Medicinrådet

Bilag til Medicinrådets anbefaling vedrørende polatuzumab vedotin (Polivy) i kombination med bendamustin og rituximab - diffust storcellet B-cellelymfom

Vers. 1.0

Bilagsoversigt

1. Medicinrådets sundhedsøkonomiske afrapportering vedr polatuzumab vedotin i kombination med bendamustin og rituximab til behandling af diffust storcellet B-cellelymfom, version 1.0
2. Forhandlingsnotat fra Amgros vedr. polatuzumab vedotin
3. Høringssvar fra ansøger
4. Medicinrådets svar til høringssvar
5. Medicinrådets vurdering vedr. polatuzumab vedotin i kombination med bendamustin og rituximab til behandling af diffust storcellet B-cellelymfom, version 1.1
6. Ansøgers endelige ansøgning, version 2.0
7. Ansøgers tillæg til endelig ansøgning
8. Ansøgers tekniske dokument til den sundhedsøkonomiske ansøgning
9. Medicinrådets protokol for vurdering vedr. polatuzumab vedotin i kombination med bendamustin og rituximab til behandling af diffust storcellet B-cellelymfom, version 1.0

Medicinrådet

Sundhedsøkonomisk afrapportering

Polatuzumab vedotin i kombination med bendamustin og rituximab

Diffust storcellet B-cellelymfom

Version 1.0

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.

Dokumentets formål

Dette dokument indeholder en beskrivelse af den sundhedsøkonomiske analyse, som ligger til grund for ansøgningen for polatuzumab vedotin i kombination med bendamustin og rituximab til patienter med recidiverende/refraktært diffust storcellet B-cellelymfom (DLBCL), samt en gennemgang af ansøgers modelantagelser til den sundhedsøkonomiske model. Sekretariatet vil kommentere på ansøgers modelantagelser under afsnittene "Sekretariatets vurdering". Her vil sekretariatets vurdering fremgå sammen med eventuelle ændrede modelantagelser og begrundelser herfor.
Afsnit 4.4 indeholder en tabel, der opsummerer både ansøgers og sekretariatets modelantagelser med det formål tydeligt at vise, hvordan sekretariatets sundhedsøkonomiske analyse afviger fra ansøgers sundhedsøkonomiske analyse. Resultatafsnittet baserer sig på sekretariatets modelantagelser og sundhedsøkonomiske analyse.

Dokumentoplysninger	
Godkendelsesdato	24. februar 2021
Dokumentnummer	107145
Versionsnummer	1.0

Sprog: dansk
Format: pdf
Udgivet af Medicinrådet 24. februar 2021

Indholdsfortegnelse

1. Liste over forkortelser ... 3

2. Opsummering ... 4

3. Baggrund for den sundhedsøkonomiske analyse ... 5
3.1 Patientpopulation ... 5
3.1.1 Komparator ... 5
3.2 Problemstilling ... 6

4. Vurdering af den sundhedsøkonomiske analyse ... 6
4.1 Antagelser og forudsætninger for model ... 7
4.1.1 Modelbeskrivelse ... 7
4.1.2 Analyseperspektiv ... 10
4.2 Omkostninger ... 11
4.2.1 Lægemiddelomkostninger ... 11
4.2.2 Hospitalsomkostninger ... 12
4.2.3 Bivirkningsomkostninger ... 14
4.2.4 Patientomkostninger ... 16
4.2.5 Behandling efter progression ... 16
4.3 Følsomhedsanalyser ... 17
4.4 Opsummering af basisantagelser ... 18

5. Resultater ... 19
5.1 Resultatet af sekretariatets hovedanalyse ... 19
5.1.1 Resultatet af sekretariatets følsomhedsanalyser ... 20

6. Budgetkonsekvenser ... 20
6.1 Ansøgers estimat af patientantal og markedsandel ... 20
6.2 Sekretariatets budgetkonsekvensanalyse ... 23

7. Diskussion ... 23
7.1 Usikkerheder ... 24

8. Referencer ... 25

9. Bilag ... 26
9.1 Resultatet af ansøgers hovedanalyse ... 26
9.2 Ansøgers budgetkonsekvensanalyse ... 26

1. Liste over forkortelser

AIP	Apotekernes indkøbspris
BSA	Kropsfladeareal *(body surface area)*
DKK	Danske kroner
DLBCL	Diffust storcellet B-cellelymfom
DRG	Diagnose Relaterede Grupper
HR	*Hazard ratio*
KM	Kaplan-Meier
NHL	Non-Hodgkin-lymfom
OS	Samlet overlevelse
PD	Progredieret sygdom
PFS	Progressionsfri overlevelse
R-benda	Bendamustin + rituximab
R-GDP	Rituximab + gemcitabin + dexamethason + cisplatin
R-GemOx	Rituximab + gemcitabin + oxaliplatin
R-ICE	Rituximab + Ifosfamid + carboplatin + etoposid
SAIP	Sygehusapotekernes indkøbspris
SmPC	Produktresumé
TTOT	*Time-to-off-treatment*

2. Opsummering

Baggrund
Polatuzumab vedotin i kombination med bendamustin og rituximab er indiceret til behandling af voksne patienter med recidiverende/refraktært diffust storcellet B-cellelymfom (DLBCL), som ikke er kandidater til hæmatopoietisk stamcelletransplantation. Omkring 100 nye patienter kandiderer årligt til behandling af den ansøgte indikation i Danmark, og patienterne udgør en meget heterogen gruppe. Sekretariatets vurdering tager udgangspunkt i dokumentation indsendt af Roche.

Analyse
Den sundhedsøkonomiske analyse estimerer de inkrementelle omkostninger pr. patient ved behandling med polatuzumab vedotin i kombination med bendamustin og rituximab over en tidshorisont på 45 år. Polatuzumab vedotin + bendamustin + rituximab (polatuzumab vedotin-R-benda) sammenlignes med bendamustin + rituximab (R-benda) til behandling af patienter med recidiverende/refraktært DLBCL, som ikke kandiderer til hæmatopoietisk stamcelletransplantation.

Inkrementelle omkostninger og budgetkonsekvenser
I det scenarie, sekretariatet mener er mest sandsynligt, er de inkrementelle omkostninger for polatuzumab vedotin-R-benda ca. [redacted] DKK pr. patient sammenlignet med R-benda. Hvis analysen udføres med AIP, bliver de inkrementelle omkostninger til sammenligning ca. 497.000 DKK pr. patient.

Sekretariatet vurderer, at budgetkonsekvenserne for regionerne ved anbefaling af polatuzumab-R-benda som standardbehandling vil være ca. [redacted] DKK i år 5. Hvis analysen udføres med AIP, er budgetkonsekvenser ca. 8,0 mio. DKK i år 5.

Konklusion
De inkrementelle omkostninger er næsten udelukkende drevet af lægemiddelomkostningerne for polatuzumab vedotin. Der er store usikkerheder forbundet med effekten af polatuzumab vedotin-R-benda grundet forskelle i baselinekarakteristika og patientantallet i det kliniske studie. Det har lille betydning for analysens resultat hvis tidshorisonten sættes til 5 år, eller om der anvendes en mixture cure rate-model eller en proportionel model for PFS og OS. Det har nogen betydning for analysens resultat, om det antages, at et hætteglas på 30 mg polatuzumab vedotin er tilgængeligt, da det reducerer spildet, når der, grundet patientens vægt, skal benyttes et ekstra hætteglas for at opnå den rette dosis. Ifølge ansøger forventes hætteglasset på 30 mg polatuzumab vedotin at være tilgængeligt i [redacted].

3. Baggrund for den sundhedsøkonomiske analyse

Roche (herefter omtalt som ansøger) er markedsføringstilladelsesindehaver af polatuzumab vedotin og har den 2. marts 2020 indsendt en ansøgning til Medicinrådet om anbefaling af polatuzumab vedotin i kombination med bendamustin og rituximab som standardbehandling på danske hospitaler til voksne patienter med recidiverende/refraktært diffust storcellet B-cellelymfom (DLBCL), som ikke er kandidater til hæmatopoietisk stamcelletransplantation. Som et led i denne ansøgning vurderer Medicinrådets sekretariat, på vegne af Medicinrådet, den sundhedsøkonomiske analyse, ansøger har sendt som en del af den samlede ansøgning til Medicinrådet. Denne rapport er sekretariatets vurdering af den fremsendte sundhedsøkonomiske analyse (herefter omtalt som analysen).

3.1 Patientpopulation

DLBCL er en aggressiv undertype af non-Hodgkin-lymfom (NHL). Der diagnosticeres årligt ca. 450 tilfælde af DLBCL i Danmark, og incidensen er stigende [1]. Risikoen for at udvikle DLBCL øges med alderen, og medianalderen ved diagnosetidspunktet er 67 år [1]. DLBCL-patienter udgør en meget heterogen gruppe, hvor behandlingsvalg efter første linje i høj grad afhænger af parametre som alder, WHO-performance score (indeks for funktionsniveau), komorbiditet, tidligere behandlinger og patientpræferencer. Det anslås, at omkring 35 % af alle DLBCL-patienter vil opleve recidiv eller være refraktære overfor behandling efter første linje. Patienter, som oplever recidiv efter første linjebehandling, er generelt i bedre tilstand end patienter, der er refraktære. Fagudvalget skønner, at 150 DLBCL-patienter om året vil få behov for behandling i anden eller tredje linje i Danmark. Af disse vil 100 ikke være egnet til stamcelletransplantation grundet alder, tidligere autolog stamcelletransplantation, komorbiditet eller toleranceproblemer i forbindelse med højdosiskemoterapi inden stamcelletransplantation og er således mulige kandidater til behandling med antistofkonjugatet polatuzumab vedotin [2].

3.1.1 Komparator

Medicinrådet har defineret følgende komparatorer, se Tabel 1.

Tabel 1: Definerede populationer og komparatorer.

Population	Komparator
Voksne med recidiverende/refraktært diffust storcellet B-cellelymfom (DLBCL), som ikke er kandidater til hæmatopoietisk stamcelletransplantation	Bendamustin + rituximab GDP + rituximab GemOx + rituximab ICE + rituximab

3.2 Problemstilling

Formålet med analysen er at estimere de gennemsnitlige inkrementelle omkostninger pr. patient og de samlede budgetkonsekvenser for regionerne ved anbefaling af polatuzumab vedotin i kombination med bendamustin og rituximab som standardbehandling på danske hospitaler til den nævnte indikation.
Medicinrådet har vurderet den kliniske merværdi af polatuzumab vedotin og specificeret følgende kliniske spørgsmål:

Klinisk spørgsmål 1:
Hvad er værdien af polatuzumab vedotin i kombination med bendamustin og rituximab sammenlignet med bendamustin, GDP, GemOx eller ICE i kombination med rituximab til voksne patienter med recidiverende/refraktært diffust storcellet B-cellelymfom, der ikke er kandidater til hæmatopoietisk stamcelletransplantation?

4. Vurdering af den sundhedsøkonomiske analyse

Ansøger har indsendt en sundhedsøkonomisk analyse, der estimerer de inkrementelle omkostninger pr. patient for polatuzumab vedotin + bendamustin + rituximab (polatuzumab vedotin-R-benda) sammenlignet med bendamustin + rituximab (R-benda). Medicinrådet ønskede en sammenligning med hhv. enkeltstofkemoterapi, R-benda, og kombinationskemoterapi, R-GDP, R-GemOx eller R-ICE, afhængigt af hvilke af disse tre der udgjorde det bedste sammenligningsgrundlag. Ansøger har vurderet, at dette gælder for rituximab + ifosfamid + carboplatin + etoposid (R-ICE), men at der ud fra det tilgængelige data ikke kan laves en direkte sammenligning mellem polatuzumab vedotin-R-benda og R-ICE. Efter forespørgsel fra sekretariatet har ansøger indsendt en følsomhedsanalyse, der har til formål at belyse den patientgruppe, hvis helbredstilstand er bedre end patienter, der vil modtage enkeltstofkemoterapi. Disse patienters bedre helbredstilstand tillader behandling med kombinationskemoterapi.

Nedenfor præsenteres den sundhedsøkonomiske model, som ligger til grund for estimeringen af de inkrementelle omkostninger pr. patient.

Sekretariatets vurdering
Sekretariatet vurderer, at en følsomhedsanalyse, hvor polatuzumab vedotin-R-benda sammenlignes med R-ICE, ikke vil være retvisende, da der ikke foreligger data, som muliggør en rimelig sammenligning mellem polatuzumab-R-benda og R-ICE. Sekretariatet vælger dermed ikke at medtage følsomhedsanalysen på trods af, at protokollen foreskriver en sammenligning af polatuzumab vedotin-R-benda og en kombinationskemoterapi med henblik på at vurdere effekten af polatuzumab vedotin-R-benda hos patienter, der vurderes at tåle kombinationskemoterapi.

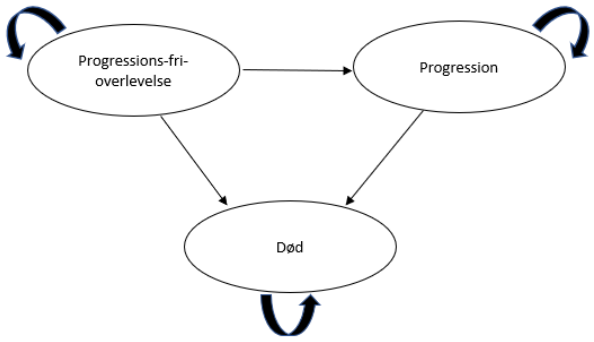
Sekretariatet accepterer ansøgers sundhedsøkonomiske analyse, men vælger ikke at præsentere følsomhedsanalysen der sammenligner polatuzumab vedotin-R-benda med R-ICE.

4.1 Antagelser og forudsætninger for model

Den sundhedsøkonomiske model har til formål at estimere de inkrementelle omkostninger mellem polatuzumab vedotin-R-benda og R-benda til behandling af patienter med DLBCL. Sammenligningen er lavet på baggrund af data fra et open-label, randomiseret fase Ib/II-studie, hvor der laves en direkte sammenligning mellem polatuzumab vedotin-R-benda og R-benda [3]. Analysen bygger på data fra et cut-off i oktober 2018.

4.1.1 Modelbeskrivelse

Ansøger har indleveret en *partitioned survival model*, der estimerer omkostninger baseret på den tid, patienten er i de tre stadier: progressionsfri overlevelse (PFS), progression (PD) og død. En cyklus i modellen er én uge, og ansøger har benyttet *half-cycle correction*. Figur 1 viser modellens struktur.



Figur 1: Beskrivelse af modelstrukturen i omkostningsanalysen.

