chemotherapy regimen • for subjects with transformed FL must have received prior chemotherapy for follicular lymphoma and subsequently have chemorefractory disease after transformation to DLBCL 4. At least one measurable lesion per revised IWG Response Criteria 5. Age 18 or older 6. ECOG performance status of 0 or 1 7. ANC ≥ 1000/uL 8. ALC >100/uL 9. Platelet count ≥ 75,000/uL 10. Adequate renal, hepatic, pulmonary and cardiac function defined as: • Creatinine clearance (as estimated by Cockcroft Gault) > 60 mL/min • Serum ALT/AST <2.5 ULN • Total bilirubin <1.5 mg/dl, except in subjects with Gilbert's syndrome • Cardiac ejection fraction >50%, no evidence of pericardial effusion as determined by an ECHO, and no clinically significant pleural effusion • Baseline oxygen saturation >92% on room air 11. All subjects or legally appointed representatives/caregivers, must personally sign and date the IRB/IEC approved consent form before initiating any study specific procedures or activities. *Key Exclusion Criteria* 1. History of malignancy other than nonmelanoma skin cancer or carcinoma in situ (e.g. cervix, bladder, breast) or follicular lymphoma unless disease free for at least 3 years 2. History of allogeneic stem cell transplantation 3. Prior CAR therapy or other genetically modified T cell therapy 4. Presence of fungal, bacterial, viral, or other infection that is uncontrolled or requiring IV antimicrobials for management. Simple UTI and uncomplicated bacterial pharyngitis are permitted if responding to active treatment 5. History of HIV infection or acute or chronic active hepatitis B or C infection. Subjects with history of hepatitis infection must have cleared their infection as determined by standard serological and genetic testing per current Infectious Diseases Society of America (IDSA) guidelines 6. Subjects with detectable cerebrospinal fluid malignant cells, or brain metastases, or with a history of CNS lymphoma or primary CNS lymphoma, cerebrospinal fluid malignant cells or brain metastases 7. History or presence of CNS disorder such as seizure disorder, cerebrovascular ischemia/hemorrhage, dementia, cerebellar disease, or any autoimmune disease with CNS involvement
Intervention	Single Arm: Administration of a conditioning chemotherapy regimen of fludarabine and cyclophosphamide followed by a single infusion of CAR transduced autologous T cells administered intravenously at a target dose of 2 x 10^6 anti-CD19 CAR T cells/kg
Primary and secondary endpoints (from clinicaltrials.gov)	*Primary outcome measure* • Phase 1: Safety (Incidence of adverse events defined as dose-limiting toxicities (DLT) [Time Frame: 30 Days] Incidence of adverse events defined as dose-limiting toxicities (DLT) • Phase 2: Overall Response Rate [Time Frame: 12 Months] Objective response rate (complete response [CR] + partial response [PR]) per the

	revised International Working Group (IWG) Response Criteria for Malignant Lymphoma • Phase 2 Expanded Cohorts: Safety [Time Frame: 12 Months] Rate and severity of CRS and neurologic toxicities *Secondary outcome measures* • Duration of Response [Time Frame: 12 Months] • Progression Free Survival [Time Frame: 12 Months] • Overall Survival [Time Frame: 24 Months] • Safety [Time Frame: 12 Months] Incidence of adverse events and clinically significant changes in safety lab values, including subgroup analyses • Phase 2 Expanded Cohorts [Time Frame: 12 Months] Objective response rate (complete response [CR] + partial response [PR]) per the revised International Working Group (IWG) Response Criteria for Malignant Lymphoma
Method of analysis (from publication)	The primary analysis was conducted at the point when 92 patients could be evaluated 6 months after the YESCARTA® (Axicabtagene Ciloleucel) infusion. Efficacy and safety analyses were reported in the modified intention to-treat population of all the patients who had received YESCARTA® (Axicabtagene Ciloleucel). An updated analysis of all the patients who had been treated in phase 121 and phase 2 of ZUMA-1 was also performed. To analyse the response rate, a single-group design was used in which the response of patients with a prespecified rate of response of 20% on the basis of historical values for refractory diffuse large B-cell lymphoma was compared. Efficacy testing had a power of at least 90% to distinguish between an active therapy with a 40% true response rate and a therapy with a response rate of 20% or less with the use of a one-sided alpha level of 0.025. The primary end point was tested with an exact binomial test. The Wilcoxon rank-sum test was used to measure the associations between outcomes and levels of CAR T cells and cytokines, with P values adjusted using Holm's procedure. Confidence intervals were calculated with the use of the Clopper–Pearson method.
Subgroup analyses	The 95% CI for the subgroup analyses was calculated with the use of the Clopper–Pearson method.

Baseline characteristics (from publication)

Table 1. Treatment Disposition and Baseline Characteristics of the Patients.*

Variable	Patients with DLBCL	Patients with PMBCL or TFL	All Patient
Treatment disposition			
No. of patients enrolled	81	30	111
Treatment with axi-cel — no. (%)			
Yes	77 (95)	24 (80)	101 (91
No	4 (5)	6 (20)	10 (9)
Death before treatment†	1 (1)	2 (7)	3 (3)
Adverse event‡	3 (4)	2 (7)	5 (5)
Other§	0	2 (7)	2 (2)
Characteristics at baseline			
No. of patients	77	24	101
Disease type — no. (%)			
DLBCL	77 (100)	0	77 (76
PMBCL	0	8 (33)	8 (8)
TFL	0	16 (67)	16 (16
Age			
Median (range) — yr	58 (25–76)	57 (23–76)	58 (23–76
≥65 yr — no. (%)	17 (22)	7 (29)	24 (24
Male sex — no. (%)	50 (65)	18 (75)	68 (67
ECOG performance-status score of 1 — no. (%)	49 (64)	10 (42)	59 (58
Disease stage — no. (%)			
I or II	10 (13)	5 (21)	15 (15
III or IV	67 (87)	19 (79)	86 (85
International Prognostic Index score — no. (%)¶			
0–2	40 (52)	13 (54)	53 (52
3 or 4	37 (48)	11 (46)	48 (48
CD-19 status — no./total no. (%)‖			
Negative	7/63 (11)	1/19 (5)	8/82 (10
Positive	56/63 (89)	18/19 (95)	74/82 (90
Prior therapies — no. (%)			
≥Three prior lines of therapy	49 (64)	21 (88)	70 (69
History of primary refractory disease**	23 (30)	3 (12)	26 (26
History of resistance to two consecutive lines	39 (51)	15 (62)	54 (53
Refractory subgroup at study entry — no. (%)			
Primary refractory	2 (3)	0	2 (2)
Refractory to second-line or subsequent therapy	59 (77)	19 (79)	78 (77
Relapse after autologous stem-cell transplantation	16 (21)	5 (21)	21 (21

7.2.2 SCHOLAR-1 study

TABLE 7-7 MAIN STUDY CHARACTERISTICS – SCHOLAR-1 STUDY

Trial name	SCHOLAR-1
NCT number	Not provided
Objective (from [4])	To evaluate responses and OS rates in patients with refractory NHL, including DLBCL-transformed follicular lymphoma and primary mediastinal B-cell lymphoma
Publications – title, author, journal, year	Outcomes in refractory diffuse large B-cell lymphoma: results from the international SCHOLAR-1 study. Crump M, Neelapu SS, Farooq U, Van Den Neste E, Kuruvilla J, Westin J, Link BK, Hay A, Cerhan JR, Zhu L, Boussetta S, Feng L, Maurer MJ, Navale L, Wiezorek J, Go WY, Gisselbrecht C. Blood. 2017 [4]
Study type and design	Patient-level analysis of outcomes of refractory DLBCL from 2 large randomised trials and 2 academic databases
Follow-up time	Not applicable
Population (inclusion and exclusion criteria) (from [4])	All patients from each data source who met criteria for refractory DLBCL, including TFL and PMBCL, who went on to receive subsequent therapy were considered for analysis. Refractory DLBCL, and subtypes PMBCL and TFL, was defined as progressive disease or stable disease as best response to chemotherapy (received ≥4 cycles of first-line therapy or 2 cycles of later line therapy, respectively) or relapse ≤12 months post-ASCT. TFL and PMBCL were included because they are histologically similar and clinically treated as large cell lymphoma.29-31 Patients must have received an anti-CD20 monoclonal antibody and an anthracycline as 1 of their qualifying regimens. For IA/MC, LY.12, and CORAL, patients were included at first instance of meeting refractory criteria, whereas for MDACC, patients who first met refractory criteria from second-line therapy onward were included. Patients with primary central nervous system lymphoma were excluded.
Intervention	**MDACC database study**: Second line rituximab-containing salvage therapies included: HyperCVAD (17%), ICE (15%), DHAP (14%), ESHAP (12%), Gem-Ox (9%) and methotrexate-cytarabine (4%), other chemotherapies (14%) and therapies on clinical trials (15%) **IA/MC database study:** anthracycline-based immunotherapy as initial treatment **LY.12 study:** GDP or DHAP as second line treatment **CORAL study:** ICE or DHAP in addition to rituximab, mesna and G-CSF
Primary and secondary endpoints	Not listed as such but as stated in the objective the endpoints are responses and OS
Method of analysis (from [4])	Scholar-1 was developed as a companion study to ZUMA-1 to provide context for interpreting the ZUMA-1 results. Patient-level data extracted using the above criteria were submitted to a central database from which a pooled analysis was performed. For the randomized studies, responses were prospectively evaluated per the study schedule of assessments. For the observational cohorts, responses were determined at the time of patient treatment/management. Responses were obtained from the electronic medical record or patient chart. Higgin's Q-statistic was used to assess the heterogeneity of response rate between the source databases. This statistic describes the percentage of variability in the effect estimates that is a result of heterogeneity rather than sampling error. A nonsignificant P value suggests that the heterogeneity does not have a strong influence on the variability in the analysis and that the data may be combined for analysis without further adjustment. In this analysis, a Higgin's Q-statistic prespecified P value >.1 was used to determine whether significant heterogeneity was present; the P value was >.1, and thus the data were pooled for