Ansøger anvender Kaplan-Meier (KM)-data til beregning af tiden, patienterne befinder sig i stadierne. På baggrund af KM-data for PFS og OS fra det kliniske studie [3] argumenterer ansøger for, at de fleste af de patienter, der modtog polatuzumab vedotin-R-benda, og som progredierede eller døde, gjorde det inden for [redacted] efter randomiseringen. Efter [redacted] progredierede eller døde nogle patienter fortsat, men kurven flader mere ud, og ansøger argumenterer for, at der opstår et plateau på PFS-kurven og OS-kurven for patienter, der modtog polatuzumab vedotin-R-benda. Dermed argumenterer ansøger for, at der tale om to grupper af patienter: patienter som dør af DLBCL, og patienter som vil være langtidsoverlevere. Se Figur 2 og Figur 3 for ansøgers PFS- og OS-kurver. Ansøger anvender derfor en mixture cure rate-model for PFS og OS. Herved er der en grundlæggende antagelse om, at patienter i PFS efter et bestemt tidspunkt vil kunne betragtes som værende langtidsoverlevere. I ansøgers analyse er dette tidspunkt sat til [redacted] (transition point). Derved er det kun patienter, der ikke har progredieret efter [redacted], som vil kunne være langtidsoverlevere. Til

ekstrapolering af PFS og OS benytter ansøger log-normal som parametrisk funktion for både PFS og OS for begge arme.

[redacted]

[redacted]

[redacted]

Det kliniske studie havde et behandlingsstop efter seks 21-dages cyklusser for begge arme. For patienter, der modtog polatuzumab vedotin-R-benda, var *time to off treatment* (TTOT) i gennemsnit [redacted], mens det for patienter, der modtog R-

benda, i gennemsnit var [redacted]. Alle patienter havde enten gennemført fuld behandling eller stoppet behandling inden studiets afslutning, og det var derfor ikke nødvendigt at ekstrapolere behandlingslængden.

Sekretariatets vurdering

Sekretariatet vurderer, at det er rimeligt at anvende mixture cure rate-modellen på baggrund af den tilgængelig data ud fra et statistisk perspektiv alene. Dog vurderer fagudvalget, at der ud fra et klinisk perspektiv er stor usikkerhed forbundet med kurverne for PFS og OS. Usikkerheden skyldes det kliniske studies lille størrelse og forskel i baselinekarakteristika i studiet, hvormed effekten af polatuzumab vedotin-R-Benda kan være overvurderet. Fagudvalget vurderer, at PFS-kurven og OS-kurven for polatuzumab vedotin-R-Benda afspejler et mere optimistisk billede, end hvad der forventes i dansk klinisk praksis. Dermed vurderes kurverne ikke at være klinisk plausible. Fagudvalget tvivler på, at man i praksis vil se patienter, der kureres for DLBCL.

Sekretariatet accepterer derfor ikke ansøgers valg om at benytte mixture cure rate-model og vælger i hovedanalysen i stedet at benytte en proportionel model og log-normal som parametrisk funktion for ekstrapoleringen af PFS og OS. Dermed afspejler kurverne for PFS og OS et, for fagudvalget, mere realistisk billede end kurverne, som er benyttet i ansøgers model. Se Figur 4 og Figur 5.

[redacted]

[redacted]

Sekretariatet accepterer, at ansøgers analyse bygger på behandlingscyklusser af 21 dage for både polatuzumab vedotin-R-benda og R-benda, men fagudvalget gør opmærksom på, at man i dansk klinisk praksis vil give polatuzumab vedotin-R-benda og R-benda i seks 28-dages cyklusser i stedet for seks 21-dages cyklusser. Herved forventes et mindre bivirkningstungt behandlingsforløb. Dette kan påvirke andelen af patienter, der stopper behandling grundet bivirkninger i dansk klinisk praksis sammenlignet med studiets andel, hvormed den gennemsnitlige behandlingslængde kan være underestimeret i analysen.

Sekretariatet accepterer ikke ansøgers modelantagelser og vælger i sekretariatets hovedanalyse at benytte en proportionel statistisk model.

4.1.2 Analyseperspektiv

Ansøgers omkostningsanalyse har et begrænset samfundsperspektiv. Analysen har en tidshorisont på 45 år. Tidshorisonten afspejler ikke, at patienterne er i behandling i 45 år, men i stedet er formålet at sikre, at omkostninger, der falder, efter behandlingen er ophørt, inkluderes i analysen. Denne tidshorisont er valgt, da ansøger argumenterer for, at alle patienter, der indgik i det kliniske studie, vil være døde inden for 45 år. Alle relevante økonomiske forskelle, der måtte være mellem patienter, der behandles med polatuzumab vedotin-R-benda, og patienter, der behandles med R-benda, vil derfor komme til udtryk i denne tidsperiode.

Omkostninger, der ligger efter det første år og frem til og med år 35, er diskonteret med 4 %. Fra år 36 er omkostningerne diskonteret med 3 %.

Sekretariatets vurdering
Sekretariatet accepterer ansøgers valg vedr. analyseperspektiv.

4.2 Omkostninger

I det følgende præsenteres ansøgers antagelser for omkostningerne i den sundhedsøkonomiske analyse af polatuzumab vedotin-R-benda sammenlignet med R-benda. De inkluderede omkostninger i ansøgers analyse er lægemiddelomkostninger, hospitalsomkostninger, bivirkningsomkostninger, patientomkostninger og omkostninger til behandling efter progression.

4.2.1 Lægemiddelomkostninger

Ansøgers estimering af lægemiddelomkostninger bygger på AIP, hvilket sekretariatet udskifter med SAIP. De anvendte doser er hentet i de respektive produkters produktresuméer (SmPC'er). Ansøger antager, at der vil være spild for alle lægemidlerne. De forventede lægemiddelomkostninger er beregnet på baggrund af KM-data for TTOT fra det kliniske studie [3]. Ligeledes benyttes studiet til beregning af doseringer af lægemidlerne. Polatuzumab vedotin doseres efter vægt, og ansøger anvender en gennemsnitlig vægt på [redacted] kg. Hætteglasset, der indeholder 140 mg polatuzumab vedotin, svarer derfor til en patient, der vejer 78 kg. Ansøger har i analysen anvendt studiedata for patienternes estimerede vægt ([redacted]). Bendamustin og rituximab doseres efter kropsoverfladeareal (BSA), og her anvendes en gennemsnitlig BSA på [redacted] m^2. Det er antaget, at der vil være spild for alle lægemidler i ansøgers analyse.

For polatuzumab vedotin-R-benda gælder følgende doseringer:

- Polatuzumab vedotin: 1,8 mg/kg på dag 1
- Bendamustin: 90 mg/m^2 på dag 1 og dag 2
- Rituximab: 375 mg/m^2 på dag 1

For R-benda gælder følgende dosering:

- Bendamustin: 90 mg/m^2 på dag 1 og dag 2
- Rituximab: 375 mg/m^2 på dag 1

De benyttede lægemiddelpriser ses i Tabel 2.

Tabel 2: Anvendte lægemiddelpriser, SAIP (januar, 2021).

Lægemiddel	Styrke	Pakningsstørrelse	Pris [DKK]	Kilde
Polatuzumab vedotin	140 mg	140 mg	[redacted]	Amgros
	30 mg	30 mg	[redacted]	Roche
Bendamustin	2,5 mg/ml	5 x 25 mg	[redacted]	Amgros
	2,5 mg/ml	5 x 100 mg	[redacted]	Amgros

Lægemiddel	Styrke	Pakningsstørrelse	Pris [DKK]	Kilde
Rituximab	100 mg	2 stk.	[redacted]	Amgros
	500 mg	1 stk.	[redacted]	Amgros

Ansøger har informeret om, at der i [redacted] forventes at blive markedsført et hætteglas, der indeholder 30 mg polatuzumab vedotin. Hermed kan hospitalerne benytte et eller flere mindre hætteglas (30 mg) i kombination med et stort hætteglas (140 mg) til patienter, der vejer mere end 78 kg. Ansøger baserer sin analyse på, at hætteglas på 30 mg polatuzumab vedotin er tilgængeligt.

Sekretariatets vurdering
Sekretariatet accepterer ansøgers tilgang til beregning af lægemiddelomkostninger, men vælger ikke at inkludere hætteglasset på 30 mg polatuzumab vedotin i sekretariatets hovedanalyse. Dette skyldes usikkerheden forbundet med, hvornår hætteglasset reelt bliver tilgængeligt på danske hospitaler. I stedet udfører sekretariatet en følsomhedsanalyse, hvor det antages, at hætteglasset på 30 mg polatuzumab vedotin er tilgængeligt.

Sekretariatets hovedanalyse bygger på, at der kun er hætteglas på 140 mg polatuzumab vedotin tilgængeligt, men præsenterer en følsomhedsanalyse hvor hætteglas på 30 mg polatuzumab vedotin også antages at være tilgængeligt.

4.2.2 Hospitalsomkostninger

Alle lægemidler administreres med intravenøs infusion (IV). Ansøger anvender DRG-taksten 17MA98 for 2020, og omkostningen er derfor 3.235 DKK. Da bendamustin gives på både dag 1 og dag 2, bliver IV-omkostningen 6.470 DKK per cyklus for både polatuzumab vedotin-R-benda og R-benda.

Ansøger har yderligere inkluderet omkostninger til monitorering og opfølgning og har inddelt aktiviteterne baseret på stadierne i modellen, og på hvornår patienterne aktivt modtager behandling, se Tabel 3 og Tabel 4. Ansøger har brugt DRG-takster for 2020 til beregning af omkostninger for alle aktiviteter forbundet med monitorering og opfølgning på nær omkostninger forbundet med sygeplejersker og specialister. Her anvender ansøger en mikrobaseret tilgang.

Tabel 3: Omkostninger til monitorering og opfølgning for patienter under behandling og i PFS.

	Frekvens under behandling (pr. år)	Frekvens i PFS (pr. år)	Enhedsomkostning [DKK]
Sygeplejerskebesøg	6	4	552,61
PET-CT	2	2	2.470

Hæmoglobin + trombocytter	6	4	31
LDH	6	4	24
Leverfunktion	6	4	72
Nyrefunktion	6	4	79
Immunglobulin G	6	4	24
Kreatin	6	4	24
Leukocytter	6	4	15
CRP	6	4	24
Sodium	6	4	14
Potassium	6	4	14
Albumin	6	4	53

Tabel 4: Omkostninger til monitorering og opfølgning for patienter i PD.

	Frekvens i PD (pr. år)	Enhedsomkostning [DKK]
Specialistkonsultation	4	552,61
Palliativ behandling	8	3.235

Ansøger har inkluderet terminalomkostninger på 68.601,90 DKK. Omkostningen er fundet i et engelsk studie fra 2015 [5], som undersøger terminalomkostninger forbundet med fire kræftformer (lungekræft, brystkræft, kolorektalkræft og prostatakræft). Ansøger har omregnet fra engelske pund til danske kroner og taget højde for den relative forskel i købekraftsparitet mellem England og Danmark.

Sekretariatets vurdering

Ansøger antager, at patienter, der modtager behandling eller fortsat befinder sig i PFS-stadiet efter behandlingen er afsluttet, vil blive tilset af en sygeplejerske. Fagudvalget vurderer, at patienterne i stedet vil blive tilset af en læge, hvorfor sekretariatet i hovedanalysen udskifter omkostningen forbundet med en sygeplejerske til 780 DKK, som jf. Medicinrådets værdisætning af enhedsomkostninger vil være omkostningen forbundet med at blive tilset af en læge. Denne ændring har minimal betydning for analysens resultat.

Ansøger har inkluderet terminalomkostninger, som bygger på et engelsk studie. Eftersom studiet bygger på en engelsk kontekst, er det usikkert, hvorvidt terminalomkostningerne vil være de samme i dansk kontekst. Sekretariatet accepterer ansøgers antagelse i mangel på mere præcise opgørelser for terminalomkostninger i dansk klinisk praksis, og fordi antagelsen har lille betydning for analysens resultat.

Sekretariatet accepterer ansøgers tilgang til beregning af hospitalsomkostninger, men vælger i sekretariatets hovedanalyse at udskifte omkostningen forbundet med sygeplejerskebesøg, så det svarer til et lægebesøg.

4.2.3 Bivirkningsomkostninger

Ansøgers model inkluderer omkostninger til bivirkninger af grad 3 eller mere, som krævede indlæggelse eller hospitalsbesøg for polatuzumab vedotin-R-benda og R-benda, og bivirkningsfrekvenserne er baseret på det kliniske studie [3], se Tabel 5. Omkostningerne er beregnet på baggrund af DRG-takster for 2020.

Tabel 5: Bivirkningsfrekvenser ved behandling med polatuzumab vedotin-R-Benda og R-benda.

	Polatuzumab vedotin-R-benda	R-benda	Enhedsomkostning [DKK]	Kilde
Akut nyreskade	2,6 %	0,0 %	22.546	Gennemsnit af DRG 2020: 11MA98 & 11MA01
Atrieflimren	2,6 %	0,0 %	8.544	Gennemsnit af DRG 2020: 05MA98 & 05MA07
Atrieflagren	2,6 %	0,0 %	8.544	Gennemsnit af DRG 2020: 05MA98 & 05MA07
Infektion med cytomegalovirus	2,6 %	0,0 %	9.603	Gennemsnit af DRG 2020: 18MA98 & 18MA06
Nedsat appetit	0,0 %	2,6 %	8.431	Gennemsnit af DRG 2020: 10MA98 & 10MA98
Diarré	0,0 %	2,6 %	5.297	DRG 2020: 06MA11
Enterocolitis	2,6 %	0,0 %	5.297	DRG 2020: 06MA11
Febril neutropeni (grad 3)	2,6 %	2,6 %	20.376	Gennemsnit af DRG 2020: 16MA98 & 16MA03

Febril neutropeni (grad 4)	0,0 %	5,1 %	37.603	DRG 2020: 16MA03
Herpes virusinfektion	0,0 %	2,6 %	43.180	DRG 2020: 18MA01
Leukoencefalopati	2,6 %	0,0 %	28.714	DRG 0123
Leukopeni	2,6 %	0,0 %	22.589	DRG 2020: 16MA10
Nedre luftvejsinfektion	5,1 %	0,0 %	27.072	Gennemsnit af DRG 2020: 04MA98 & 4MA05
Herpes meningoencephalitis	0,0 %	2,6 %	58.620	DRG 2020: 1MA03
Myelodysplastisk syndrom	0,0 %	2,6 %	44.533	DRG 2020: 17MA01
Neutropeni	2,6 %	0,0 %	37.603	DRG 2020: 16MA03
Neutropenisk sepsis	2,6 %	0,0 %	37.603	DRG 2020: 16MA03
Perifert ødem	2,6 %	0,0 %	4.082	DRG 2020: 23MA03
Lungebetændelse (grad 3)	0,0 %	2,6 %	19.425	Gennemsnit af DRG 2020: 04MA98 & 04MA13
Lungebetændelse (grad 5)	0,0 %	2,6 %	37.050	DRG 2020: 04MA13
Lungeødem	0,0 %	2,6 %	34.746	DRG 2020: 04MA10
Pyreksi	0,0 %	2,6 %	19.268	DRG 2020: 8MA04
Septisk chok	2,6 %	0,0 %	43.180	DRG 2020: 18MA01
Supraventrikulær takykardi	2,6 %	0,0 %	8.544	Gennemsnit af DRG 2020: 05MA98 & 05MA07
Trombocytopeni	0,0 %	2,6 %	37.603	DRG 2020: 16MA03
Opkast	0,0 %	2,6 %	5.297	DRG 2020: 06MA11

Sekretariatets vurdering

Sekretariatet accepterer ansøgers tilgang vedr. bivirkningsomkostninger.