	analysis. Data were pooled at the patient-record level, and response rates were estimated from the pooled data with a random effects model. Covariates for response were evaluated with a Cochran-Mantel-Haenszel test stratified by institution. Survival was estimated, and covariates were assessed by a Cox proportional hazards model stratified by data source. When covariates assessed after commencement of therapy for refractory status were used in survival models, survival time was calculated from the day of covariate assessment. A nominal P value of .05 from the Cochran-Mantel-Haenszel tests and Cox models was used to evaluate the effect of covariates on response and survival.
Subgroup analyses (from [4])	Covariates included IPI risk category (low risk, 0-1 points; low-intermediate risk, 2 points; high intermediate to high risk, ≥3 points), ECOG PS, stage of disease, and line of therapy before refractory status. For the observational cohorts, covariates were determined at diagnosis. For the randomized study cohorts, covariates were determined at randomization. For all cohorts, in some cases, covariates were also measured later in the treatment course, depending on data availability and accessibility or study design. The determination of refractory status may have been distant in time from the measurement of the covariate. For summaries of patient characteristics, the covariate measured closest in time to the determination of refractory status was used. For subgroup analyses, patients were included in the covariate subgroup analysis only if the covariate was measured within 3 months of the determination of refractory status. Refractory subgroups were defined as refractory to first-line therapy, refractory to second-line or later-line therapy, or relapsed ≤12 months post-ASCT. Categorization of refractory subgroup was defined by the first time a patient met the criteria for refractory disease in the IA/MC, LY.12, and CORAL study cohorts. Patients in the MDACC study cohort were categorized only as refractory to second-line or later-line therapy and relapsed ≤12 months post-ASCT. The line of therapy before refractory status was determined based on the first time a patient was determined to be refractory.
Baseline characteristics (from [4])	Referring to Table 1 “Baseline patient characteristics” in “Outcomes in refractory diffuse large B-cell lymphoma: results from the international SCHOLAR-1 study”. Crump et al. 2017

CORAL study

TABLE 7-8 STUDY CHARACTERISTICS – CORAL STUDY

Trial name (official title from clinicaltrials.gov)	Randomized Study of ICE Plus RITUXIMAB Versus DHAP Plus Rituximab in Previously Treated Patients With Diffuse Large B-cell Lymphoma, Followed by Randomized Maintenance With Rituximab (CORAL)
NCT number	NCT00137995
Objective	The primary objective of this study was to evaluate the efficacy and safety of induction therapy R-ICE in comparison to R-DHAP after 3 cycles adjusted to successful mobilization of stem cells in patients with previously treated diffuse large B-cell lymphoma CD20. The other objective was to evaluate the efficacy and safety of MabThera maintenance therapy after transplantation as measured by the event free survival
Publications – title, author, journal, year	Gisselbrecht C, Schmitz N, Mounier N, Singh Gill D, Linch DC, Trneny M, Bosly A, Milpied NJ, Radford J, Ketterer N, Shpilberg O, Dührsen U, Hagberg H, Ma DD, Viardot A, Lowenthal R, Brière J, Salles G, Moskowitz CH, Glass B. 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. J Clin Oncol. 2012 Dec 20;30(36):4462-9.[15]

	Gisselbrecht C, Glass B, Mounier N, Singh Gill D, Linch DC, Trneny M, Bosly A, Ketterer N, Shpilberg O, Hagberg H, Ma D, Brière J, Moskowitz CH, Schmitz N. Salvage regimens with autologous transplantation for relapsed large B-cell lymphoma in the rituximab era. J Clin Oncol. 2010 Sep 20;28(27):4184-90. Epub 2010 Jul 26. Erratum in: J Clin Oncol. 2012 May 20;30(15):1896.[14]
Study type and design	Phase 3, multicenter, randomized, open-label trial
Follow-up time	3 years
Population (inclusion and exclusion criteria) (from clinicaltrials.gov)	*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.
Intervention	In both regimens, rituximab (375 mg/m^2) was administered before chemotherapy, and in the first course, additional rituximab was given on day 1. The R-ICE regimen consisted of etoposide (100mg/m^2 per day) on days 1 through 3, ifosfamide (5,000mg/m^2) infused continuously for 24 hours on day 2 with mesna; and carboplatin (area under the curve = 5; maximum dose, 800 mg) on day 2. The R-DHAP regimen

	consisted of cisplatin (100mg/m^2) on day 1 via continuous 24-hour infusion, followed on day 2 by cytarabine (2g/m^2) in a 3-hour infusion repeated after 12 hours, and dexamethasone (40 mg/d) for 4 consecutive days. G-CSF was administered after R-ICE and, depending on site policy, with R-DHAP, but always after the third cycle until the end of leukaphereses.
Primary and secondary endpoints	Primary outcome measure • MARR (mobilization adjusted response rate) [Time Frame: 3 months] • EFS (event free survival) [Time Frame: 2 years post transplantation] Secondary outcome measures • Progression rate [Time Frame: 2 years post transplantation] • Overall survival [Time Frame: 2 years post transplantation] • Duration of response [Time Frame: 2 years post transplantation]
Method of analysis	Administration of an alternative treatment was considered as an event. EFS was defined as the time from the start of treatment to progression, relapse, new treatment, or death (irrespective of cause), whichever event occurred first. PFS was defined as the time from study entry until disease progression or death. OS was defined as the time from the start of treatment to death. The Kaplan-Meier method was used to estimate EFS, PFS, and OS, and 95% CIs were calculated.16 Cox regression analysis was used to calculate the hazard ratio between the two arms. All analyses were carried out with SAS9.1.3 software (SAS Institute, Cary,NC).
Subgroup analyses	Not applicable
Baseline characteristics (from [14])	Referring to Table 1. Baseline Patient Demografics and Clinical Characteristics (ITT) in "Salvage regimens with autologous transplantation for relapsed large B-cell lymphoma in the rituximab era". Gisselbrecht et al. 2012.

LY.12 study

TABLE 7-9 STUDY CHARACTERISTICS – LY.12 STUDY

Trial name (official title from clinicaltrials.gov)	A Phase III Study Of Gemcitabine, Dexamethasone, And Cisplatin Compared To Dexamethasone, Cytarabine, And Cisplatin Plus/Minus Rituximab [(R)-GDP vs (R)-DHAP] As Salvage Chemotherapy For Patients With Relapsed Or Refractory Aggressive Histology Non-Hodgkin's Lymphoma Prior To Autologous Stem Cell Transplant And Followed By Maintenance Rituximab Versus Observation
NCT number	NCT00078949
Objective	This randomized phase III trial was studying salvage chemotherapy using dexamethasone, cisplatin, and gemcitabine to see how well it worked compared to dexamethasone, cisplatin, and cytarabine given before ASCT in treating patients with relapsed or refractory aggressive NHL. This trial also was studying giving rituximab as maintenance therapy to see how well it worked compared to no further therapy after stem cell transplantation. Rituximab was added to both salvage treatment arms for CD20+ patients in a protocol amendment in 2005.
Publications – title, author, journal, year	Crump M, Kuruvilla J, Couban S, MacDonald DA, Kukreti V, Kouroukis CT, Rubinger M, Buckstein R, Imrie KR, Federico M, Di Renzo N, Howson-Jan K, Baetz T, Kaizer L, Voralia

	M, Olney HJ, Turner AR, Sussman J, Hay AE, Djurfeldt MS, Meyer RM, Chen BE, Shepherd LE. Randomized comparison of gemcitabine, dexamethasone, and cisplatin versus dexamethasone, cytarabine, and cisplatin chemotherapy before autologous stem-cell transplantation for relapsed and refractory aggressive lymphomas: NCIC-CTG LY.12. J Clin Oncol. 2014 Nov 1;32(31):3490-6.[13] Bosch M, Akhter A, Chen BE, Mansoor A, Lebrun D, Good D, Crump M, Shepherd L, Scott DW, Stewart DA. A bioclinical prognostic model using MYC and BCL2 predicts outcome in relapsed/refractory diffuse large B-cell lymphoma. Haematologica. 2018 Feb;103(2):288-296. doi: 10.3324/haematol.2017.179309. Epub 2017 Nov 2. Davison K, Chen BE, Kukreti V, Couban S, Benger A, Berinstein NL, Kaizer L, Desjardins P, Mangel J, Zhu L, Djurfeldt MS, Hay AE, Shepherd LE, Crump M. Treatment outcomes for older patients with relapsed/refractory aggressive lymphoma receiving salvage chemotherapy and autologous stem cell transplantation are similar to younger patients: a subgroup analysis from the phase III CCTG LY.12 trial. Ann Oncol. 2017 Mar 1;28(3):622-627. doi: 10.1093/annonc/mdw653. Kuruvilla J, MacDonald DA, Kouroukis CT, Cheung M, Olney HJ, Turner AR, Anglin P, Seftel M, Ismail WS, Luminari S, Couban S, Baetz T, Meyer RM, Hay AE, Shepherd L, Djurfeldt MS, Alamoudi S, Chen BE, Crump M. Salvage chemotherapy and autologous stem cell transplantation for transformed indolent lymphoma: a subset analysis of NCIC CTG LY12. Blood. 2015 Aug 6;126(6):733-8. doi: 10.1182/blood-2015-01-622084. Epub 2015 Jun 24.
Study type and design	Phase 3, open-label, randomized, controlled, multicenter trial
Follow-up time	Median duration of follow-up time was 53 months[13]

Population (inclusion and exclusion criteria)
(from clinicaltrials.gov)
	DISEASE CHARACTERISTICS:
	• Histologically confirmed aggressive non-Hodgkin's lymphoma of 1 of the following subtypes:
	  ○ Diffuse large cell lymphoma (includes primary mediastinal B-cell lymphoma and T-cell-rich B-cell lymphoma)
	  ○ Prior indolent lymphoma (e.g., follicular center cell lymphoma; marginal zone lymphoma, including extranodal mucosa-associated lymphoid tissue [MALT] lymphoma; and lymphoplasmacytoid lymphoma) with transformation to diffuse large B-cell lymphoma at relapse
	  ▪ Must be histologically confirmed
	  ▪ No transformed lymphoma at diagnosis with subsequent indolent histology without transformation at relapse
	  ○ Peripheral T-cell lymphoma
	  ○ Anaplastic large cell lymphoma
	  ○ Small noncleaved Burkitt-like lymphoma
	• T-cell or B-cell lineage confirmed by immunohistochemistry
	• Clinically or radiologically documented disease meeting either of the following criteria:
	  ○ Measurable disease, defined as at least 1 bidimensionally measurable site of disease using clinical exam, CT scan, or MRI
	  ▪ Lymph nodes must be > 1.5 cm by physical exam or CT scan
	  ▪ Other non-nodal lesions must be ≥ 1.0 cm by physical exam, CT scan, or MRI
	  ▪ Bone lesions are not considered measurable
	  ○ Evaluable disease, defined as only nonmeasurable disease, including any of the following:
	  ▪ Marrow infiltration

	▪ Cytology-confirmed ascites or effusions ▪ Bony involvement ▪ Enlarged liver or spleen ▪ Unidimensionally measurable intrathoracic or abdominal masses • Previously treated with 1, and only 1, chemotherapy regimen including an anthracycline and excluding cisplatin, cytarabine, and gemcitabine • No uncontrolled CNS involvement by lymphoma o No CNS disease at time of relapse o CNS disease diagnosed at initial presentation allowed provided a complete response for CNS disease was achieved and maintained PATIENT CHARACTERISTICS: Age • 16 to 65 Performance status • ECOG 0-3 Life expectancy • At least 12 weeks Hematopoietic • Absolute granulocyte count ≥ 1,000/mm^3 • Platelet count ≥ 75,000/mm^3 Hepatic • Bilirubin ≤ 1.5 times upper limit of normal (ULN) • AST or ALT ≤ 2.5 times ULN (5 times ULN if liver involvement with lymphoma) • Hepatitis B status known (for patients with a history of hepatitis B or who are at high risk of hepatitis B infection) Renal • Creatinine ≤ 1.5 times ULN Cardiovascular • No significant cardiac dysfunction or cardiovascular disease Other • Not pregnant or nursing • Negative pregnancy test • Fertile patients must use effective contraception • Willing to complete quality of life questionnaires • HIV negative • No active, uncontrolled bacterial, fungal, or viral infection • No other malignancy within the past 5 years except adequately treated basal cell skin cancer or carcinoma in situ of the cervix • No other concurrent serious illness or medical condition that would preclude study participation PRIOR CONCURRENT THERAPY: Biologic therapy • See Chemotherapy • Prior rituximab allowed

	Chemotherapy • See Disease Characteristics • At least 4 weeks since prior IV chemotherapy • No prior high-dose chemotherapy with stem cell transplantation Endocrine therapy • No concurrent corticosteroids except for physiologic replacement Radiotherapy • At least 4 weeks since prior radiotherapy and recovered ○ Exceptions may be made for low-dose, non-myelosuppressive radiotherapy • No prior radiotherapy to more than 25% of functioning bone marrow • Involved-field radiotherapy may be given to areas of bulky disease at relapse (≥ 5 cm) after stem cell transplantation, according to the center's policy Surgery • At least 2 weeks since prior major surgery Other • No other concurrent anticancer therapy • No other concurrent experimental agents
Intervention	Patients received cisplatin IV over 60 minutes on day 1, dexamethasone IV or orally on days 1-4, and gemcitabine IV over 30 minutes on days 1 and 8 OR Patients received cisplatin IV over 24 hours on day 1, dexamethasone as in arm I, and cytarabine IV over 3 hours every 12 hours for a total of 2 doses on day 2. Beginning on day 28 post-transplantation, patients received rituximab IV once every 2 months for 6 doses (a total of 12 months) in the absence of disease progression or unacceptable toxicity.
Primary and secondary endpoints	*Primary outcome measures* • Response Rate of Patients After 2 Courses of Chemotherapy [Time Frame: After 2 cycle of treatment] • Transplantation Rate of Patients After 2 Courses of Chemotherapy [Time Frame: During period 1 (salvage chemotherapy)] • Event-free Survival of Patients on Maintenance Randomization (Period 2) [Time Frame: during the period 2 (up to10 years)] *Secondary Outcome Measures* • Mobilization Rate of Patients on Treatment Arm I Assessed by CD34 Count After 2 Courses of Therapy and Stem Cell Harvesting [Time Frame: 10 years] • Toxicity Assessed by NCI CTC v2.0 for 2 Years in Patients on Treatment Arm II [Time Frame: 10 years]
Method of analysis	The Kaplan and Meier life table method was used to calculate event-free and overall survivals, and groups were compared using the log-rank test with incorporation of the stratification factors used at random assignment. Using clinically important change score criteria, responses to each QoL item were categorized into improved, stable, and worse categories, and a χ^2 test was performed to compare the distributions of these categories between the two treatment arms.

Subgroup analyses	Not applicable
Baseline characteristics (from [13])	Referring to Table 1 “Patient Characteristics at Study Entry” in “Randomized comparison of gemcitabine, dexamethasone, and cisplatin versus dexamethasone, cytarabine, and cisplatin chemotherapy before autologous stem-cell transplantation for relapsed and refractory aggressive lymphomas: NCIC-CTG LY.12”. Crump et al 2014.

Expert answers from associate professor, Chief Physician Peter Brown, Rigshospitalet

Questions for Key Opinion Leaders in Denmark
regarding the treatment of B-cell lymphoma with CAR-T therapy
Axicabtagene ciloleucel (Axi-cel)

Background

Axicabtagene ciloleucel (Axi-cel) is a CAR-T-cell therapy which consists of autologous human T-cells that have been engineered to identify and lock onto cells expressing the antigen CD19. Axi-cel has been developed for the treatment of patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), transformed follicular lymphoma (TFL) and primary mediastinal large B-cell lymphoma (PMBCL). The safety and efficacy of Axi-cel was evaluated in ZUMA-1, a phase-2, multicentre, open-label, single arm clinical trial.

A model is used to show the value of Axi-cel compared to best supportive care (BSC) in Denmark. The input from key opinion leaders in Denmark is needed to realistically adapt the model to local clinical practice.

Patient population of Axi-cel

1. Are the patient ZUMA-1 baseline characteristics for relapsed/refractory patients relevant for same patient population in Denmark?

a. Median age of 56 years

§ Median age for disease onset in Denmark is 67 for DLBCL but patients treated with CAR-T may be younger, on average, like in ZUMA-1. Do you think this expectation is realistic for Denmark? *Yes, I think it matches our median age of autologous DLBCL pt.*

· What could be the possible reason(s) that patients treated with CAR-T are younger? *CAR-T pt will match transplant eligble pt, although comorbidity should allow a higher age for CAR-T*

§ What characteristics could qualify / disqualify a patient for CAR-T treatment? High age

b. 33% females. *We have approx. 60% males in DK material*

Danish treatment landscape: Axi-cel and best supportive care (BSC)

2. SCHOLAR-1 is an international, multicohort retrospective non-Hodgkin lymphoma database study. SCHOLAR-1 retrospectively evaluated outcomes in patients with refractory DLBCL and pooled data from two phase 3 clinical trials (Lymphoma Academic Research Organization-CORAL and Canadian Cancer Trials Group (CCTG) LY.12) and two observational cohorts (MD Anderson Cancer Center (MDACC) and University of Iowa/Mayo Clinic Lymphoma Specialized Program of Research Excellence (MC/IA)).