4.2.4 Patientomkostninger

Patientomkostninger er estimeret på baggrund af tiden patienterne bruger til administration af lægemidlerne og tiden brugt til opfølgning og monitorering. Tiden til lægemiddeladministrationen er beregnet ud fra SmPC'erne for de respektive lægemidler, mens tiden til monitorering og opfølgning er antaget af ansøger, se Tabel 6. Ansøger anvender en timeomkostning på 179 DKK. Ansøgers model inkluderer også transportomkostninger, som er beregnet på baggrund af antagelsen, at patienterne i gennemsnit har 28 kilometers afstand til hospitalerne med en tilhørende omkostning på 3,56 DKK pr. kilometer.

Tabel 6: Patienttid til lægemiddeladministration og monitorering og opfølgning.

	Frekvens pr. uge	Patienttid [timer]
Lægemiddeladministration	0,67	1,5
Monitorering og opfølgning i PFS	0,08	1,5
Monitorering og opfølgning i PD	0,08	1,5

Sekretariatets vurdering

Sekretariatets accepterer ansøgers tilgang til beregning af patientomkostninger.

4.2.5 Behandling efter progression

Ansøger har inkluderet omkostninger til behandling efter progression. Modellen indebærer fire mulige behandlinger: kemoterapi, kemoterapi i kombination med rituximab, antiCD20 og strålebehandling, se Tabel 7. Andelen af patienter, som modtager behandling med de respektive regimer, er bestemt ud fra poolet data fra det kliniske studie [3], undtaget andelen af patienter som modtager strålebehandling. Størrelsen på denne andel er estimeret af danske kliniske eksperter. Ansøger antager, at patienter fordeler sig ens mellem behandlingsmulighederne i Tabel 7, uanset om patienterne tidligere har modtaget polatuzumab vedotin-R-benda eller R-benda. Omkostningerne forbundet med kemoterapi er antaget at svare til behandling med ICE, mens omkostningerne forbundet med antiCD20 antages at svare til behandling med rituximab.

Tabel 7: Behandling efter progression.

	Andel af patienterne	Totale omkostninger [DKK]
Kemoterapi (3 cyklusser)	12,5 %	26.742
Rituximab + kemoterapi (3 cyklusser)	7,5 %	27.365
AntiCD20 (mono 3 cyklusser)	1,3 %	20.033
Strålebehandling	2,5 %	2.877

Sekretariatets vurdering
Fagudvalget vurderer, at man i dansk klinisk praksis ikke vil behandle patienter med ritixumab + kemoterapi eller antiCD20, når patienterne er progredieret. Fagudvalget estimerer, at 10 % af patienterne der progredierer, vil modtage kemoterapi, og 2 % vil modtage strålebehandling.

Sekretariatet tilpasser hovedanalysen således, at 10 % modtager kemoterapi, og 2 % modtager strålebehandling efter progression.

4.3 Følsomhedsanalyser

Formålet med følsomhedsanalyserne er at undersøge usikkerhederne i analysen. Ansøger har udarbejdet en række følsomhedsanalyser. Følgende følsomhedsanalyser er udført:

- Tidshorisont: 5 år/50 år
- Deling af hætteglas mellem patienter medregnes
- Diskonteringsrenten: 0 %/8 %
- Parametriske funktioner og statistisk model varieres

[redacted]

- Sammenligning mellem polatuzumab vedotin-R-benda og R-ICE

Sekretariatets vurdering
Ansøgers model anvender en tidshorisont på 45 år, og sekretariatet vurderer det relevant at præsentere ansøgers følsomhedsanalyse, hvor tidshorisonten reduceres til 5 år for at belyse omkostningernes omfang inden for de første 5 år. Diskonteringsrenterne i ansøgers model stemmer overens med Medicinrådets metodevejledning, hvorfor sekretariatet vælger ikke at præsentere følsomhedsanalysen for ændring af diskonteringsrenten.

Sekretariatet vælger ikke at præsentere ansøgers følsomhedsanalyse, hvor deling af hætteglas mellem patienter medregnes. I stedet præsenterer sekretariatet en følsomhedsanalyse, hvor det antages, at hætteglas på 30 mg polatuzumab vedotin er tilgængeligt. Dermed kan hospitalerne benytte et eller flere mindre hætteglas i kombination med et hætteglas på 140 mg til patienter, der vejer over 78 kg.

Sekretariatet vælger ikke at præsentere følsomhedsanalysen, [redacted]. I stedet præsenterer sekretariatet en følsomhedsanalyse, hvor mixture cure rate-modellen anvendes. Sekretariatet har undersøgt betydningen af at vælge andre parametriske funktioner til ekstrapoleringen af PFS og OS. Da valget af parametrisk funktion har lille betydning for analysens resultat, vælger sekretariatet ikke at præsentere disse følsomhedsanalyser.

På baggrund af fagudvalgets vurdering vælger sekretariatet ikke at præsentere følsomhedsanalysen, hvor polatuzumab vedotin-R-benda og R-ICE sammenlignes, da fagudvalget ikke har fundet det retvisende at anvende det foreliggende data.

Sekretariatet præsenterer følsomhedsanalyserne, hvor tidshorisonten sættes til 5 år, en følsomhedsanalyse, hvor det antages, at hætteglas på 30 mg polatuzumab vedotin er tilgængelig, og en følsomhedsanalyse hvor mixture cure rate-modellen anvendes.

4.4 Opsummering af basisantagelser

I Tabel 8 opsummeres basisantagelserne for ansøgers hovedanalyse sammenlignet med de ændringer, som sekretariatet har lavet i egen hovedanalyse.

Tabel 8: Basisantagelser for ansøgers og sekretariatets hovedanalyse.

Basisantagelser	Ansøger	Sekretariatet
Tidshorisont	45 år	45 år
Diskonteringsrate	4 % ≤ 35 år, 3 % > 35 år	4 % ≤ 35 år, 3 % > 35 år
Inkluderede omkostninger	Lægemiddelomkostninger Hospitalsomkostninger Bivirkningsomkostninger Patientomkostninger Omkostninger til behandling efter progression	Lægemiddelomkostninger Hospitalsomkostninger Bivirkningsomkostninger Patientomkostninger Omkostninger til behandling efter progression
Dosering af polatuzumab vedotin	1,8 mg/kg i seks serier i 21-dages cyklusser.	1,8 mg/kg i seks serier i 21-dages cyklusser.
Tilgængelige hætteglas med polatuzumab vedotin	30 mg og 140 mg	140 mg
Behandlingslinje	Behandlingserfarne patienter, uanset behandlingslinje	Behandlingserfarne patienter, uanset behandlingslinje
Statistisk model (PFS og OS)		
Polatuzumab vedotin-R-benda	Mixture cure rate-model	Proportionel model
R-benda	Mixture cure rate-model	Proportionel model
Parametriske overlevelsesfunktioner for PFS og OS		
Polatuzumab vedotin-R-benda	Log-normal	Log-normal
R-benda	Log-normal	Log-normal

Basisantagelser	Ansøger	Sekretariatet
Deling af hætteglas mellem patienter	Nej	Nej

5. Resultater

5.1 Resultatet af sekretariatets hovedanalyse

Sekretariatets hovedanalyse bygger på samme antagelser som ansøgers hovedanalyse, men med følgende justeringer:

- Proportionel model anvendes for PFS og OS i stedet for mixture cure rate til at ekstrapolere data.
- Ved beregningen af hospitalsomkostningerne antages det, at patienter, som endnu ikke er progredierede efter behandlingsophøret, monitoreres af en læge. Derfor udskiftes omkostningen for et sygeplejerskebesøg med omkostningen for et lægebesøg.
- Omkostningen for et sygeplejerskebesøg udskiftes med omkostningen for et lægebesøg.
- I beregningen af omkostninger ved behandling efter progression ekskluderes rituximab + kemoterapi og antiCD20 og andelene for, hvor mange patienter, som behandles med kemoterapi og stråleterapi, justeres.
- Ved beregningen af lægemiddelomkostningerne antages det, at hætteglas med 30 mg polatuzumab vedotin ikke er tilgængeligt.

Den inkrementelle omkostning pr. patient bliver ca. [redacted] DKK over en tidshorisont på 45 år i sekretariatets hovedanalyse. Udføres analysen med AIP, bliver den inkrementelle omkostning pr. patient ca. 497.000 DKK.

Resultaterne fra sekretariatets hovedanalyse præsenteres i Tabel 9.

Tabel 9: Resultatet af sekretariatets hovedanalyse, DKK, diskonterede tal.

	Polatuzumab vedotin-R-benda	R-benda	Inkrementelle omkostninger
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Hospitalsomkostninger	100.042	91.212	8.830
Bivirkningsomkostninger	7.984	10.488	-2.504
Patientomkostninger	13.069	6.977	6.092

	Polatuzumab vedotin-R-benda	R-benda	Inkrementelle omkostninger
Behandling efter progression	[redacted]	[redacted]	[redacted]
Totale omkostninger	[redacted]	[redacted]	[redacted]

5.1.1 Resultatet af sekretariatets følsomhedsanalyser

Ved samme antagelser som i sekretariatets hovedanalyse for meromkostninger udfører sekretariatet en følsomhedsanalyse, hvor tidshorisonten sættes til 5 år, en følsomhedsanalyse hvor det antages, at hætteglas på 30 mg polatuzumab vedotin er tilgængelig og en følsomhedsanalyse, hvor mixture cure rate-modellen anvendes som statistisk model, se Tabel 10.

Tabel 10: Resultatet af sekretariatets følsomhedsanalyse sammenlignet med hovedanalysen, DKK.

Scenarie	Inkrementelle omkostninger
Resultatet af hovedanalysen	[redacted]
Tidshorisont: 5 år	[redacted]
Hætteglas på 30 mg polatuzumab vedotin tilgængeligt	[redacted]
Mixture cure rate-model anvendes	[redacted]

6. Budgetkonsekvenser

Budgetkonsekvenserne pr. år er baseret på antagelsen om, at polatuzumab vedotin-R-benda vil blive anbefalet som standardbehandling. Man ser derfor på to scenarier:

- Polatuzumab vedotin-R-benda bliver anbefalet som standardbehandling af Medicinrådet til indikationen, som denne analyse omhandler
- Polatuzumab vedotin-R-benda bliver ikke anbefalet som standardbehandling

Budgetkonsekvenserne bliver differencen mellem budgetkonsekvenserne i de to scenarier.

6.1 Ansøgers estimat af patientantal og markedsandel

I ansøgers analyse indgår R-ICE og tisagenlecleucel i budgetkonsekvenserne. R-ICE udgør det bedste sammenligningsgrundlag for de kombinationsterapier, som er nævnt i protokollen, idet ansøger argumenterer for, at R-ICE er den hyppigst anvendte

behandling, og at omkostninger for kemoterapi generelt er lave. Tisagenlecleucel er inkluderet som repræsentant for CAR-T-behandlinger. Begge regimer gives ved intravenøs infusion. R-ICE gives i cyklusser a 3 uger, mens tisagenlecleucel gives som én dosis. Lægemiddelpriserne kan ses i Tabel 11.

For R-ICE gælder følgende dosering:

- Rituximab: 375 mg/m^2 på dag 1
- Ifosfamid: 3.000 mg/m^2 på dag 1 og dag 2
- Carboplatin: 635 mg/m^2 på dag 2
- Etoposid: 100 mg/m^2 på dag 1

For tisagenlecleucel gælder følgende dosering:

- 1 mg på dag 1

Tabel 11: Anvendte lægemiddelpriser, SAIP, (januar 2021).

Lægemiddel	Styrke	Pakningsstørrelse	Pris [DKK]	Kilde
Rituximab	100 mg	2 stk.	[redacted]	Amgros
	500 mg	1 stk.	[redacted]	Amgros
Ifosfamid	1 g	1 g	[redacted]	Amgros
Carboplatin	10 mg/ml	15 ml	[redacted]	Amgros
	10 mg/ml	45 ml	[redacted]	Amgros
Etoposid	20 ml/mg	5 ml	[redacted]	Amgros
	20 mg/ml	25 ml	[redacted]	Amgros
Tisagenlecleucel	1 dosis	1 dosis	[redacted]	Amgros

Ansøger har inkluderet budgetkonsekvenser for 76 patienter, som ansøger antager er den samlede patientpopulation. Yderligere har ansøger opdelt den samlede patientpopulation i 48 patienter, der modtager 2. linjebehandling, og 29 patienter, der modtager behandling i 3. og efterfølgende linjer. Tabel 12 viser ansøgers antagelser vedrørende fordelingen af nye patienter for den samlede patientpopulation.

[redacted]. Ansøger antager et markedsoptag på [redacted], hvis polatuzumab vedotin-R-benda anbefales som standardbehandling. Hvis polatuzumab vedotin-R-benda ikke anbefales som standardbehandling, antager ansøger, at markedsoptaget vil være på [redacted] %.

Tabel 12: Ansøgers estimat af antal nye patienter pr. år for den samlede patientpopulation.

Anbefales					
	År 1	År 2	År 3	År 4	År 5
Polatuzumab vedotin-R-Benda	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
R-benda	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tisagenlecleucel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
R-ICE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anbefales ikke					
	År 1	År 2	År 3	År 4	År 5
Polatuzumab vedotin-R-benda	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
R-benda	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tisagenlecleucel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
R-ICE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Sekretariatets vurdering

Ansøger har estimeret, at i alt 76 patienter kandiderer til behandling med polatuzumab vedotin-R-benda. Fagudvalget vurderer, at det kun er patienter, der ellers ville blive behandlet med R-benda, som vil modtage polatuzumab vedotin-R-benda, og sekretariatet præsenterer derfor kun budgetkonsekvenserne for disse patienter. Dette vedrører 20 patienter, hvoraf 25 % forventes ikke at blive behandlet med polatuzumab vedotin-R-benda. R-ICE og tisagenlecleucel ekskluderes derfor fra sekretariatets budgetkonsekvensanalyse. Fagudvalget fremhæver i forlængelse heraf, at CAR-T-behandling ikke er anbefalet som mulig standardbehandling i Danmark. Se Tabel 13 for sekretariatets estimering af patientantal.