	MDACC (n=165)	MC/IA (n=82)	CCTG LY.12 (n=219)	CORAL (n=170)	Integrated (n=636)
Median age	56	60	54	54	55
RR, %	20	26	26	31	26
CR	7	7	2	15	7
PR	13	18	25	16	18
RR by subgroup, %					
Primary refractory	0	25	27	10	20
Refractory to 2nd line Tx	20	21	20	40	26
Relapse < 1 year post ASCT	19	35	n/a	39	34
Median OS, months	6.6	5.0	6.6	6.5	6.3

a. Do the treatments used in Danish practice show similar effect in terms of responses and OS as in SCHOLAR-1? *Yes*

b. SCHOLAR-1 did not include PFS data instead this has been approximated using the same OS/PFS ratio as in the ZUMA-1 trial. In your opinion, is this a valid assumption? If not, please indicate what would be a more justifiable assumption. *It is the best possible, and probably also most realistic estimate*

Axi-cel treatment and treatment effect

3. Current literature suggests that patients with DLBCL who have not progressed at 24 months after treatment have the same mortality and quality of life as the age- and sex-matched general population.

(Maurer MJ, et al. Event-free survival at 24 months is a robust end point for disease-related outcome in diffuse large B-cell lymphoma treated with immunochemotherapy. *J Clin Oncol*. 2014; 32(10):1066-73)

a. In the cost/effect model it is assumed that patients on long-term remission live as long as the average Danish of the same age. Is this assumption in line with your experience? *More or less, follow up in these studies are not very long, so you need to have 15-20 years of follow up to be "sure", but the assumption is not very wrong*

c. In the cost/effect model it is assumed that patients on long-term remission have as high quality of life as the average Danish of the same age. Is this assumption in line with your experience?. *The literature Is sparse, but there is no documentation that the assumption is wrong*

d. In the cost/effect model it is assumed that patients on long-term remission (>24 months) do not undergo check-ups related to their disease. Is this assumption in line with your experience? If no, what would be the check-up schedule? *Patients with high IPI are followed for 5 years*

Allogeneic stem cell transplant

4. Can you estimate the share of DLBCL patients who are refractory, or have relapsed after two or more lines of systemic therapy that receives allogeneic stem cell transplant in Denmark? (29% in the SCHOLAR-1 Study; an international, multicohort retrospective non-Hodgkin lymphoma research study). *In DK it is 7 DLBCL patients / year.*

5. How does the medical follow up after an allogeneic stem cell transplant look like and how long are patients followed-up? *Lifelong follow up, frequent follow up in the first 6-12 month, thereafter 3-6 month*

Productivity loss

6. What percentage of the relapsed/refractory DLBCL patients (<65 yrs) is able to work and how many hours per week do they then work on average?

a. In progression free state *50%, it is not known how many have parttime work*

b. In progressed disease state *Close to zero*

Expert answers from Chief Physician Judit MeszaroJørgensen, Aarhus University Hospital
Chairman of Danish Lymphoma Group 2018-11-05

Questions for Key Opinion Leaders in Denmark regarding the treatment of B-cell lymphoma with CAR-T therapy Axicabtagene ciloleucel (Axi-cel)

Background

Axicabtagene ciloleucel (Axi-cel) is a CAR-T-cell therapy which consists of autologous human T-cells that have been engineered to identify and lock onto cells expressing the antigen CD19. Axi-cel has been developed for the treatment of patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), transformed follicular lymphoma (TFL) and primary mediastinal large B-cell lymphoma (PMBCL). The safety and efficacy of Axi-cel was evaluated in ZUMA-1, a phase-2, multicentre, open-label, single arm clinical trial.

A model is used to show the value of Axi-cel compared to best supportive care (BSC) in Denmark. The input from key opinion leaders in Denmark is needed to realistically adapt the model to local clinical practice.

About CAR-T & Axi-cel

1. Do you think the introduction of CAR-T will be important for future treatment of B-cell lymphomas in Denmark? Why? Yes. Patients, who are refractory or relapsed after 2 line treatment or relapsed after ASCT have a very poor prognosis (appr. 6 month OS) . No standard treatment available for this population.

Patient population of Axi-cel

2. Are the patient ZUMA-1 baseline characteristics for relapsed/refractory patients relevant for same patient population in Denmark?
    a) Median age of 56 years
        - Median age for disease onset in Denmark is 67 for DLBCL but patients treated with CAR-T may be younger, on average, like in ZUMA-1. Do you think this expectation is realistic for Denmark? Yes
            - What could be the possible reason(s) that patients treated with CAR-T are younger? Elderly patients are more likely to have co-morbidity or poor performance status which can make them ineligible to a further treatment, also CAR T
        - What characteristics could qualify / disqualify a patient for CAR-T treatment? Qualify: relapsed/refraktær large B-cell lymphoma, transformed FL, without comorbidity

        Disqualify:

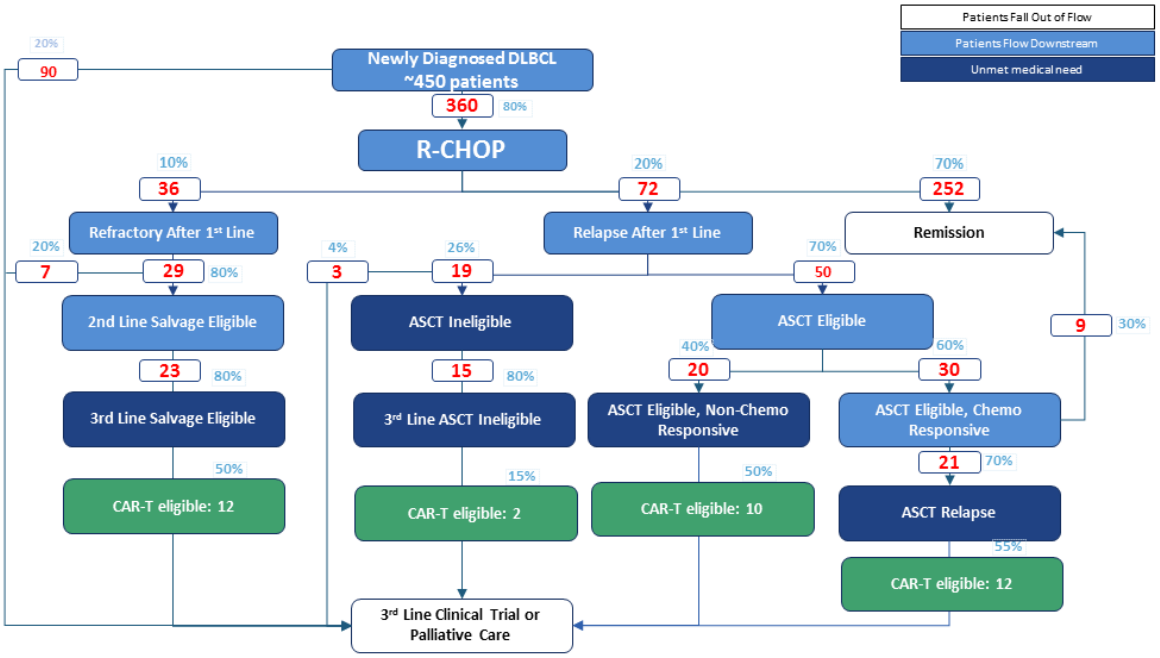
        - Co-morbidity, especially cardial, pulmonal and renal.
        - Poor performance score.
        - Very aggressive relapse with life-threatening conditions: fx. v.cava superior syndrome or other tumor compression symptoms, CNS involvement.

- Some rare and CD19 neg subtypes, as plasmablastic lymphoma, ALK pos anaplastik Large B-cell lymphoma.
- DLBCL transformed from other low grade B-cell malignancies: Waldentröm, CLL, SLL
- HIV or hepatitis B pos;
- infections.

b) 33% females : The incidence of lymphomas is higher in men (LYFO årsrapport, all lymphomas: 56.3% men, 43,7% women)

Danish treatment landscape: Axi-cel and best supportive care (BSC)

3. The graph below shows the clinical pathway of care for relapsed/refractory aggressive Non-Hodgkin lymphoma in the UK and the proposed placement of Axi-cel. Is this graph a relevant description of the potential usage of Axi-cel in Denmark? Yes



a) Are there any patient groups in the graph not relevant for CAR-T in Danish clinical practice? No

b) Are there any other patient groups than those showed in the graph that could receive CAR-T? Transformed FL

c) Which patient population(s) in this pathway do you think are most relevant for CAR-T? Refractory after 1. And 2 line; ASCT eligible, non chemo responsive, relapse after ASCT. (most of the ASCT ineligible are also ineligible for CAR T)

d) The HTA guidelines state that we need to compare this new treatment with the treatment that will be replaced with the introduction of CAR-T/Axi-cel. Which treatment do you think CAR-T will replace? For instance palliative treatment? Or other treatments? Younger patients: 3. Or 4. line salvage treatment as R-ICE, PREBEN, R-GEMOX, R-GDP; experimental drugs after application to second opinion committee (ibrutinib, venetoclax, revlimid, bispecific antibodies). Clinical trials. Pixantrone is registred to 3.line treatment of DLBCL by EMA (not FDA), but not widely used.

e) Can you give an estimate of around how many patients (percentage or absolute number) you expect in each patient group to be eligible for CAR-T every year in Denmark? The flow chart above is a pretty good estimate. The number of DLBCL in DK is appr.500/year- 30-40 patients could be candidate to CAR T.

4. Danish treatment guidelines list many treatments potentially used in relapsed/refractory DLBCL. The following treatments are those most commonly used in SCHOLAR-1 (see question 5 for more details on SCHOLAR-1 study) and also included in the Danish guidelines. Can you advice if they are commonly used for relapsed/refractory DLBCL in Danish clinical practice:
   - DHAP (Betamethasone, Cisplatin, Cytarabine, +/- Rituximab) yes (dexamethason in DK)
   - ICE (Ifosfamid, Carboplatin, Etoposide) yes
   - GDP (Gemcitabine, Prednisolone, Cisplatin, +/- Rituximab) yes

   a) If no, please specify the most commonly used treatments (R-GEMOX)
   b) Please give an approximate proportion of the patients treated with each of the treatments (e.g. 50% DHAP, 25% GDP, 25% ICE) 2 line: 60-70% R-DHAP, 20-30% R-ICE, 10-15 % GDP), 3. Line ?probable less R-DHAP, more R-ICE and GDP, GEMOX
   c) For dosing schedules, can we refer to the Swedish dosing schedules defined by the Regionalt Cancercentrum Sydost for the treatment of lymphoma (included as appendix)?
      - How many treatment cycles are administered, on average? Before ASCT: 3 cycle, relapse after or transplant ineligible 3-4
      - Is 500mg carboplatin a realistic average dose estimate for this patient group and when given as part of combination therapy. If no, which dose is realistic?
   d) Are TFL and PMBCL patients treated in the same way as DLBCL patients in clinical practice? Yes.

5. SCHOLAR-1 is an international, multicohort retrospective non-Hodgkin lymphoma database study. SCHOLAR-1 retrospectively evaluated outcomes in patients with refractory DLBCL and pooled data from two phase 3 clinical trials (Lymphoma Academic Research Organization-CORAL and Canadian Cancer Trials Group (CCTG) LY.12) and two observational cohorts (MD Anderson Cancer Center (MDACC) and University of Iowa/Mayo Clinic Lymphoma Specialized Program of Research Excellence (MC/IA)).

	MDACC (n=165)	MC/IA (n=82)	CCTG LY.12 (n=219)	CORAL (n=170)	Integrated (n=636)
Median age	56	60	54	54	55
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CR	7	7	2	15	7
PR	13	18	25	16	18
RR by subgroup, %					
Primary refractory	0	25	27	10	20
Refractory to 2nd line Tx	20	21	20	40	26
Relapse < 1 year post ASCT	19	35	n/a	39	34
Median OS, months	6.6	5.0	6.6	6.5	6.3

   a) Do the treatments used in Danish practice (as specified above in question 4), show similar effect in terms of responses and OS as in SCHOLAR-1? Yes, probably.

Unfortunately, LYFO doesn´t register RR after 2.line treatment and later treatments are not registered.

b) SCHOLAR-1 did not include PFS data instead this has been approximated using the same OS/PFS ratio as in the ZUMA-1 trial. In your opinion, is this a valid assumption? Yes If not, please indicate what would be a more justifiable assumption.?

c) In which aspects (e.g. OS, PFS, HRQoL) do you think Axi-cel represents a significant improvement over current treatment options? ORR, CR rate, PFS, probably also OS

Axi-cel treatment and treatment effect

6. Current literature[1] suggests that patients with DLBCL who have not progressed at 24 months after treatment have the same mortality and quality of life as the age- and sex-matched general population.
   a) In the CE-model it is assumed that patients on long-term remission live as long as the average Danish of the same age. Is this assumption in line with your experience? yes, see Danish data (attached publication)
   c) In the CE-model it is assumed that patients on long-term remission have as high quality of life as the average Danish of the same age. Is this assumption in line with your experience? Yes
   d) In the CE-model it is assumed that patients on long-term remission (>24 months) do not undergo check-ups related to their disease. Is this assumption in line with your experience? If no, what would be the check-up schedule? Clinical controls every 6 month with laboratory tests and physical examination in year 2-5 post-treatment

Allogeneic stem cell transplant

7. Can you estimate the share of DLBCL patients who are refractory, or have relapsed after two or more lines of systemic therapy that receives allogeneic stem cell transplant in Denmark? (29% in the SCHOLAR-1 Study; an international, multicohort retrospective non-Hodgkin lymphoma research study) 5-10%

8. How does the medical follow up after an allogeneic stem cell transplant look like and how long are patients followed-up? Clinical control every 2-3 day in the first 2-3 month´, 1-2 x / month in the first 6-12 month after treatment. Immunosuppressive treatment, regularly CMV monitoring. PET-CT scan and lumbal puncture 3 month after transplantation, than CT scans every 6. Month. Min 5 years FU.

Resource utilisation

9. The following table shows an estimate of average resource utilisation for the progression free state and progressed disease state largely based on an estimate for similar patients in 2016[2]

[1] Maurer MJ, Ghesquieres H, Jais JP, et al. Event-free survival at 24 months is a robust end point for disease-related outcome in diffuse large B-cell lymphoma treated with immunochemotherapy. *J Clin Oncol*. 2014; 32(10):1066-73

[2] TLVs Underlag för beslut ilandstingen: Pixuvri (pixantron)

a) Please validate the estimates given in the table and specify your own estimates wherever different from those given in the table.

	Resource utilisation estimates based on similar patient population		Fill in here if your estimate is different from the estimates to the left	
Resource	**Progression free state**	**Progressed disease state**	**Progression free state**	**Progressed disease state**
Outpatient care				
Physician visit (e.g. oncologist, haematologist)	1 visit per month	1 visit per month	1 visit every 3.-6. month	2-4 visit pr month
Nurse visit	2 visits per month	2 visits per month	No visit	2-4 visit pr month
Inpatient care				
Inpatient days	3 visits per month	3 visits per month	No	4-10 days pr month
Other care				
Home care	10% of patients, every day	30% of patients, every day		
Tests				
Full blood counts	3 tests per month	1 test per month	Every 3.-6month	4-8 test /month
LDH	2 tests per month	1 test every 3 months	Every 3.-6month	4-8 test /month
Immunoglobulin	1 test every 2 months	1 test every 3 months	Every 3.-6month	
Renal function	3 tests per month	1 test every 3 months	Every 3.-6month	4-8 test /month
Liver function	3 tests per month	1 test per month	Every 3.-6month	4-8 test /month
Calcium phosphate	1 test every 2 months	1 test per month		

Productivity loss

10. What percentage of the relapsed/refractory DLBCL patients (<65 yrs) is able to work and how many hours per week do they then work on average?
    a) In progression free state ~ 80%
    b) In progressed disease state 0 %

APPENDIX:

Dosing regimes according to Regionalt Cancercentrum Sydost
(http://www.ocsyd.se/Cytostatika/Sidor/regimer.asp)

IKE

Aggressiva lymfom, recidiv

Preparat	Dos/ dostillfälle mg/m²	Maxdos/ dostillfälle mg	Antal doser/ dygn	Dos interv. tim	Antal doser/ cykel	Administreringssätt		Dag
1. Etoposid	100		1		2	iv inf	1 tim	1 och 3
Etoposid	100		1		1	iv inf	1 tim	2
2. Karboplatin	5 × (GFR + 25)*	800	1		1			
3. Ifosfamid	5000		1		1	iv inf	24 tim	2
4. Mesna	3000		1		1			
Mesna	1000		3		3	iv inj**	4, 8 och 12 tim efter ifosfamid inf	

*totaldos

Calverts formel: Dos = AUC x (GFR + 25)

AUC = 5 mg/ml × min

GFR = ... ml/min, okorrigerat värde

Dos = ... mg, totaldos

Prep				
1	**1**	**1**	**1**	
2		**2**		
3		**3**		**Ny cykel** ↓
4		**4**	**4**	
Dag	1	2	3	15

Cykellängd: 14 d

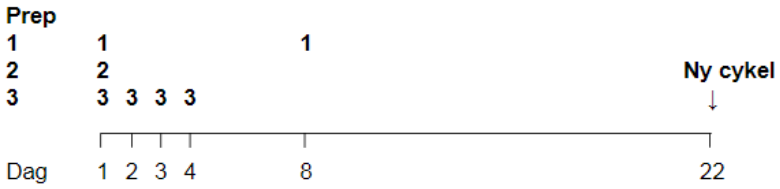
Beredning och administrering v g v

GDP

Malignt lymfom, recidiv

Preparat	Dos/ dostillfälle mg/m²	Maxdos/ dostillfälle mg	Antal doser/ dygn	Dos interv. tim	Antal doser/ cykel	Administreringssätt		Dag
1. Gemcitabin	1000		1		2	iv inf	30 min	1, 8
2. Cisplatin	75		1		1	iv inf	2 tim	1
3. Betametason	30*		1		4	po/iv		1–4

* totaldos



Cykellängd: 21 d

Beredning och administrering v g v

R – DHAP

Malignt lymfom

Preparat	Dos/ dostillfälle mg/m²	Maxdos/ dostillfälle mg	Antal doser/ dygn	Dos interv. tim	Antal doser/ cykel	Administreringssätt		Dag
1. Rituximab	375		1		1	iv se omst.sida		1
2. Betametason	30*		1		1	po/iv		1–4
3. Cytarabin	2000		2	12	2	iv inf	1 tim	2
4. Cisplatin	100		1		1	iv inf	24 tim	1