Tabel 13: Sekretariatets estimat af antal nye patienter pr. år for den samlede population.

Anbefales					
	År 1	År 2	År 3	År 4	År 5
Polatuzumab vedotin-R-benda	15	15	15	15	15
R-benda	5	5	5	5	5
Anbefales ikke					
	År 1	År 2	År 3	År 4	År 5

Polatuzumab vedotin-R-benda	0	0	0	0	0
R-Benda	20	20	20	20	20

Sekretariatet udfører sin egen budgetkonsekvensanalyse, hvor patientantallet ændres til 20. Behandling med CAR-T og R-ICE ekskluderes, og det antages, at 25 % af patienterne, der behandles med R-benda, ikke vil modtage behandling med polatuzumab vedotin-R-benda, uanset om polatuzumab vedotin-R-benda anbefales.

6.2 Sekretariatets budgetkonsekvensanalyse

Sekretariatet har korrigeret følgende estimater i sin budgetkonsekvensanalyse forhold til ansøgers budgetkonsekvensanalyse:

- Reducering af patientantallet, der kandiderer til behandling med polatuzumab vedotin-R-benda til 20
- 25 % af patienterne, der behandles med R-benda, vil ikke modtage polatuzumab vedotin-R-benda
- Ekskludering af R-ICE og tisagenlecleucel

Sekretariatet estimerer, at anvendelse af polatuzumab vedotin-R-benda vil resultere i budgetkonsekvenser på ca. [redacted] DKK i år 5. Resultatet er præsenteret i Tabel 14.

Hvis analysen udføres med AIP, bliver budgetkonsekvenserne ca. 8,0 mio. DKK i år 5.

Tabel 14: Sekretariatets analyse af totale budgetkonsekvenser, mio. DKK, ikke-diskonterede tal.

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

7. Diskussion

Behandling med polatuzumab vedotin-R-benda er forbundet med betydelige inkrementelle omkostninger pr. patient sammenlignet med behandling med R-benda. De inkrementelle omkostninger er næsten udelukkende drevet af lægemiddelomkostningerne for polatuzumab vedotin.

7.1 Usikkerheder

Patienter med DLBCL, som ikke kandiderer til stamcelletransplantation, udgør en heterogen gruppe, og valget mellem enkeltstofkemoterapi eller kombinationskemoterapi beror på en individuel vurdering af den enkelte patients tilstand. Fagudvalget vurderer, at polatuzumab vedotin-R-benda vil blive tilbudt til patienter, som ellers ville blive tilbudt R-benda (enkeltstofkemoterapi). Effektestimaterne fra det kliniske studie, som ansøger baserer sin sundhedsøkonomiske analyse på, er forbundet med usikkerhed, idet patienternes baselinekarakteristika i studiet er forskellige mellem de to behandlingsarme. Usikkerheden kan betyde, at effektestimaterne for polatuzumab vedotin-R-benda er overestimerede. Derudover indgik få patienter i det kliniske studie, hvilket øger usikkerheden omkring effekten af polatuzumab vedotin-R-benda.

Det er usikkert, hvilken betydning det har, at data fra det kliniske studie bygger på behandlingscyklusser a 21 dage for både polatuzumab vedotin-R-benda og R-benda, når man i dansk klinisk praksis vil behandle i 28-dages cyklusser. Det forventes, at behandlingsforløbet vil være mindre bivirkningstungt, og der er derfor sandsynlighed for, at flere patienter vil modtage behandling i længere tid, hvormed den gennemsnitlige behandlingslængde kan være underestimeret.

Det har lille betydning for analysens resultat, om tidshorisonten sættes til 5 år, da størstedelen af omkostningerne falder inden for de første år. Det har ligeledes lille betydning for analysens resultat om der anvendes en mixture cure rate-model eller proportionel model for PFS og OS.

Det har nogen betydning for analysens resultat, om det antages, at et hætteglas på 30 mg polatuzumab vedotin er tilgængelig. Dette skyldes, at de inkrementelle omkostninger hovedsageligt er drevet af lægemiddelomkostningen for polatuzumab vedotin. Ved at antage, at patienter der vejer over 78 kg, kan nøjes med at benytte et hætteglas på 30 mg ekstra for at opnå den rette dosis, reduceres lægemiddelomkostningerne sammenlignet med, hvis der skulle benyttes et ekstra hætteglas på 140 mg. De inkrementelle omkostninger pr. patient falder fra ca. [redacted] DKK til ca. [redacted] DKK, hvis det antages, at hætteglasset på 30 mg er tilgængelig. Ifølge ansøger forventes hætteglasset på 30 mg polatuzumab vedotin at være tilgængeligt i [redacted].

8. Referencer

[1] D. Lymfomgruppe, “Diffust Storcellet B-celle Lymfom - Klinisk Retningslinje,” pp. 1–41, 2019.

[2] Medicinrådet, “Medicinrådets protokol for vurdering af polatuzumab vedotin i kombination med bendamustin og rituximab til behandling af diffust storcellet Bcellelymfom,” pp. 0–16, 2019, [Online]. Available: https://medicinraadet.dk/media/12742/protokol-10-polatuzumab-vedotin-diffust-storcellet-b-celle-lymfom_godkendt-af-formandskabet.pdf.

[3] L. H. Sehn *et al.*, “Polatuzumab vedotin in relapsed or refractory diffuse large B-cell lymphoma,” *J. Clin. Oncol.*, vol. 38, no. 2, pp. 155–165, 2020, doi: 10.1200/JCO.19.00172.

[4] M. J. Maurer *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.*, vol. 32, no. 10, pp. 1066–1073, 2014, doi: 10.1200/JCO.2013.51.5866.

[5] J. Round, L. Jones, and S. Morris, “Estimating the cost of caring for people with cancer at the end of life: A modelling study,” *Palliat. Med.*, vol. 29, no. 10, pp. 899–907, 2015, doi: 10.1177/0269216315595203.

9. Bilag

9.1 Resultatet af ansøgers hovedanalyse

I ansøgers hovedanalyse bliver den inkrementelle omkostning pr. patient ca. [redacted] DKK over en tidshorisont på 45 år. Resultaterne fra ansøgers hovedanalyse er præsenteret i Tabel 15.

Tabel 15: Resultatet af ansøgers hovedanalyse, DKK, diskonterede tal.

	Polatuzumab vedotin-R-benda	R-benda	Inkrementelle omkostninger
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Hospitalsomkostninger	[redacted]	[redacted]	[redacted]
Bivirkningsomkostninger	[redacted]	[redacted]	[redacted]
Patientomkostninger	[redacted]	[redacted]	[redacted]
Behandling efter progression	[redacted]	[redacted]	[redacted]
Totale omkostninger	[redacted]	[redacted]	[redacted]

9.2 Ansøgers budgetkonsekvensanalyse

Ansøger har inkluderet R-ICE og tisagenlecleucel som mulige behandlingsmetoder, der indgår i budgetkonsekvenserne. Med de ovenstående antagelser om patientantal og markedsandel estimerer ansøger, at anvendelse af polatuzumab vedotin vil resultere i budgetkonsekvenser på ca. [redacted] DKK i år 5. Ansøgers estimat af budgetkonsekvenserne fremgår af Tabel 16.

Tabel 16: Ansøgers hovedanalyse for totale budgetkonsekvenser, mio. DKK, ikke-diskonterede tal.

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

Amgros I/S
Dampfærgevej 22
2100 København Ø
Danmark

T +45 88713000
F +45 88713008

Medicin@amgros.dk
www.amgros.dk

Forhandlingsnotat

Dato for behandling i Medicinrådet	27.01.2021
Leverandør	Roche
Lægemiddel	Polatuzumab vedotin (Polivy)
Ansøgt indikation	Polatuzumab vedotin i kombination med bendamustin og rituximab som standardbehandling på danske hospitaler til voksne patienter med recidiverende/refraktært diffust storcellet B-cellelymfom (DLBCL), som ikke er kandidater til hæmatopoietisk stamcelletransplantation.

Forhandlingsresultat

Amgros har opnået følgende pris på polatuzumab vedotin:

Lægemiddel	Styrke/dosis	Pakningsstørrelse	AIP	Nuværende SAIP (kr)	forhandlet SAIP (kr)	Rabat procent ift. AIP
Polatuzumab vedotin	140 mg	1 hætteglas	74.588	[redacted]	[redacted]	[redacted]
Polatuzumab vedotin	30 mg*	1 hætteglas			[redacted]	

*30 mg hætteglas kommer i handlen feb/mar 2021. Pakningerne har samme pris pr mg uanset pakningsstørrelse.

Amgros har d 24.11.2020 indgået en aftale med en mindre rabat, som løber indtil d. 31.12.2021, med mulighed for forlængelse. [redacted]

Vurdering af forhandlingsresultatet

Det er Amgros' vurdering, at vi ikke har opnået den bedst mulige pris. Denne vurdering baserer vi på følgende punkter:

- Prisen anses som værende høj i forhold til vurdering "kan ikke kategoriseres".

[redacted]

Konklusion

Amgros vurderer, at prisen på lægemidlet er høj i forhold til værdien den ikke kategoriseres. [redacted]

Status fra andre lande

Norge: Nye metoder. Har publiceret deres vurderingsrapport i december 2020 og beslutningen er en godkendelses d.18.1.2021[1].
Sverige: NT-rådet har godkendt behandlingen i september 2020[2].

Relation til markedet

Det er på nuværende tidspunkt ingen godkendte lægemidler til denne indikation. I løbet af 2021 vil der formodentlig komme flere ansøgninger på nye lægemidler samt genansøgninger fra tidligere CAR-t behandlinger. [redacted]

[1] ID2019_035_Polatuzumabvedotin_Polivy_kombinasjonsbehandling ved DLNCL- hurtig metodevurdering-offentlig versjon.pdf (nyemetoder.no)
[2] Rekommendation Polivy (janusinfo.se)

Høringssvar

Roche har følgende kommentarer til vurderingsrapporten på polatuzumab vedotin, og til den øvrige kommunikation fra sekretariatet, hvor sagen synes at have gennemgået en meget uhensigtsmæssig og bemærkelsesværdig sagsbehandling.

Vurderingsrapporten

Det forekommer uforståeligt, at den rådsmødegodkendte vurderingsrapport adskiller sig så markant både fra det tidligere fremsendte udkast til vurderingsrapport fra fagudvalget, og fra internationale HTA-vurderinger af værdien af polatuzumab.

Det tidligere fremsendte 1. udkast til en vurderingsrapport, udarbejdet af fagudvalget (26/08/2020), anerkendte polatuzumabs datagrundlag og tildelte polatuzumab en merværdi af ukendt størrelse, der bl.a. er baseret på den højest mulige merværdikategori på den relative effekt for rapportens eneste "kritiske" effektmål, som er samlet overlevelse. På det effektparameter har polatuzumab jvnf. Medicinrådets metoder en "stor" merværdi.

Herudover er vurderingen af polatuzumab - grundet Medicinrådets meget langvarige sagsbehandlingstid - for længe siden færdigbehandlet i en række andre lande, herunder i en fælles europæisk vurderingsrapport fra EUnetHTA[1]. Rapporter fra andre lande anerkender alle polatuzumabs datagrundlag, og polatuzumab anbefales således i bl.a. England og Sverige. I England angiver rapporten fra NICE, at lægemidlet har kurativt potentiale[2] og i Sverige konkluderes det, at effekten er "måttlig" (moderat)[3].

Den danske rådsmødegodkendte vurderingsrapport ser tilsyneladende anderledes på data end omverdenen og problematiserer nu hovedstudiet[4] i en grad, så der rejses tvivl om hele datagrundlaget. Dette på trods af at Roche siden det først fremsendte udkast til en vurderingsrapport - og på opfordring fra Medicinrådet, har indsendt modnere data, som bekræfter effekten af polatuzumab yderligere[5]

Roche anerkender, at polatuzumabs datagrundlag (fase II studie) tilsiger behovet for klinisk input, som supplement studiedata. Derfor udarbejder man også i Norge en vurdering af polatuzumab efter en model, hvor det kliniske input vægtes højt i den sundhedsøkonomiske analyse. I Norge forventes det at "Beslutningsforum for nye metoder" tager stilling til polatuzumab i januar 2021. Det danske Medicinråd ser ud til initialt, at have valgt en model, hvor fagudvalgsformanden ikke var til stede på rådsmødet til at

---

[1] https://eunethta.eu/wp-content/uploads/2020/02/PTJA06-Final-Assessment-Report-V1.0.pdf

[2] https://www.nice.org.uk/guidance/ta649/evidence/committee-papers-pdf-8840199997

[3] https://janusinfo.se/download/18.21dd9ddd174519824617407c/1599810018260/Polivy%202020-09-11.pdf

[4] Sehn LH, Herrera AF, Flowers CR, Kamdar MK, McMillan A, Hertzberg M, et al. Polatuzumab Vedotin in Relapsed or Refractory Diffuse Large B-Cell Lymphoma. J Clin Oncol. 2020;38(2):155–65.

[5] http://www.globenewswire.com/news-release/2020/12/07/2140210/0/en/New-data-presented-at-ASH-2020-reinforces-the-benefit-risk-profile-of-fixed-duration-Polivy-plus-bendamustine-and-MabThera-Rituxan-in-patients-with-relapsed-or-refractory-diffuse-l.html

bidrage med klinisk input. I referatet fra rådsmødet i august angives det, at sagen blev præsenteret af sekretariatet[6]

Den nyligt rådsmødegodkendte vurderingsrapport (december 2020) er ledsaget af en mail fra sekretariatet, hvor der står følgende:

Medicinrådet var enigt med fagudvalgets konklusion om lægemidlets værdi, som derfor svarer til det resultat, I har i høring. Bemærk dog, at Medicinrådet finder, at den kliniske værdi af polatuzumab vedotin ikke kan vurderes og at problemerne med randomiseringen i studiet er af en sådan karakter, at de ikke finder det relevant at udarbejde en sundhedsøkonomisk afrapportering.

Roche savner en forklaring på, hvilke problemer der præcist henvises til her ift. *randomiseringen*, men må antage, at det er følgende tekst i vurderingsrapporten, som der tales om:

"Den ulige fordeling i baselinekarakteristika øger samlet set risikoen for, at effekten af polatuzumab vedotin er overestimeret."(Medicinrådets vurderingsrapport, side 10).

Resultaterne af polatuzumab studiet problematiseres ligeledes i vurderingsrapporten på side 10, hvor der står:

"Der fremgår en række justerede analyser i EPAR'en, hvor der er forsøgt korrigeret for forskelle mellem armene for en række prognostiske markører. Disse analyser viser, at flere effektparametre er sensitive over for justering"

Punkt 1. Udsagn om ulige fordeling i baselinekarakteristika

Der synes at mangle en uddybning af hvilke analyser, som Medicinrådet har anvendt til at teste, hvorvidt der er en ulige fordeling i baselinekarakteristika mellem grupperne. Og hvordan de analyser i så fald har ført til konklusionen "samlet set". Er der anvendt statistiske metoder med tilhørende p-værdier? Sensitivitetsanalyser frem for hovedanalysen? Andet?

Roche har testet baselineværdier for de to grupper i hovedstudiet[7] (Table 1 kolonne 4 vs. 5) , og kan ikke genfinde objektiviteten i udsagnet. Der er m.a.o. ikke statistisk signifikante forskelle på de forskellige baseline parametre, hverken enkeltvis eller "samlet set". Roche har også grupperet IPI-score, ligesom man har valgt at gøre i vurderingsrapporten, og testet IPI score 4+5 mod "resten", og heller ikke der er der en statistisk signifikant forskel. Roche vil i den forbindelse gerne påpege, at sammenligninger af en lang række baseline værdier i helt veludførte randomiseringer "by chance" vil medføre skæve værdier i ca. hvert 20. tilfælde. Det er dog værd at bemærke, at dette ikke forekommer i studiet på polatuzumab. Desuden er en korrelation mellem baselineværdier, der måler på "samme sag" er forventelig. Randomiseringer fjerner kun koblingen mellem baseline og "treatment", og ikke internt mellem baselinevariabler.

Roche vil også gerne henlede opmærksomhed på, at der i EPARen for lægemidlet[8] er foretaget analyser for at imødekomme eventuelle forskelle i baselineværdier (propensity score weighed analyse), der balancerer

---

[6] https://medicinraadet.dk/media/snfdserw/referat-44-r%C3%A5dsm%C3%B8de-i-medicinr%C3%A5det-26-08-2020-final-08-09-2020_adlegacy.pdf

[7] Sehn LH, Herrera AF, Flowers CR, Kamdar MK, McMillan A, Hertzberg M, et al. Polatuzumab Vedotin in Relapsed or Refractory Diffuse Large B-Cell Lymphoma. J Clin Oncol. 2020;38(2):155–65.

[8] https://www.ema.europa.eu/en/documents/assessment-report/polivy-epar-public-assessment-report_en.pdf

baselineværdierne mellem de to grupper. Denne vægtede analyse viser lignende effektstørrelser og bredder på konfidensintervallerne, som de øvrige analyser, og signalerer derfor heller ikke, at randomiseringen skulle give anledning til fortolkningsproblemer.

Punkt 2. Udsagn om justerede analyser fra EPAR, der viser at effektparametre er sensitive overfor justering

Roche undrer sig over, at Medicinrådet ser ud til at have lagt meget vægt på afsnittet i EPARen, hvor effektstørrelserne er justerede. Roche har udført analyser på resultaterne fra artiklen (figur 2), og effektstørrelserne ændrer sig ikke særligt meget, når der justeres, men konfidensintervallerne bliver selvfølgeligt bredere, fordi datasættet splittes op i mindre grupper. Konklusionen forekommer i øvrigt ikke overraskende, da studiet ser ud til at have været dimensioneret til at have styrke for den ujusterede analyse, der matcher randomiseringen.

Punkt 3. Udsagn om manglende udarbejdelse af en sundhedsøkonomisk analyse

Roche noterer sig, at man på augustmødet i Rådet fandt en sundhedsøkonomisk afrapportering på sagen helt relevant, og i referatet fra mødet konkluderer følgende:

Rådet ønskede også tilføjet en ekstra følsomhedsanalyse vedr. ekstrapolationen til den sundhedsøkonomiske model.[9]

Roche har d. 10. december, 2020 bedt om en uddybelse af, hvorfor der dengang godt kunne laves sundhedsøkonomi og hvorfor der nu ikke kan? Data er kun blevet mere robuste siden, grundet længere opfølgningstid. Det har desuden vist sig fuldt ud muligt i de andre lande, der i HTA-regi har vurderet polatuzumab, at udarbejde sundhedsøkonomiske afrapporteringer[10][11] Roche har ved udarbejdelsen af dette dokument (15/12-2020) fortsat ikke modtaget et svar fra sekretariatet herpå.

Sagsbehandlingen

Roche er ligeledes uforstående over for den sagsbehandlingsproces, der har været anvendt i vurderingen af polatuzumab. Dels har sagsbehandlingen været ekstremt langtrukken (endelig ansøgning blev godkendt d. 02/03/2020), dels bærer processen præg af mangel på transparens om, hvem der reelt står bag den faglige vurdering af lægemidlet.

I en mail fra sekretariatet (Snezana Djurisic) sendt til Roche d. 2 november, 2020 oplyses følgende:

I forbindelse med fagudvalgets opdatering af vurderingsrapporten for polatuzumab vedotin med nye data, har sekretariatet forelagt fagudvalgets vurdering for Medicinrådets formandskab. Dette er sket forud for rådsmødet den 18. november, hvor polatuzumab vedotin var programsat. Formandskabet har ønsket flere drøftelser med fagudvalget, og vi har desværre været nødt til at taget polatuzumab vedotin af rådsmødet

---

[9] https://medicinraadet.dk/media/snfdserw/referat-44-r%C3%A5dsm%C3%B8de-i-medicinr%C3%A5det-26-08-2020-final-08-09-2020_adlegacy.pdf

[10] https://www.tlv.se/download/18.29a1f319172779733433318b/1591376116427/bes_200601_underlag_polivy.pdf

[11] https://www.nice.org.uk/guidance/ta649/evidence/committee-papers-pdf-8840199997

endnu engang. Det er ikke muligt for os på nuværende tidspunkt at udtale os yderligere om sagen, men vi er i færd med at arrangere et møde, hvor drøftelserne kan finde sted. I vil blive orienteret, når vi har nye oplysninger.

Hvorfor skal vurderingsrapporten efter fagudvalget 2. behandling forelægges formandsskabet inden den forelægges Rådet? Hvorfor har formandsskabet har bilaterale drøftelser med fagudvalget forud for rådsmødet? Dette synes ikke at være i overensstemmelse med hverken metodehåndbog eller forretningsordenen for Medicinrådet.[12]

Med venlig hilsen
Roche a/s

DocuSigned by:
Mads Ekstrand-Olsen

Mads Ekstrand-Olsen
Medical/Scientific Director

Medicinrådet

Vedr. høringssvar fra Roche i forbindelse med sagsforløbet og kategoriseringen af polatuzumab vedotin til behandling af diffust storcellet T-cellelymfom

12. januar 2021

Medicinrådet
Dampfærgevej 27-29, 3. th.
2100 København Ø

+45 70 10 36 00
medicinraadet@medicinraadet.dk

www.medicinraadet.dk

På baggrund af jeres høringssvar fra den 15. december 2020 i forbindelse med Medicinrådets fastsættelse af den kliniske værdi for polatuzumab vedotin (Polivy), finder Medicinrådet, at der ikke har været anledning til at foretage ændringer i den kliniske vurdering, som fremgår af den seneste version af vurderingsrapporten.

Da jeres høringssvar er omfangsrigt, har vi valgt at adressere nogle punkter vi finder særligt væsentlige i det følgende.

Ændring i fagudvalgets kategorisering af polatuzumab vedotin
Det oprindelige udkast til vurderingsrapport, som blev præsenteret ved rådsmødet den 26. august 2020, tog udgangspunkt i data ud fra et perspektiv om, at randomiseringen i hovedstudiet var vellykket, hvorfor usikkerhederne på daværende tidspunkt, foruden en observeret ubalance i baseline karakteristika, primært bestod af studiets størrelse samt manglende modenhed af data. Roche indsendte efter rådsmødet data med længere opfølgningstid, hvor usikkerheden vedr. datamodenhed blev reduceret.

Fagudvalget har på et efterfølgende møde, hvor de supplerende data indsendt af Roche blev drøftet, gransket hovedstudiet nærmere og vurderet, at randomiseringen ikke var vellykket i forhold til vigtige prognostiske kriterier. I denne vurdering har fagudvalget inddraget de justerede analyser, som omtales i EPAR'en. Mere konkret i forhold til *propensity score weighting* i EPAR'en vurderede fagudvalget, at der er en betydelig risiko for at den anvendte vægtemodel er overspecificeret og ikke retvisende. Samme forhold er gældende i forhold til *full multivariate model, backward selection model*, for hvilke resultaterne også er præsenteret i EPAR'en. Fagudvalgets samlede vurdering af værdien af polatuzumab vedotin er baseret på en tolkning af resultater ud fra en vurdering af klinisk relevante forskelle mellem armene i baselinekarakteristika løsrevet fra statistisk signifikans.

Fagudvalget anså efter det seneste møde ikke længere den oprindelige kategorisering af lægemidlets værdi (selv baseret på de mere modne data) som pålidelig, og udkastet til vurderingsrapporten blev opdateret på denne baggrund. Det seneste udkast til vurderingsrapporten blev præsenteret af fagudvalgsformanden, og Rådet havde ingen indvendinger til fagudvalgets konklusioner ved rådsmødet den 9. december 2020.

Sagsbehandlingsprocessen

Roche har per mail den 4. november 2020 spurgt ind til sagsbehandlingsforløbet og fået følgende svar i et brev fra Medicinrådet: ”*I forbindelse med en sags behandling kan der opstå behov for yderligere undersøgelse og forberedelse af en sag, før Rådet kan træffe en beslutning […]. Formandskabet kan blive involveret i denne forberedelse, forud for en sag forelægges for Rådet*.” Det anses derfor ikke som værende udenfor normal praksis, hverken at vurderingsrapporten for polatuzumab vedotin forelægges formandskabet inden resten af Rådet ser rapporten, eller at formandskabet eller enkelte rådsmedlemmer mødes med et fagudvalg inden et rådsmøde. Det resterende Råd er blevet informeret om den ene af formændenes møde med fagudvalget, og hvad det medførte af diskussioner, ændringer og konklusioner i vurderingen. Rådet havde ingen indvendinger til dette.

Vedr. den sundhedsøkonomiske afrapportering
Sekretariatet kan oplyse, at Rådet på sit næste møde vil fortsætte drøftelsen af den sundhedsøkonomiske analyse til vurdering af polatuzumab vedotin.

Med venlig hilsen

Snezana Djurisic
Sundhedsvidenskabelig specialkonsulent
Cand.scient., ph.d.
sdj@medicinraadet.dk
+45 21 34 43 98

Medicinrådet

Medicinrådets vurdering vedrørende polatuzumab vedotin i kombination med bendamustin og rituximab til behandling af diffust storcellet B-cellelymfom

Version 1.1

Medicinrådet

Om Medicinrådet

Medicinrådet er et uafhængigt råd etableret af Danske Regioner.

Medicinrådet vurderer, om nye lægemidler og indikationsudvidelser skal anbefales som mulig standardbehandling. Medicinrådet udarbejder også behandlingsvejledninger og rekommandationer for anvendelse af medicin på sygehusene. Derudover kan Medicinrådet tage andre typer sager op, der handler om medicinanvendelse.

Om vurderingsrapporten

Vurderingsrapporten indeholder Medicinrådets vurdering af, hvilken værdi lægemidlet har for patienten i forhold til nuværende standardbehandling.

Værdien for patienten og omkostningerne for samfundet danner grundlaget for Medicinrådets beslutning om, hvorvidt lægemidlet anbefales som mulig standardbehandling. Dette sammenfatter vi i Medicinrådets anbefaling vedr. lægemidlet.

Lægemidlet er vurderet efter Håndbog for Medicinrådets proces og metode vedr. nye lægemidler og indikationsudvidelser, som du kan finde på Medicinrådets hjemmeside under siden Metoder.

Godkendt af Medicinrådet: 27. januar 2021
Dokumentnummer 105485
Versionsnummer 1.1

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

Indhold

1 Medicinrådets konklusion 3
2 Begreber og forkortelser 4
3 Introduktion 5
3.1 Baggrund 5
3.2 Polatuzumab vedotin 6
3.3 Nuværende behandling 6
4 Metode 6
5 Resultater 8
5.1.1 Litteratur 8
5.1.2 Databehandling og -analyse 11
5.1.3 Evidensens kvalitet 12
5.1.4 Effektestimater og kategorier 12
5.1.5 Fagudvalgets konklusion 18
6 Andre overvejelser 19
7 Relation til behandlingsvejledning 19
8 Referencer 20
9 Sammensætning af fagudvalg og kontaktinformation til Medicinrådet 21
10 Versionslog 22
11 Bilag 1: Evidensens kvalitet 23
11.1 Cochrane, Risk of Bias 23
11.2 GRADE-profil 24

1 Medicinrådets konklusion

Medicinrådet vurderer, at polatuzumab vedotin i kombination med bendamustin og rituximab til voksne patienter med recidiverende/refraktært diffust storcellet B-cellelymfom, der ikke er kandidater til hæmatopoietisk stamcelletransplantation, ikke kan kategoriseres. Baggrunden er, at datagrundlaget baserer sig på et lille klinisk studie, hvor randomiseringen ikke anses at være vellykket i forhold til vigtige prognostiske parametre og derfor ikke er pålideligt til at vurdere den kliniske værdi af polatuzumab vedotin. Medicinrådet finder, at det for patientpopulationen bør være muligt at supplere data med større og mere pålidelige kliniske studier.

Medicinrådet kategoriserer lægemidlers værdi i en af følgende kategorier:

• **Stor merværdi:** Der er påvist en stor forbedring i effektforhold i forhold til gældende standardbehandling, eksempelvis markant forbedret overlevelse, markant reduktion i forekomsten af alvorlige symptomer og/eller alvorlige bivirkninger.

• **Moderat merværdi:** Der er påvist en moderat forbedring i forhold til gældende standardbehandling, eksempelvis moderat forbedret overlevelse, moderat reduktion i forekomsten af symptomer og/eller bivirkninger.

• **Lille merværdi:** Der er påvist en lille forbedring i forhold til gældende standardbehandling, eksempelvis en dokumenteret forbedret overlevelse, en reduktion i forekomsten af symptomer og/eller bivirkninger.

• **Merværdi af ukendt størrelse:** Der er påvist en forbedring i forhold til gældende standardbehandling, men størrelsen af forbedring kan ikke bestemmes. Lægemidlets merværdi er som minimum lille, men kunne også være moderat eller stor.

• **Ingen dokumenteret merværdi:** Der er ikke påvist en merværdi i forhold til gældende standardbehandling. Omvendt tyder den tilgængelige evidens heller ikke på, at der er en negativ værdi.

• **Negativ værdi:** Der er påvist en negativ værdi i forhold til gældende standardbehandling.