*totaldos

Cykellängd: 21 d

Beredning och administrering v g v

Medicinrådet

Medicinrådets protokol for vurdering af klinisk merværdi for axicabtagene ciloleucel til behandling af diffust storcellet B-celle-lymfom

Handelsnavn	AXI-CEL
Generisk navn	Axicabtagene ciloleucel
Firma	Gilead
ATC-kode	L01X
Virkningsmekanisme	Patientens egne T-celler genmodificeres til at udtrykke receptorer (chimeric antigen receptor (CAR)), der genkender den generelle B-celle-markør, CD19. De modificerede T-celler indgives intravenøst til patienten, hvor de binder sig til B-celler og slår disse ihjel.
Administration/dosis	Administration af én intravenøs infusion af axicabtagene ciloleucel med en target dosis på 2 x 10^6 CAR T celler/kg kropsvægt (dag 0). Før transfusion af axicabtagene ciloleucel behandles patienten med lavdosis konditionerende kemoterapi bestående af fludarabinphosphat (30 mg/m^2/d) og cyclophosphamid (500 mg/m^2/d) på dag -5, -4 og -3.
EMA-indikation	Axicabtagene ciloleucel er indiceret til behandling af voksne patienter (≥ 18 år) med relaps eller refraktær diffust storcellet B-celle-lymfom (DLBCL) og primær mediastinal storcellet B-celle-lymfom (PMBCL) efter to eller flere linjer af systemisk behandling.
Godkendelsesdato Offentliggørelsesdato Dokumentnummer Versionsnummer	20. september 2018 20. september 2018 27014 1.0

Indhold

Forkortelser

ARR:	Absolut risikoreduktion
CAR:	*Chimeric antigen receptor*
CEOP:	Cyclophosphamid, vincristin, epirubicin og prednison
CNS:	Centralnervesystem
CR:	Komplet remission
CRS:	*Cytokine release syndrome*
CVP:	Cyclophosphamid, vincristin og prednison
DHAP:	Cisplatin, cytarabin, dexamethason)
DLBCL:	Diffust storcellet B-celle-lymfom
EFS:	Eventfri overlevelse
EMA:	*European Medicines Agency*
EPAR:	*European public assessment reports*
FACT-Lym:	*Functional asessment of cancer therapy - lymfoma*
GDP:	Gemcitabin, dexamethason og cisplatin
GemOx:	Gemcitabin og oxaliplatin)
HR:	*Hazard ratio*
ICE:	Ifosfamid, carboplatin, etoposid
IPI:	*International Prognostic Score*
ITT:	*Intention-to-treat*
NHL:	Non-Hodgkins lymfom
OR:	Odds ratio
ORR:	*Overall response rate*
OS:	Samlet overlevelse
PBMC:	Perifær blodmononukleær celle
PFS:	Progressionsfri overlevelse
PMBCL:	Primært mediastinal B-celle-lymfom
RR:	Relativ risiko
SAE:	*Serious adverse events*
SMD:	*Standardized mean difference*
SF-36:	Kort version af det generiske spørgeskema til livskvalitet (Short form 36)
TFL:	Transformeret follikulært lymfom

1 Formål

Protokollen har til formål at definere de kliniske spørgsmål, der ønskes belyst i vurderingen af axicabtagene ciloleucel som mulig standardbehandling af patienter med B-celle-lymfom. I protokollen angives en definition af populationer, komparator og effektmål, der skal præsenteres i den endelige ansøgning, samt de metoder, der ønskes anvendt til den komparative analyse. Arbejdet med protokollen er igangsat på baggrund af den foreløbige ansøgning vedrørende axicabtagene ciloleucel modtaget den 14. juni 2018.

Protokollen danner grundlaget for den endelige ansøgning for vurderingen af den kliniske merværdi af axicabtagene ciloleucel sammenlignet med dansk standardbehandling. Alle effektmål, der er opgivet i denne protokol, skal besvares med en sammenlignende analyse mellem axicabtagene ciloleucel og standardbehandlingen af både absolutte og relative værdier for de udspecificerede populationer i de angivne måleenheder (se Tabel 1). Litteratursøgning og databehandling udføres som beskrevet i protokollen.

2 Baggrund

Diffust storcellet B-celle-lymfom (DLBCL) er en aggressiv undertype af Non-Hodgkin lymfom (NHL). DLBCL udgør omkring 40 % af NHL. I Danmark diagnosticeres ca. 500 patienter årligt med DLBCL [1,2]. Risikoen for at udvikle DLBCL stiger med alderen, og medianalderen i Danmark ved diagnose er 67 år [2]. Prognosen er forholdsvis god, med en 5-års overlevelse på 65-90 %, afhængigt af risikoprofil (IPI). Patienter med DLBCL præsenterer sig typisk med et eller flere hurtigtvoksende lymfeknuder, ofte lokaliseret på hals, i mediastinum og/eller i abdomen. Hos 40 % af patienterne præsenterer sygdommen sig dog med ekstranodal involvering af mavetarmkanalen, testikler, knogler, skjoldbruskkirtlen, spytkirtler, lever, bryst, binyrer, bihuler eller det centrale nervesystem (CNS) [1,2]. Flere ekstranodale manifestationer er forbundet med dårlig prognose, og visse lokalisationer er forbundet med øget risiko for CNS-recidiv. Primær mediastinalt B-celle-lymfom (PMBCL) er en sjælden DLBCL-undertype. PMBCL er et aggressivt lymfom, og tilbagefald forekommer ofte inden for de første måneder. Incidencen estimeres at være omkring 5-10 patienter årligt [2].

Det estimeres, at omkring 100 patienter med DLBCL årligt er refraktære eller oplever recidiv efter to eller flere linjer af systemisk behandling. Af disse patienter forventes ca. 25-50 patienter årligt at være kandidater til axicabtagene ciloleucel, vurderet på baggrund af alder, performance status og tidligere behandling.

2.1 Nuværende behandling

I henhold til de nuværende retningslinjer findes der ikke evidens for at anbefale et bestemt regime til 3. linjebehandling af patienter med refraktær eller recidiverende DLBCL [2,4]. Denne patientgruppe tilbydes den bedste tilgængelige behandling. Hvis sygdommen er kemosensitiv, kan allogen transplantation bruges til at konsolidere behandlingen, og behandlingen er potentielt kurativ. Hvis der ikke er mulighed for allogen transplantation, kan det ikke forventes at 3. linjebehandling vil være kurativ. Det anbefales at overveje eksperimentel behandling, når denne er tilgængelig. Behandlingsregimerne har forskellig intensitet og bivirkningsprofil. Valget af behandling vurderes for den enkelte patient og afhænger blandt andet af muligheden for allogen stamcelletransplantation, performance status, komorbiditet, tidligere behandlinger og alder. Følgende regimer kan overvejes med eventuelt tillæg af CD20 antistof (rituximab), såfremt det vurderes, at patienten kan tolerere behandlingen:

- GDP (gemcitabin, dexamethason og cisplatin)
- CEOP (cyclophosphamid, vincristin, epirubicin og prednison)
- CVP (cyclophosphamid, vincristin og prednison)
- GemOx (gemcitabin og oxaliplatin)

- DHAP (cisplatin, cytarabin, dexamethason)
- ICE (ifosfamid, carboplatin, etoposid)

Alternativt kan følgende enkeltstofbehandlinger overvejes:

- Gemcitabin
- Pixantrone
- Bendamustin

Herudover findes behandling med et palliativt sigte, hvor der eksempelvis anvendes peroral CCVP (cyclophosphamid, etoposid, lomustine og prednison) med eller uden rituximab. Stråleterapi bør overvejes ved lokaliseret recidiv.

2.2 Axicabtagene ciloleucel

Axicabtagene ciloleucel er en autolog anti-CD19 chimeric antigen receptor (CAR) T-celleterapi [5] indiceret til 3. linjebehandling af patienter med refraktær eller recidiverende DLBCL.

Patientens perifære blodmononukleære celler (PBMC'er) opsamles ved brug af leukaferese. Herfra isoleres T-cellerne, som modificeres genetisk ved brug af en retroviral vektor, som indsætter CAR i T-cellerne. De CAR modificerede T-celler ekspanderes og føres tilbage til patienten via blodbanen, hvor de lokaliserer og binder sig til alle CD19-positive B-celler og dræber disse [5].

Axicabtagene ciloleucel gives som en enkelt intravenøs infusion i en dosis på 2 x 10^6 CAR T-celler / kg legemsvægt (dag 0). Forud for administration af axicabtagene ciloleucel (dag -5, -4 og -3) behandles patienten med lavdosis kemoterapi bestående af fludarabin (30 mg /m^2 /d) og cyclofosfamid (500 mg / m^2 / d) [6]. Dette skal sikre, at T-cellerne ekspanderer optimalt i patienten og udviser optimal antitumoraktivitet.

3 Klinisk spørgsmål

Hvilken klinisk merværdi tilbyder axicabtagene ciloleucel sammenlignet med nuværende standardbehandling til voksne patienter (>18 år) med relaps eller refraktær DLBCL eller PMBCL efter to eller flere linjer af systemisk behandling?