I nogle situationer er det ikke muligt at kategorisere lægemidlets samlede værdi. De situationer opstår, når evidensgrundlaget for vurderingen er for usikkert til at kategorisere værdien jf. Medicinrådets metoder (fx på grund af usikkerheder omkring effektforhold og spinkelt datagrundlag). Medicinrådet konkluderer da, at samlet værdi ikke kan kategoriseres. Medicinrådet vil i disse tilfælde argumentere for, om der er grund til at formode, at det nye lægemiddel er dårligere eller evt. bedre end gældende standardbehandling, eller der ikke er grund til at skelne mellem behandlingerne. Det sker på baggrund af det foreliggende datagrundlag og fagudvalgets kliniske erfaring. Vurderingen er forbundet med større usikkerhed end vurderinger, hvor lægemidlets værdi kan kategoriseres.

Medicinrådet vurderer kvaliteten af de data, der ligger til grund for vurderingen af lægemidlet (evidensens kvalitet) i en af følgende GRADE-kategorier:

• **Høj:** Nye studier vil med meget lav sandsynlighed ændre konklusionen.

• **Moderat:** Nye studier vil med lav sandsynlighed ændre konklusionen.

• **Lav:** Nye studier vil med moderat sandsynlighed ændre konklusionen.

• **Meget lav:** Nye studier vil med høj sandsynlighed ændre konklusionen.

2 Begreber og forkortelser

CI	Konfidensinterval
DLBCL	Diffust storcellet B-cellelymfom
EMA	Det Europæiske Lægemiddelagentur (*European Medicines Agency)*
EPAR	*European Public Assessment Report*
FACT-LYM	*Functional Assessment of Cancer Treatment-Lymphoma*
GRADE	System til at vurdere evidens (*Grading of Recommendations, Assessment, Development and Evaluation*)
HR	*Hazard ratio*
IPI	*International Prognostic Index*
ITT	*Intention to Treat*
NHL	non-Hodgkin-lymfom
OR	*Odds ratio*
OS	*Overall Survival* (overordnede overlevelse)
PET-CT	Positron-emissionstomografi-computer-tomografi
PFS	*Progression Free Survival* (progressionsfri overlevelse)
PICO	Population, intervention, komparator og effektmål (*Population, Intervention, Comparator and Outcome)*
PP	*Per-protocol*
RCT	Randomiseret kontrolleret studie *(Randomised Controlled Trial)*
RR	Relativ risiko
R-Benda	Rituximab i kombination med bendamustin
R-DHAP	Rituximab i kombination med dexamethason, højdosis cytarabin og cisplatin
R-GDP	Rituximab i kombination med gemcitabin, dexamethason og cisplatin
R-GemOx	Rituximab i kombination med gemcitabin og oxaliplatin
R-ICE	Rituximab i kombination med ifosfamid, carboplatin og etoposid
SF-36	*Short Form 36*
SMD	*Standardized Mean Difference*
TNAS	*Therapy-induced Neuropathy Assessment Scale*

3 Introduktion

Formålet med Medicinrådets vurdering af polatuzumab vedotin i kombination med bendamustin og rituximab til behandling af diffust storcellet B-cellelymfom (DLBCL) er at vurdere den værdi, lægemidlet har sammenlignet med dansk standardbehandling.

Vurderingen er udarbejdet, fordi Medicinrådet den 11. februar 2020 modtog en endelig ansøgning fra Roche. Medicinrådet modtog den 16. september 2020 et tillæg til datagrundlaget.

Det kliniske spørgsmål er:

Hvad er værdien af polatuzumab vedotin i kombination med bendamustin og rituximab sammenlignet med bendamustin, GDP, GemOx eller ICE i kombination med rituximab til voksne patienter med recidiverende/refraktært diffust storcellet B-cellelymfom, der ikke er kandidater til hæmatopoietisk stamcelletransplantation?

3.1 Baggrund

DLBCL er en aggressiv undertype af non-Hodgkin-lymfom (NHL), der kan opstå *de novo* eller udvikles fra andre undertyper af NHL. Der diagnosticeres ca. 450 tilfælde årligt i Danmark, og incidensen er stigende [1]. Risikoen for at udvikle DLBCL øges med alderen, og medianalderen ved diagnosetidspunktet er 67 år [1]. DLBCL-patienter udgør en meget heterogen gruppe, hvor behandlingsvalg efter første linje i høj grad afhænger af parametre som alder, WHO-performance score (indeks for funktionsniveau), komorbiditet, tidligere behandlinger og patientpræferencer. En stor andel over 65 år vil være i stand til at tåle standardbehandling i form af kombinationskemoterapi. Efter standardbehandling kan patienter under 65-70 år tilbydes konsoliderende højdosis kemoterapi i kombination med stamcelletransplantation [1]. Alder over 75 år og en performancestatus større end 2 er forbundet med en højere rate af komplikationer og et dårligere udfald [1,2].

DLBCL viser sig typisk som en eller flere forstørrede lymfeknuder, ofte på hals, i mediastinum og/eller i abdomen [1]. Hos 40 % af patienterne kan sygdommen lokaliseres til andet væv. Prognosen er stadieafhængig og forværres med antallet af ekstranodale manifestationer [1].

Omkring 35 % af alle DLBCL-patienter vil opleve recidiv eller være refraktære overfor behandling efter første linje (typisk R-CHOP: rituximab, cyclophosphamid, doxorubicin, vincristin, og prednison) [1,2]. Fagudvalget skønner, at 150 DLBCL-patienter årligt vil være kandidater til behandling i anden eller tredje linje i Danmark. Af disse vil 100 patienter ikke være egnet til stamcelletransplantation grundet alder, tidligere autolog stamcelletransplantation, komorbiditet eller toleranceproblemer i forbindelse med højdosiskemoterapi inden stamcelletransplantation og er således mulige kandidater til behandling med antistofkonjugatet polatuzumab vedotin.

Den samlede population af patienter med recidiverende/refraktært DLBCL har en dårlig prognose [1,3,4]. I en litteraturgennemgang estimeres den mediane overlevelse (*overall survival*; OS) hos patienter med recidiverende/refraktært DLBCL egnet til stamcelletransplantation til 10-44 måneder sammenlignet med 3-9 måneder hos patienter uegnet til stamcelletransplantation [5]. Fagudvalget vurderer, at patienter, der er refraktære overfor behandling, har en dårligere prognose end patienter, der oplever recidiv. Behandlingsmulighederne er som udgangspunkt ens for patienter med recidiv eller refraktær sygdom, der ikke er kandidater til **stamcelletransplantation** [1].

3.2 Polatuzumab vedotin

Polatuzumab vedotin er et antistoflægemiddelkonjugat rettet mod CD79b på celleoverfladen af B-celler. Efter optag i cellen kløves polatuzumab vedotin, og en mindre del af konjugatet (en kemoterapeutisk fraktion; MMAE) binder til tubulin. Binding af B-cellernes tubulin medfører stop af celledeling og deraf celledød.

Polatuzumab vedotin produceres som koncentrat til infusionsvæske, der gives intravenøst. Den anbefalede dosis er 1,8 mg/kg og gives hver 21. dag i kombination med bendamustin og rituximab i seks cyklusser. Polatuzumab vedotin, bendamustin og rituximab kan administreres på dag et i hver cyklus. Ved koadministrering med polatuzumab vedotin er den anbefalede dosis af bendamustin 90 mg/m^2 på dag et og dag to i hver cyklus, og den anbefalede dosis af rituximab er 375 mg/m^2 på dag et i hver cyklus.

I kombination med bendamustin og rituximab er polatuzumab vedotin indiceret til behandling af voksne patienter med recidiverende/refraktært DLBCL, som ikke tåler stamcelletransplantation.

3.3 Nuværende behandling

I henhold til de nuværende kliniske retningslinjer anbefales remissionsinducerende kemoterapi efterfulgt af højdosiskemoterapi med stamcelletransplantation til patienter under 65-70 år med recidiverende/refraktært DLBCL [1]. Der findes ikke evidens for at anbefale et bestemt regime til den undergruppe af patienter, som ikke er kandidater til stamcelletransplantation [1]. Disse patienter udgør en meget heterogen gruppe med varierende prognose, om end prognosen altid er dårlig. Behandlingsvalget baseres på individuelle vurderinger af patientens almentilstand, hvor bl.a. alder, komorbiditet, tidligere behandlinger, performancestatus og patientpræferencer spiller en rolle. Ifølge den foreløbige ansøgning fra ansøger var bendamustin evt. i kombination med rituximab (R-Benda) i perioden 2013-2018 den hyppigst anvendte behandling til patienter, der ikke er kandidater til stamcelletransplantation. Det fremgår dog ikke af opgørelsen, i hvilken behandlingslinje bendamustin har været anvendt, eller hvor hyppigt rituximab blev valgt i kombination.

Patienter, som ikke er kandidater til stamcelletransplantation, der har en god almen tilstand, kan ofte tilbydes en kombinationskemoterapi (f.eks. R-GDP; rituximab, gemcitabin, dexamethason og cisplatin, R-GemOx; rituximab, gemcitabin og oxaliplatin eller R-ICE; rituximab, ifosfamid, carboplatin og etoposid), mens patienter, der har en dårligere almen tilstand, ofte tilbydes enkeltstof(kemo)terapi (f.eks. bendamustin, prednisolon alene eller blot "best supportive care") i kombination med rituximab, der generelt er veltolereret.

Behandling af patienter med recidiverende/refraktært DLBCL, som ikke tåler stamcelletransplantation, har med nuværende behandlingsmuligheder et pallierende, og i visse tilfælde, livsforlængende sigte. Nye behandlinger vil derfor primært blive bedømt ud fra en potentiel længere levetid og/eller forbedret livskvalitet.

4 Metode

Medicinrådets protokol for vurdering af polatuzumab vedotin beskriver sammen med Håndbog for Medicinrådets proces og metode vedr. nye lægemidler og indikationsudvidelser, hvordan vi vil vurdere lægemidlets værdi for patienterne.

Det kliniske spørgsmål er:

Hvad er værdien af polatuzumab vedotin i kombination med bendamustin og rituximab sammenlignet med bendamustin, GDP, GemOx eller ICE i kombination med rituximab til voksne patienter med

recidiverende/refraktært diffust storcellet B-cellelymfom, der ikke er kandidater til hæmatopoietisk stamcelletransplantation?

Population
Voksne patienter med recidiverende/refraktært diffust storcellet B-cellelymfom, der ikke er kandidater til hæmatopoietisk stamcelletransplantation.

Intervention
Polatuzumab vedotin plus R-Benda.

Komparatorer
Enkeltstofkemoterapi:

Bendamustin (70 mg/m^2 eller 90 mg/m^2 dag 1-2) og rituximab (375 mg/m^2 dag 1)

Kombinationskemoterapi (én af nedenstående valgt ud fra bedste sammenligningsgrundlag):

GDP og rituximab (375 mg/m^2 dag 1)

GemOx og rituximab (375 mg/m^2 dag 1)

ICE og rituximab (375 mg/m^2 dag 1)

Effektmål
Effektmål fremgår af tabel 1.

Tabel 1.

Effektmål*	**Vigtighed**	**Effektmåls-gruppe**	**Måleenhed**	**Mindste klinisk relevante forskel**
Samlet overlevelse (OS)	Kritisk	Dødelighed/ overlevelse	Medianoverlevelse i måneder	6 måneder
			Andel af patienter, der opnår 2-års overlevelse	10 %-point
Helbredsrelateret livskvalitet	Vigtig	Livskvalitet, alvorlige symptomer og bivirkninger	Gennemsnitlig ændring fra baseline på SF-36 til efter endt behandling	5 point
			Gennemsnitlig ændring fra baseline på SF-36 til efter endt opfølgning	5 point
			Gennemsnitlig ændring fra baseline på FACT-Lym til efter endt behandling	4 point
			Gennemsnitlig ændring fra baseline på FACT-Lym til efter endt opfølgning	4 point
Progressionsfri overlevelse (PFS)	Vigtig	Livskvalitet, alvorlige symptomer og bivirkninger	Medianoverlevelse i måneder	6 måneder
			Andel af patienter, der opnår 2-års progressionsfri overlevelse	10 %-point

Uønskede hændelser	Vigtig	Alvorlige symptomer og bivirkninger	Andel frafald pga. uønskede hændelser (behandlingsophør)	10 %-point
			Andel patienter med uønskede hændelser grad 3 og grad 4	10 %-point

* For alle effektmål ønskes data med længst mulig opfølgningstid, medmindre andet er angivet.

Da DLBCL udgør en meget heterogen gruppe af patienter, ønskede fagudvalget, at ansøger indsendte en oversigt over hvilke DLBCL-undertyper, der er inkluderet i studierne.

5 Resultater

5.1.1 Litteratur

Nedenfor beskriver og vurderer vi den litteratur, som ansøger har anvendt i sin endelige ansøgning.

Ansøger har søgt litteratur med søgestrengen fra protokollen og har fundet tre fuldtekstartikler, der rapporterer resultater fra tre studier. Det ene er et randomiseret studie, der direkte sammenligner kombinationen af polatuzumab vedotin og R-Benda med den ene af de definerede komparatorer, R-Benda (GO29365). De to andre studier er observationelle og rapporterer data fra to forskellige kohorter af patienter, der udspringer af det samme oprindelige CORAL-studie. CORAL er et randomiseret fase III-studie, der sammenligner effekten af R-ICE og R-DHAP efterfulgt af stamcelletransplantation med eller uden efterfølgende vedligeholdelsesbehandling med rituximab.

Tabel 2 viser en oversigt over de tre publikationer.

Tabel 2: Oversigt over inkluderede artikler. De grå celler angiver hvilke data, der ikke er medtaget i vurderingen.

Titel	**Forfatter og publikationsår**	***N*** **Studienavn (NCT-nr.)**	**Intervention**	**Komparator**	**Opfølgnings-tid, median, måneder**	**Studiedesign**
Polatuzumab Vedotin in Relapsed or Refractory Diffuse Large B-Cell Lymphoma	Sehn et al. JClinOncol, 2019. [6]	*N* = 80 GO29365 (02257567)	Polatuzumab vedotin Bendamustin Rituximab	Bendamustin Rituximab	22,3*	Fase II randomiseret, ublindet
Outcomes of diffuse large B-cell lymphoma patients relapsing after autologous stem cell transplantation: an analysis of patients included in the CORAL study	Den Neste et al. Bone Marrow transplantation, 2017 [7]	*N* = 75 CORAL EXT-1 (00137995)	ICE-like DHAP-like Gemcitabin-holdigt	Ingen	32,8	Observationelt studie af patienter fra randomiseret studie
Outcome of patients with relapsed diffuse large B-cell lymphoma who fail secondline salvage regimens in the International CORAL study	Den Neste et al. Bone Marrow transplantation, 2016 [8]	*N* = 203 CORAL EXT-2 (00137995)	ICE-like DHAP-like Gemcitabin-holdigt DEXA-beam CHOP-like	Ingen	30,1	Observationelt studie af patienter fra randomiseret studie
**opfølgningstiden i Clinical Study Report er 42,2-42,9 måneder*						

Herudover har fagudvalget valgt at inddrage følgende data fra hovedstudiet GO29365 i vurderingen:

- Opdaterede OS- og PFS-data med længere opfølgningstid fra den endelige *Clinical Study Report* af juni 2020.