Population

Voksne patienter med aggressiv diffus storcellet B-celle-lymfom eller primær mediastinalt B-celle-lymfom med relaps eller refraktær sygdom efter to eller flere linjer af systemisk behandling, som vurderes at være kandidater til axicabtagene ciloleucel.

Subgruppe: Der ønskes en subgruppeanalyse for de patienter, der med nuværende behandlingsmuligheder vurderes at kunne behandles med kurativt sigte, dvs. patienter, som er yngre end 65 år, har performancestatus 0-1 og beskeden komorbiditet.

Intervention

Axicabtagene ciloleucel.

Komparator

Da der i Danmark ikke findes en standardbehandling til den definerede population, er komparator 'bedste tilgængelige behandling'. De patienter, som vil være kandidater til behandling med interventionen, vil være

selekteret på baggrund af alder, performance status og tidligere behandlinger. Til denne gruppe vil typisk vælges en kombinationsbehandling, og følgende er derfor valgt som komparatorer:

- GDP (gemcitabin, dexamethason og cisplatin) +/- R (rituximab)
- DHAP (cisplatin, cytarabin, dexamethason) +/- R (rituximab)
- ICE (ifosfamid, carboplatin, etoposid) +/- R (rituximab)

Effektmål

De valgte effektmål fremgår af Tabel 1.

3.1 Valg af effektmål

Tabel 1 summerer de valgte effektmål, deres vigtighed, mindste klinisk relevante forskel og kategori. For alle effektmål ønskes både absolutte og relative værdier. For de relative værdier vurderes den kliniske relevans (merværdi), jævnfør væsentlighedskriterierne beskrevet i Medicinrådets metodehåndbog for vurdering af nye lægemidler. De relative effektestimater skal angives i relativ risiko (RR), odds ratio (OR) eller hazard ratio (HR). Det skal begrundes i ansøgningen, hvis der afviges fra de ønskede effektmål.

Tabel **1**. Oversigt over valgte effektmål. For hvert effektmål er angivet deres vigtighed, måleenhed og mindste klinisk relevante forskel samt indplacering i en af de fire kategorier (dødelighed, alvorlige symptomer og bivirkninger, livskvalitet og ikkealvorlige symptomer og bivirkninger).

Effektmål*	**Vigtighed**	**Kategori**	**Måleenhed**	**Mindste klinisk relevante forskelle (absolutte værdier)**
Samlet overlevelse (overall survival, OS)	Kritisk	Dødelighed	Andel af patienter, der opnår 2 års overlevelse	10 procentpoint
Uønskede hændelser (adverse events, AEs)	Vigtig	Alvorlige symptomer og bivirkninger	Andel af patienter, der oplever ≥ 1 alvorlige uønskede hændelser (SAEs)^	10 procentpoint
			Narrativ beskrivelse af cytokin release syndrom og neurologiske bivirkninger. Dertil ønskes en detaljeret opgørelse af grad 3, 4 og 5 bivirkninger.	-
Helbredsrelateret livskvalitet	Vigtig	Helbredsrelateret livskvalitet	SF-36, ændring fra baseline til 1 år	En forskel mellem grupperne svarende til 0,5 SD af de poolede baseline score
			FACT-Lym, ændring fra baseline til 1 år	En forskel på 4 point mellem grupperne
Responsrate	Vigtig	Alvorlige symptomer og bivirkninger	Andel af patienter, der har opnået og fortsat er i CR ved 1 års opfølgning	10 procentpoint
Progressionsfri overlevelse (PFS)	Vigtig	Alvorlige symptomer og bivirkninger	Median PFS	3 måneder

OS = Overall Survival, CR = komplet resmission
**For alle effektmål ønskes data med længst mulig opfølgningstid.*
^Der ønskes, udover den overordnede opgørelse, en specifik opgørelse over andelen af patienter, der oplever CRS (cytokine release syndrome).

Den samlede kliniske merværdi af axicabtagene ciloleucel baseres på en tidshorisont ud fra data med længst mulig opfølgningstid.

Kritiske effektmål

Samlet overlevelse (overall survival): Er guldstandard for at demonstrere klinisk effekt i cancerstudier, herunder lymfomer. Det er et patientrelevant effektmål, der belyser patienternes levetid efter en fast opfølgningstid. Overlevelse defineres som tiden fra randomisering eller opstart af behandling til død uanset årsag. Fagudvalget finder det relevant at se på overlevelse efter 2 år. Denne tidshorisont er valgt ud fra et klinisk rationale om, at man efter 2 års opfølgning kan forvente, at evt. recidiv vil have vist sig, og at man har kendskab til, hvorvidt en kurativ behandling har været succesfuld. Fagudvalget estimerer, at omkring 20 % af den definerede population, svarende til 10 patienter, overlever mindst 2 år med nuværende behandlingsmuligheder. Fagudvalget vurderer, at 10 procentpoint vil være en klinisk relevant forskel i andelen af patienter, der opnår 2 års overlevelse.

Vigtige effektmål

Uønskede hændelser (adverse events, AE): Er et effektmål, der har til formål at vurdere sikkerheden af axicabtagene ciloleucel og inkluderer bivirkninger, som har stor betydning for den enkelte patients livskvalitet og kan føre til ophør af behandling. Fagudvalget ønsker uønskede hændelser opgjort som andel af patienter, der oplever ≥ 1 alvorlig uønsket hændelse. En forskel mellem grupperne på 10 procentpoint anses som klinisk relevant, hvilket skal ses i lyset af, at behandlingen potentielt er kurativ. Derudover ønskes en særskilt opgørelse over andelen af patienter, der oplever cytokine release syndrome (CRS), som er en potentielt fatal bivirkning ved behandlingen. Fagudvalget ønsker desuden i forbindelse med vurderingen at der foretages en kvalitativ gennemgang af to betydende bivirkninger ved behandlingen: CRS samt neurologiske bivirkninger. Fokus her er at vurdere alvorlighed, hyppighed og håndterbarhed af hændelserne. Dertil ønskes en detaljeret opgørelse af grad 3, 4 og 5 bivirkninger.

Helbredsrelateret livskvalitet: SF-36 er et generisk instrument, som bygger på 36 spørgsmål udarbejdet til at vurdere livskvalitet. Spørgeskemaet er inddelt i 8 helbredsrelaterede domæner: fysisk funktion, fysisk betingede begrænsninger, psykisk betingede begrænsninger, social funktion, fysisk smerte, psykisk helbred, energi samt alment helbred. Scoren måles på en skala fra 0-100, hvor højere score repræsenterer bedre livskvalitet [7]. Livskvalitet skal opgøres på den globale score af SF-36, hvor forskellen mellem grupperne i ændring fra baseline skal angives. For helbredsrelateret livskvalitet anses 0,5 SD af baselineværdier at være en klinisk relevant forskel [8], og fagudvalget har derfor valgt at anvende 0,5 SD af de poolede baselinescore som den mindste klinisk relevante forskel. Såfremt der ikke findes data for livskvalitet målt på SF-36, ønskes livskvalitet opgjort med det sygdomsspecifikke spørgeskema Functional asessment of cancer therapy - lymfoma (FACT-Lym), som er opdelt i subskalaerne: fysisk velvære, social-/familievelvære, følelsesmæssigt velvære, funktionelt velvære og yderligere bekymringer. Spørgeskemaet er valideret til patienter med Non-Hodgkins lymfom [9], og den mindste klinisk relevante score for denne patientgruppe er 3-5 point, ud af en total score der går fra 0-60 point [9]. På den baggrund har fagudvalget valgt 4 point som den mindste klinisk relevante forskel.

Responsrate: Fagudvalget ønsker effektmålet responsrate opgjort som andelen af patienter, der opnår komplet remission (CR). CR er defineret som forsvinden af alle synlige tegn på sygdom, jævnfør responskriterier for maligne lymfomer [10]. CR er et relevant effektmål, da opnåelse af komplet remission åbner muligheden for helbredelse, evt. via stamcelletransplantation. CR opgøres traditionelt umiddelbart efter afsluttet kemoterapi, dvs. efter 1-2 mdr. Farmakodynamikken omkring opnåelse af respons på CAR-T er ukendt, men fagudvalget antager at responset formentligt kommer langsommere end ved kemoterapi. Derfor er andelen af patienter, der har opnået og fortsat er i CR ved 1 års opfølgning valgt som effektmål. Fagudvalget vurderer, at en forskel på 10 procentpoint er en klinisk relevant forskel.

Progressionsfri overlevelse (PFS): Er defineret som tiden fra initiering af behandling til progression eller død uafhængigt af årsag. PFS anvendes som et udtryk for graden og længden af sygdomskontrol, som opnås efter behandling. Længden af den progressionsfrie periode for patienter, der behandles med nuværende standardbehandling, er meget varierende. Baseret på fagudvalgets erfaringer med de nuværende behandlingsmuligheder vurderer fagudvalget, at det nye lægemiddel skal tilbyde en forbedring i median PFS på minimum 3 måneder.