På tidspunktet for inddragelse af OS- og PFS-data med længere opfølgningstid var det pågældende data ikke publiceret, men vurderet relevant jf. Medicinrådets kriteriepapir vedr. upubliceret data. Data er sidenhen blevet publiceret. Studierne gennemgås enkeltvis nedenfor.

GO29365

GO29365 er et randomiseret fase Ib/II-studie, der blandt andet undersøger effekten af polatuzumab vedotin-R-Benda sammenlignet med R-Benda i patienter med recidiverende/refraktært DLBCL eller follikulært lymfom, som ikke er kandidater til stamcelletransplantation.

Der er tale om et kompliceret studiedesign med samlet otte behandlingsarme (benævnt A-H). Behandlingsarmene C (n = 40) og D (n = 40) er dedikeret til evaluering af effekten og sikkerheden af polatuzumab vedotin-R-Benda versus R-Benda alene hos patienter med recidiverende/refraktært DLBCL og er således de relevante for vurderingen. Samlet er 80 patienter randomiseret 1:1 til henholdsvis polatuzumab vedotin-R-Benda og R-Benda. Patienterne blev stratificeret efter responsvarighed på deres seneste behandlingslinje (over eller under 12 måneder). Studiets mediane opfølgningstid er ved tidspunktet for opgørelse af data i hovedpublikationen 22,3 måneder. Studiets mediane opfølgningstid med længst mulig opfølgning er opgjort efter hovedpublikationen til 42,2-42,9 måneder (opgjort efter *reverse* Kaplan-Meier-metode).

Diagnosen DLBCL bekræftes ved biopsi. De inkluderede patienter blev vurderet at være uegnede til stamcelletransplantation eller alternativt at have oplevet behandlingssvigt i forbindelse med en tidligere stamcelletransplantation. Patienternes baselinekarakteristika fremgår af tabel 3.

Tabel 3: Baselinekarakteristika GO29365.

	Polatuzumab vedotin-R-Benda	**R-Benda**
	N = 40	N = 40
Median alder, år (range)	67,0 (33-86)	71,0 (30-84)
Andel ≥ 65 år, n (%)	23 (57,5)	25 (65)
Kvinder, n (%)	12 (30)	15 (27,5)
ECOG performancestatus, n (%)		
0-1	33 (82,5)	31 (77,5)
2	6 (15,0)	8 (20,0)
WHO 2016 Classification, n (%)		
DLBCL, NOS	38 (95,0)	40 (100,0)
ABC	19 (47,5)	19 (47,5)
GCB	15 (37,5)	17 (42,5)
Burkitt lymfom	1 (2,5)	0
Follikulært lymfom	1 (2,5)	0
IPI-score, n (%)		
0-2	18 (45)	11 (27,5)
> 2	22 (55)	29 (72,5)
0-1	9 (22,5)	3 (7,5)
2-3	22 (55,0)	20 (50)
4-5	9 (22,5)	17 (42,5)
Ann-Arbor stadie III/IV, n (%)	34 (85,0)	36 (90,0)
Bulky disease (≥ 7 cm), n (%)	10 (25,0)	15 (37,5)
Tidligere stamcelletransplantation, n (%)	10 (25,0)	6 (15,0)
Antal tidligere behandlinger, %		
Median, n (range)	2 (1-7)	2 (1-5)
1	27,5	30,0
2	27,5	22,5
≥ 3	45	47,5

Studiets primære effektmål var komplet respons målt med PET-CT i henhold til gældende klinisk praksis ved slutningen af behandling. PFS var et sekundært effektmål og OS et eksplorativt effektmål. Livskvalitet blev målt med *Therapy-induced Neuropathy Assessment Scale* (TNAS).

Patienterne var hovedsageligt mænd (70,0 % vs. 62,5 %). Den mediane alder var højere hos patienter i komparatorarmen (71 år vs. 67 år). Patienterne havde tidligere modtaget to forudgående behandlinger (median, maksimalt op til syv). Hovedparten af patienterne havde refraktær sygdom overfor seneste behandling, med en overvægt af refraktære patienter i komparatorarmen (85,0 % vs. 75,0 %). Den mediane tid fra seneste behandling var længere i polatuzumab vedotinarmen i forhold til komparatorarmen (131 dage vs. 82 dage), hvilket indikerer, at patienterne i polatuzumab vedotinarmen har en mere favorabel prognose end patienterne i komparatorarmen.

Den primære årsag til at patienterne blev vurderet uegnede til stamcelletransplantation adskiller sig også i de to behandlingsarme. Flere blev vurderet uegnet på grund af alder i R-Bendaarmen (47,5 % vs. 32,5 %), mens færre patienter oplevede transplantationssvigt (15,0 % vs. 25,0 %) eller utilstrækkelig respons på behandling forud for transplantation (22,5 % vs. 30,0 %).

Fordelingen af DBLCL-undertyper jf. WHO 2016-klassificeringen er balanceret mellem armene. Der ses en højere andel af patienter med *bulky disease* (37,5 % vs. 25,0 %) og en højere andel med *International Prognostic Index* (IPI)-score på 4-5 (42,5 % vs. 22,5 %) i komparatorarmen, hvilket antyder, at patienterne behandlet med R-Benda alene havde en mere alvorlig sygdom ved baseline.

Den ulige fordeling i baselinekarakteristika øger samlet set risikoen for, at effekten af polatuzumab vedotin er overestimeret. Der fremgår en række justerede analyser i EPAR'en, hvor der er forsøgt korrigeret for forskelle mellem armene for en række prognostiske markører. Disse analyser viser, at flere effektparametre er sensitive overfor justering. For eksempel studiets primære effektparameter *complete response*, hvor effektforskellen ikke længere er statistisk signifikant ved justering for IPI-score. Samme tendens ses ved det kritiske effektmål OS, hvor justering alene for IPI-score eller for en række forskellige variable rykker punktestimatet fra 0,42 (0,24; 0,73) til henholdsvis 0,54 (0,30; 0,97) og 0,56 (0,31; 1,04). Det bør dog bemærkes, at studiets størrelse udfordrer udførsel af en justering for flere prognostiske markører (multivariate analyse). IPI-scoren anses af fagudvalget at være en af de væsentligste markører for patienternes prognose, og den generelle svækkelse af den statistiske styrke, der ses ved de justerede analyser, bidrager med yderligere usikkerheder omkring pålideligheden af data for polatuzumab vedotin.

Det er fagudvalgets vurdering, at anvendelsen af R-Benda i dansk klinisk praksis langt overvejende er til patienter, som vurderes ikke at kunne tolerere mere intensiv behandling. Baggrunden kan være høj alder, mange tidligere behandlinger eller betydende komorbiditet. R-Benda gives i Danmark mere som palliation end med henblik på remission. I studiet kan der således potentielt være en subgruppe af patienter, som man i dansk praksis ville tilbyde et mere intensivt regime, som også ofte er mere toksisk. Det intensive regime ville tilbydes med henblik på at forlænge patienternes levetid, og hvis patienterne i komparatorarmen, der kunne tolerere en mere intensiv behandling, havde fået det, ville effektforskellen mellem polatuzumab vedotin og komparator potentielt fremstå mindre overbevisende. Fagudvalget fremhæver, at evidensgrundlaget for valg af behandling er lavt og i praksis derfor kan variere, også mellem behandlingssteder i Danmark. Der findes således ikke studier, som undersøger de indbyrdes effektforhold mellem de nuværende behandlinger, f.eks. R-Benda vs. kombinationskemoterapi.

På trods af, at en andel af studiepopulationen i komparatorarmen sandsynligvis ville blive tilbudt et mere intensivt behandlingsregime i Danmark, vurderer fagudvalget, at populationen i studiet stemmer så godt overens med den danske population, som behandles med R-Benda, at studiet kan anvendes som grundlag for vurderingen af polatuzumab-R-Benda i forhold til R-Benda.

CORAL EXT-1 og EXT-2

CORAL-studiet er et randomiseret fase III-studie, som undersøger effekten af to forskellige kombinationskemoterapier før stamcelletransplantation i en patientpopulation med recidiverende/refraktært DLBCL, som vurderes egnet til stamcelletransplantation. De to extensionsstudier CORAL EXT-1 og CORAL EXT-2 er to observationelle studier, som følger to separate subgrupper af patienter fra CORAL-studiet.

Fagudvalget har valgt ikke at medtage CORAL-extensionsstudierne i vurderingsrapporten, hvorfor det ikke er muligt at kategorisere en eventuel merværdi af polatuzumab vedotin i forhold til andre behandlinger end R-Benda anvendt i dansk klinisk praksis. De primære årsager til, at fagudvalget ikke medtager CORAL-extensionsstudierne i vurderingen, er forskelle i det prognostisk udgangspunkt hos patienterne, forskellige in- og eksklusionskriterier i studierne og studiernes design.

Nedenfor følger beskrivelser af extensionsstudierne.

CORAL EXT-1 inkluderer 75 patienter, som har oplevet tilbagefald efter stamcelletransplantation i CORAL og er derfor kandidater til tredjelinjebehandling. Den mediane opfølgningstid er 32,8 måneder. Tredjelinjebehandling bestod hovedsagelig af kombinationskemoterapier: ICE-lignende (17,3 %), DHAP-lignende (24 %), gemcitabinindeholdende (28 %), CHOP-lignende (13,3 %) og diverse andre regimer (17,3 %). Omtrent 22 % af patienterne (16/75) fortsætter til stamcelletransplantation efter tredjelinjebehandling.

CORAL EXT-2 inkluderer 203 patienter, som ikke opnåede et tilfredsstillende respons på andenlinjebehandling i CORAL-studiet, eller som af anden årsag ikke kunne gennemføre en planlagt stamcelletransplantation. Der er dermed også tale om patienter, som skal modtage tredjelinjebehandling. Den mediane opfølgningstid er 30,1 måneder. Tredjelinjebehandling bestod hovedsagelig af kombinationskemoterapier: ICE-lignende (18,5 %), DHAP-lignende (18 %), gemcitabinindeholdende (13,8 %), Dexa-BEAM (9 %), CHOP-lignende (8,4%) og diverse andre regimer (31,9 %). Ca. 32 % af patienterne (64/203) fortsætter til stamcelletransplantation efter tredjelinjebehandling.

CORAL-extentionsstudierne illustrerer, at der ikke findes en egentlig standardbehandling hos patienter med recidiverende/refraktært DLBCL, som ikke tåler stamcelletransplantation. De forskellige valg af kombinationskemoterapier, som er afspejlet i studierne, stemmer godt overens med dansk klinisk praksis.

Ansøger har foretaget en narrativ sammenligning mellem CORAL extensionsstudierne og polatuzumab vedotin-R-Bendaarmen fra GO29365-studiet. Fagudvalget vurderer, at patienterne i CORAL-extensionsstudierne generelt har et bedre prognostisk udgangspunkt sammenlignet med GO29365-studiet. Dette baseres på, at en undergruppe modtager højdosisbehandling og transplanteres i CORAL-extensionsstudierne, at populationen i CORAL-extensionsstudierne generelt er yngre og har modtaget færre behandlingslinjer. Dette behæfter en indirekte sammenligning med bias, hvor patienter behandlet med polatuzumab vedotin-R-Benda har det prognostisk dårligste udgangspunkt. Fagudvalget fremhæver, at de vigtigste parametre er, at in- og ekslusionskriterier og studiernes design er forskellige. Som tidligere nævnt har fagudvalget derfor valgt ikke at medtage CORAL-extensionsstudierne i vurderingen.

5.1.2 Databehandling og -analyse

Nedenunder beskriver vi ansøgers datagrundlag, databehandling og analyse for hvert effektmål.

Det oprindeligt indsendte datagrundlag inkluderer en direkte sammenligning mellem polatuzumab vedotin-R-Benda og den ene komparator, R-Benda, som kan danne grundlag for en kategorisering af værdien af polatuzumab vedotin-R-Benda sammenlignet med R-Benda. I henhold til protokollen indeholder ansøgningen direkte sammenligninger for effektmålene OS, PFS og uønskede hændelser. Det indsendte datagrundlag indeholder ikke data for helbredsrelateret livskvalitet. Datagrundlaget er blevet suppleret med

OS- og PFS-data med længere opfølgningstid. Efter opfordring fra Medicinrådet har ansøger også indsendt data for to ukontrollerede arme (arm G og H) i GO29365. Fagudvalget har ikke fundet grundlag for at inkludere de to ukontrollerede arme i vurderingen. Dette skyldes, at der er tale om ukontrollerede studier med kort opfølgningstid og forskelle i baselinekarakteristika. Den korte opfølgningstid udfordrer tolkbarheden af data i forhold til polatuzumab vedotin-R-Benda-armen fra den komparative sammenligning (arm C). Det er i øvrigt vanskeligt at vurdere sammenligneligheden mellem de ukontrollerede arme G og H i forhold til arm C, da det ikke er muligt at vurdere betydningen af de forskelle, som observeres i baselinekarakteristika mellem armene. Der indgår tilsyneladende færre lavrisiko patienter i de ukontrollerede arme og dermed også flere højrisiko patienter end tilfældet er i arm C. Samtidig tyder det på, at der samlet set indgår flere ældre patienter i de ukontrollerede arme, end tilfældet er i arm C.

Som angivet i afsnit 5.1.1 ovenfor har fagudvalget vurderet, at de identificerede studier med kombinationskemoterapi ikke er tilstrækkeligt sammenlignelige med GO29365, og der er derfor ikke foretaget nogen sammenligninger mellem polatuzumab vedotin-R-Benda og kombinationskemoterapi i vurderingsrapporten.

De manglende data bidrager med usikkerheder til vurderingen af lægemidlets samlede værdi.

5.1.3 Evidensens kvalitet

Fagudvalget har vurderet kvaliteten af GO29365-studiet ved brug af GRADE, som er et værktøj til en systematisk og transparent vurdering af evidensens kvalitet. Nedenfor følger en beskrivelse af vurderingen af de væsentligste domæner for hvert klinisk spørgsmål. Den fuldstændige GRADE-vurdering og begrundelserne er samlet i en GRADE-profil (bilag 11). Kvaliteten af det observationelle data fra de to CORAL-kohorter er ikke vurderet. Evidensens kvalitet samlet vurderet for det kliniske spørgsmål er meget lav.

Der er risiko for bias i GO29365-studiet, hvilket der skal tages højde for. Det fremgår ikke tydeligt, hvordan randomiseringen er foregået, og der observeres ubalance på flere betydende baselinekarakteristika. Samtidig er der tale om et ikkeblindet studie, som kan medføre risiko for bias for visse effektmål.