Mindre vigtige effektmål

Eventfri overlevelse (EFS): Tid fra randomisering til tidspunktet hvor sidste induktionsbehandling ikke giver anledning til komplet remission eller ved relaps eller død, uanset årsag. Dette effektmål vurderes som mindre vigtigt, da samlet overlevelse er medtaget som et kritisk effektmål.

Behandlingsrelateret mortalitet: Alvorlige bivirkninger er et vilkår ved alle behandlingsalternativerne til patienter med refraktær eller relaps efter to eller flere behandlinger for DLCBL. Disse bivirkninger har stor betydning for patienternes livskvalitet og kan i nogle tilfælde være fatale. Fagudvalget vurderer imidlertid, at den viden, som effektmålet ville give, belyses under effektmålet 'samlet overlevelse'.

4 Litteratursøgning

Databaser for søgningen

Relevant litteratur søges i databaserne MEDLINE (via PubMed eller Ovid) og CENTRAL (via Cochrane Library).

Derudover skal EMAs European public assessment reports (EPAR) konsulteres for både det aktuelle lægemiddel og dets komparator(er).

Søgetermer

Søgningen skal inkludere det generiske navn og handelsnavnet for både det aktuelle lægemiddel og dets komparator(er), som kombineres med termer for indikationen. Søgningen skal som minimum indeholde termer, som er beskrivende for de områder, der angivet i Tabel 2. Både indekseret (f.eks. Medical Subject Headings, MeSH) og fritekstsøgning skal anvendes.

Tabel 2. Søgetermer

Lægemiddel/komparator(er)	**Indikation**
axicabtagene ciloleucel, AXI-CEL, Yescarta *Termer for det generiske navn, handelsnavn og alternative stavemåder og eventuelle MeSH/Supplementary Concepts kombineres med OR.*	Diffust storcellet B-celle-lymfom (DLBCL), primær mediastinal storcellet B-celle-lymfom, transformeret follikulært lymfom *Termer for indikationen, alternative stavemåder og eventuelle MeSH kombineres med **OR**. AND kan bruges, hvor flere termer skal forekomme samtidigt for at beskrive indikationen korrekt.*
GDP (gemcitabin, dexamethason og cisplatin) +/- R (rituximab), DHAP (cisplatin, cytarabin, dexamethason) +/- R (rituximab), ICE (ifosfamise, carboplatin, etoposid) +/- R (rituximab) *Termer for de generiske navne, handelsnavne og alternative stavemåder og eventuelle MeSH/Supplementary Concepts kombineres med **OR**.*	

De anvendte søgetermer, og hvordan de er blevet kombineret, dokumenteres separat for hver af de to databaser.

Kriterier for udvælgelse af litteratur
Der ekskluderes først på titel- og abstractniveau, dernæst ved gennemlæsning af fuldtekstartikler. Artikler, der ekskluderes ved fuldtekstlæsning, skal fremgå med forfatter, årstal og titel i en eksklusionsliste, hvor eksklusionen begrundes kort. Den samlede udvælgelsesproces skal afrapporteres ved brug af et PRISMA-flowdiagram (http://prisma-statement.org/PRISMAStatement/FlowDiagram.aspx).

Ved usikkerheder om, hvorvidt en artikel på titel- og abstractniveau lever op til inklusions- og eksklusionskriterierne, skal der anvendes et forsigtighedsprincip til fordel for artiklen, hvorved fuldtekstartiklen vurderes.

Inklusionskriterier: populationen skal svare til den der er angivet i det kliniske spørgsmål, mindst ét af de kritiske eller vigtige effektmål skal være rapporteret.

Vurderingen af klinisk merværdi baseres på data fra publicerede fuldtekstartikler og data fra EMAs EPAR. Data skal derudover stemme overens med protokollens beskrivelser. Upublicerede data og data fra f.eks. abstracts kan fremsendes og vil indgå i vurderingen, såfremt Medicinrådet finder, at de er nødvendige for at sikre en fair sammenligning. Data skal i så fald stamme fra de forsøg, som hovedpublikationerne rapporterer fra, og ansøger skal acceptere, at Medicinrådet offentliggør dem i ansøgningsskemaet og i rapporten vedr. klinisk merværdi.

5 Databehandling/analyse

De inkluderede studier og baselinekarakteristikken af studiepopulationerne beskrives i Medicinrådets ansøgningsskema. Det skal angives, hvilke studier der benyttes til at besvare hvilke kliniske spørgsmål.

Al relevant data skal som udgangspunkt ekstraheres ved brug af Medicinrådets ansøgningsskema. Der skal udføres en komparativ analyse for hvert enkelt effektmål på baggrund af relevant data fra inkluderede studier. For hvert effektmål og studie angives analysepopulation (f.eks. intention-to-treat (ITT), per-protocol) samt metode. Resultater for ITT-populationen skal angives, hvis muligt, hvis komparative analyser ikke i udgangspunktet er baseret på denne population. Alle ekstraherede data skal krydstjekkes med de resultater, der beskrives i EPAR'en. Findes uoverensstemmelser, gives en mulig grund herfor.

Hvis ekstraherede data afviger fra det forhåndsdefinerede kliniske spørgsmål, specielt i forhold til præspecificeret population og effektmål, begrundes dette.

Hvis data for et effektmål ikke er tilgængelig for alle deltagere i et studie, vil der ikke blive gjort forsøg på at erstatte manglende data med en meningsfuld værdi. Det vil sige, at alle analyser udelukkende baseres på tilgængelige data på individniveau.

For effektmål (ORR, SAE, behandlingsstop pga. bivirkninger og ikkealvorlige bivirkninger), hvor det er naturligt at beregne både absolut og relativ forskel, vil den relative forskel være basis for statistiske analyser. Den absolutte forskel vil derefter blive beregnet, baseret på den estimerede relative forskel for et antaget niveau på hændelsesraten i komparatorgruppen. Det antagne niveau vil afspejle det forventede niveau i Danmark ved behandling med komparator (hvis RR = 0,5 og antaget andel med hændelse i komparatorgruppen er 30 %, da er den absolutte risiko reduktion (ARR) = 30 – 30 x 0,5 = 15 procentpoint).

Hvis der er mere end ét sammenlignende studie, foretages en metaanalyse for de effektmål, hvor det er metodemæssigt forsvarligt. Hvis der ikke foreligger sammenlignende studier, kan data eventuelt syntetiseres indirekte (evt. i form af formelle netværksmetaanalyser eller ved brug af Buchers metode), hvis intervention og komparator er sammenlignet med samme alternative komparator i separate studier. Medicinrådet

forbeholder sig retten til at foretage sensitivitets- og subgruppeanalyser på baggrund af studiernes validitet og relevans.

For effektmål, hvor forskellige måleinstrumenter er brugt på tværs af de inkluderede studier, vil eventuelle metaanalyser blive baseret på standardized mean difference (SMD). Den estimerede SMD vil blive omregnet til den foretrukne skala for effektmålet. Til dette formål anvendes medianen af de observerede standardafvigelser i de inkluderede studier.

Hvis det ikke er en mulighed at udarbejde metaanalyser (herunder netværksmetaanalyser), syntetiseres data narrativt. Studie- og patientkarakteristika samt resultater fra de inkluderede studier beskrives narrativt og i tabelform med angivelse af resultater pr. effektmål for både intervention og komparator(er). Forskelle i patientkarakteristika og studiekontekst (f.eks. geografi og årstal) mellem studier skal beskrives og vurderes for at afgøre, hvorvidt resultaterne er sammenlignelige.

Valget af syntesemetode (metaanalyse eller narrativ beskrivelse) begrundes, og specifikke analysevalg truffet i forhold til metoden skal fremgå tydeligt.

Det skal angives hvilke studier, der benyttes til at besvare det kliniske spørgsmål. Ansøger skal krydstjekke ekstraherede data med EPAR og begrunde eventuelle afvigelser. Vedr. data på effektmål: Oplysning om, hvor data på de enkelte effektmål stammer fra, begrundelse for eventuelle afvigelser fra EPAR samt beskrivelse af hvilke analysemetoder, der er blevet anvendt til hvilke effektmål, skal fremgå.

Population

Fagudvalget ønsker en præcisering af den population, der beskrives i den forventede EMA-indikation samt angivelse af, hvilken sygdomsklassifikation, der anvendes.

Effektanalyser

Ansøger har i den foreløbige ansøgning angivet, at effektanalyserne forventes at blive baseret på indirekte analyser med udgangspunkt i SCHOLAR-studiet [6]. Fagudvalget bemærker i relation til dette, at analyserne bør tage højde for forskelle i patientpopulationerne, herunder f.eks.:

- Patienternes alder
- Forskelle i performance status
- Tidligere behandlinger.

Det er vigtigt, at både effektmodificerende og prognostiske faktorer, defineret i forbindelse med analyserne, beskrives. Desuden skal fordelingen af (individ)vægte i analyserne beskrives f.eks. ved hjælp af histogrammer og deskriptiv statistik.

6 Referencer

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7 Sammensætning af fagudvalg og kontaktinformation til Medicinrådet

Medicinrådets fagudvalg vedrørende lymfekræft (lymfomer)

Formand	***Indstillet af***
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Michael Boe Møller *Overlæge*	Dansk Patologiselskab
Jørn Søllingvraa *Patient/patientrepræsentant*	Danske Patienter
En patient/patientrepræsentant	Danske Patienter

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