Evidensens kvalitet er overordnet nedjusteret for inkonsistens idet der blot forelægger et mindre sammenlignende studie. Der er desuden nedjusteret for indirekthed, idet fagudvalget vurderer, at der i studiepopulationen potentielt indgår patienter, som man i dansk praksis ville tilbyde et mere intensivt regime.

5.1.4 Effektestimater og kategorier

I tabellen herunder fremgår de absolutte og relative effektforskelle, de foreløbige og aggregerede kategorier, den samlede kategori og den samlede kvalitet af evidensen for det kliniske spørgsmål, der vedrører sammenligningen mellem polatuzumab vedotin-R-Benda overfor R-Benda. Sammenligningen mellem polatuzumab vedotin-R-Benda overfor kombinationsterapi er i det følgende ikke foretaget, eftersom CORAL-extensionsstudierne ikke er medtaget i vurderingen.

Tabel 4. Resultater for klinisk sammenligningen mellem polatuzumab-R-Benda og R-Benda

Effektmål	Måleenhed (MKRF)	Vigtighed	Forskel i absolutte tal		Forskel i relative tal		Aggregeret værdi for effektmålet
			Forskel (95 % CI)	Foreløbig værdi	Forskel (95 % CI)	Foreløbig værdi	
Samlet overlevelse (OS)	Median overlevelse i antal måneder (6 mdr.)	Kritisk	7,7	Kan ikke kategoriseres*	0,40 (0,2-0,7)£	Stor merværdi¥	Kan ikke kategoriseres
	Andel af patienter, der opnår 2-årsoverlevelse (10 %-point)		21,2	Kan ikke kategoriseres*			
Helbredsorienteret livskvalitet	Gennemsnitlig ændring fra baseline på SF-36 til efter endt behandling (5 point)	Vigtig	Intet data	Kan ikke kategoriseres**	Intet data	Kan ikke kategoriseres**	Kan ikke kategoriseres
	Gennemsnitlig ændring fra baseline på SF-36 til efter endt opfølgning (5 point)						
	Gennemsnitlig ændring fra baseline på FACTLym til efter endt behandling (4 point)						
	Gennemsnitlig ændring fra baseline på FACTLym til efter endt opfølgning (4 point)						
Progressionsfri overlevelse (PFS)	Median PFS i antal måneder (6 mdr.)	Vigtig	5,5£	Kan ikke kategoriseres*	0,38 (0,22; 0,65)£	Stor merværdi¥	Kan ikke kategoriseres
	Andel af patienter, der opnår 2-års PFS (10%-point)		19,3£	Kan ikke kategoriseres*			
Uønskede hændelser	Andel frafald pga. uønskede hændelser (behandlingsophør) (10 %-point)	Vigtig	15,7 (-2,7-32,4)	Kan ikke kategoriseres***	2,02 (0,86-4,75)	Kan ikke kategoriseres***	Kan ikke kategoriseres
	Andel patienter med uønskede hændelser grad 3 og grad 4 (10 %-point)		12,6 (-5,0-30,0)	Kan ikke kategoriseres***	1,18 (0,93-1,49)	Kan ikke kategoriseres***	
Samlet kategori for lægemidlets værdi		Kan ikke kategoriseres					
Kvalitet af den samlede evidens		Meget lav					

CI = konfidensinterval, HR = Hazard ratio, OR = Odds ratio, RR = relativ risiko *Der kan ikke beregnes et konfidensinterval for den absolutte forskel på to mediane værdier. ** Der er ikke data, der kan danne grundlag for en kategorisering. ***Usikkerheden omkring punktestimatet er så stor, at det indeholder både negativ og positiv værdi. £ Data fra Clinical Study Report, juni 2020. ¥Kategoriseringen af de foreløbige værdier tager ikke højde for ubalance i prognostiske parametre ved baseline.

Overlevelse (kritisk)

Sammenligningen med R-Benda

Fagudvalget ønskede det kritiske effektmål OS opgjort som median OS og en 2-års OS-rate. Det fremsendte data fremgår af tabel 5 (suppleret med data fra *Clinical Study Report, juni 2020*). Medianen for OS-data er nået ved længst mulig opfølgningstid. 2-års OS-raterne er baseret på data fra få patienter, og der er mange censureringer i polatuzumab vedotin-R-Bendaarmen efter 18 måneder. Fagudvalget finder dog, at det er betydende, at der tilsyneladende indfinder sig et plateau på 'halen' af Kaplan-Meier-kurven, hvilket indikerer nogen pålidelighed af effektestimatet. Usikkerhederne i det lille datasæt er dog fortsat store.

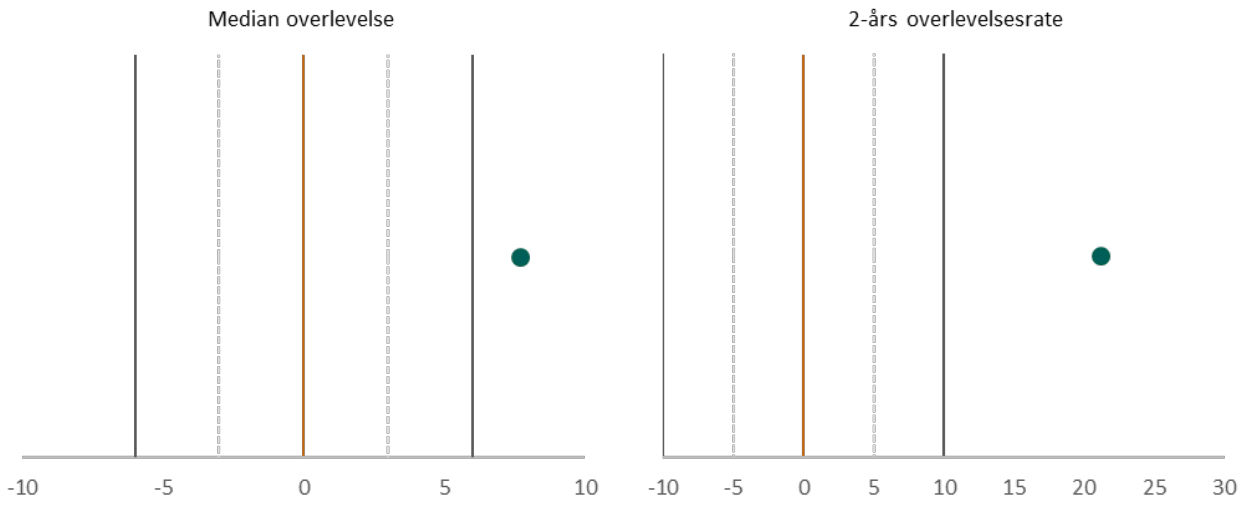
Tabel 5: Data for median overlevelse og 2-årsoverlevelse

	GO29365	
	Polatuzumab vedotin-R-Benda	R-Benda
Medianoverlevelse, måneder	12,4 (9,0-32)	4,7 (3,7-8,3)
Forskel, måneder	7,7	
HR for overlevelse	0,40 (0,2-0,7)	
2-års overlevelsesrate, %	38,2 (22,5-53,9)	17,0 (3,6-30,4)
Forskel, %-point	21,2	

De absolutte forskelle er afbildet i figur 1.

Punktestimatet for den absolutte forskel i median OS afspejler en klinisk relevant effektforskel, da forskellen på 7,7 måneder er større end den mindste klinisk relevante forskel på 6 måneder. Beregninger af konfidensintervaller for forskelle i median OS er ikke veldefinerede, hvorfor den foreløbige værdi ikke kategoriseres.

Punktestimatet for den absolutte forskel mellem OS-raterne efter 2 år afspejler også en klinisk relevant forskel, da forskellen på 21,2 %-point er større end den mindste klinisk relevante forskel på 10 %-point. Der er ikke noget konfidensinterval omkring forskellen på, hvorfor den foreløbige værdi ikke kan kategoriseres.



Figur 1. Punktestimat og 95 % konfidensinterval for den absolutte forskel for medianoverlevelse og 2-års overlevelsesrate. De optrukne linjer indikerer den mindste klinisk relevante forskel. De stiplede linjer indikerer grænserne for Medicinrådets kategorier svarende til halvdelen af den mindste klinisk relevante forskel.

Den relative effektforskel på effektmålet OS er angivet ved en hazard ratio baseret på Kaplan Meier-kurverne. Baseret på den relative effektforskel HR 0,40 (0,2-0,7) har polatuzumab vedotin-R-Benda en foreløbig stor merværdi. Kategoriseringen af de foreløbige kategorier er baseret på de ujusterede estimater, og tager dermed ikke højde for den før omtalte usikkerhed grundet den ulig fordeling af baseline karakteristika.

I den aggregerede værdi for effektmålet OS tager fagudvalget højde for usikkerheden i, at der er tale om et meget lille studie og den ubalance, som observeres i flere betydende prognostiske parametre ved baseline. De justerede analyser for OS viser, at effektforskellen er påvirkelig overfor justering. Fagudvalget vurderer, at usikkerhederne i datagrundlaget er så store, at den aggregerede værdi for effektmålet OS jf. Medicinrådets metoder ikke kan kategoriseres.

Livskvalitet (vigtigt)

Fagudvalget ønskede livskvalitet målt med enten SF-36 eller FACT-LYM og ønskede at se forskelle i ændringer fra baseline opgjort efter endt behandling og efter endt opfølgning.

I GO29365 er livskvalitet belyst med det patientrapporterede effektmål TNAS (therapy-induced neuropathy assessment scale), som ikke måler livskvalitet, men neuropati som komplikation til kræftsygdomme eller kræftbehandling. Fagudvalget vurderer ikke, at TNAS kan anvendes som et mål for livskvalitet.

Lægemidlets værdi kan ikke kategoriseres for effektmålet livskvalitet på baggrund af det indsendte data. Det manglende data bidrager med yderligere usikkerheder til vurderingen af lægemidlets samlede værdi.

Progressionsfri overlevelse (vigtigt)

Fagudvalget ønskede at vurdere effekten på PFS som et mål for graden og længden af sygdomskontrol, som opnås under og efter behandling. Længden af den progressionsfri periode for patienter, der behandles med nuværende behandlingsmuligheder, er meget varierende, dog oftest kun af måneders varighed. Omkring 10 % af den definerede population overlever mindst 2 år med nuværende behandlingsmuligheder. Fagudvalget ønskede derfor PFS opgjort både som median PFS og 2-års PFS-rate.

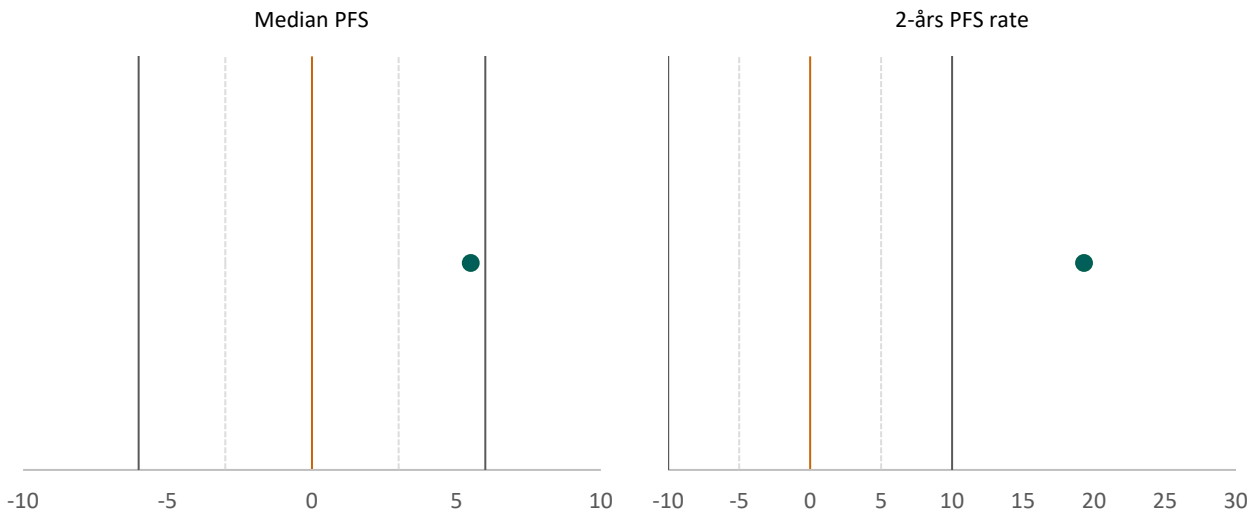
Sammenligning med R-Benda

Ansøger har indsendt data for PFS fra den direkte sammenligning med R-Benda i hovedpublikationen for GO29365, som er suppleret med data fra *Clinical Study Report, juni 2020*. Data for PFS vurderes at være pålideligt, men 2-års PFS-raterne er forbundet med usikkerhed, da de er baseret på få patienter.

Punktestimatet for forskellen i median PFS afspejler ikke en klinisk relevant forskel, da punktestimatet på 5,5 måneder er mindre end den mindste klinisk relevante forskel på 6 måneder. Da der ikke er et konfidensinterval omkring punktestimatet, kan den foreløbige værdi ikke kategoriseres.

Punktestimatet for forskellen i 2-års PFS-rate afspejler en klinisk relevant forskel, da punktestimatet på 19,3 %-point er større end den mindste klinisk relevante forskel på 10 %-point. Da der ikke er et konfidensinterval omkring punktestimatet, kan den foreløbige værdi ikke kategoriseres.

De absolutte forskelle af afbildet i figur 2.



Figur 2. Punktestimat og 95 % konfidensinterval for den absolutte forskel for PFS. De optrukne linjer indikerer den mindste klinisk relevante forskel. De stiplede linjer indikerer grænserne for Medicinrådets kategorier svarende til halvdelen af MKRF.

Det relative effektestimat HR 0,38 (0,22-0,65) kategoriserer polatuzumab vedotin-R-Benda med en foreløbig stor merværdi.

Samlet set vurderer fagudvalget, at polatuzumab vedotin-R-Benda på tværs af absolutte og relative forskelle jf. Medicinrådets metoder ikke kan kategoriseres for effektmålet PFS.

Uønskede hændelser (vigtigt)

Fagudvalget ønskede at belyse effektmålet uønskede hændelser ved at vurdere behandlingsophør/frafald på grund af uønskede hændelser og andelen af patienter med ≥ 1 alvorlige uønskede hændelser grad 3 og 4. Derudover ønskede fagudvalget at foretage en narrativ vurdering af følgende betydende uønskede hændelser under og efter behandling:

- Neuropati
- infektioner, herunder særskilt pneumonier
- infusionsrelaterede hændelser
- immunologiske hændelser

Sammenligning med R-Benda

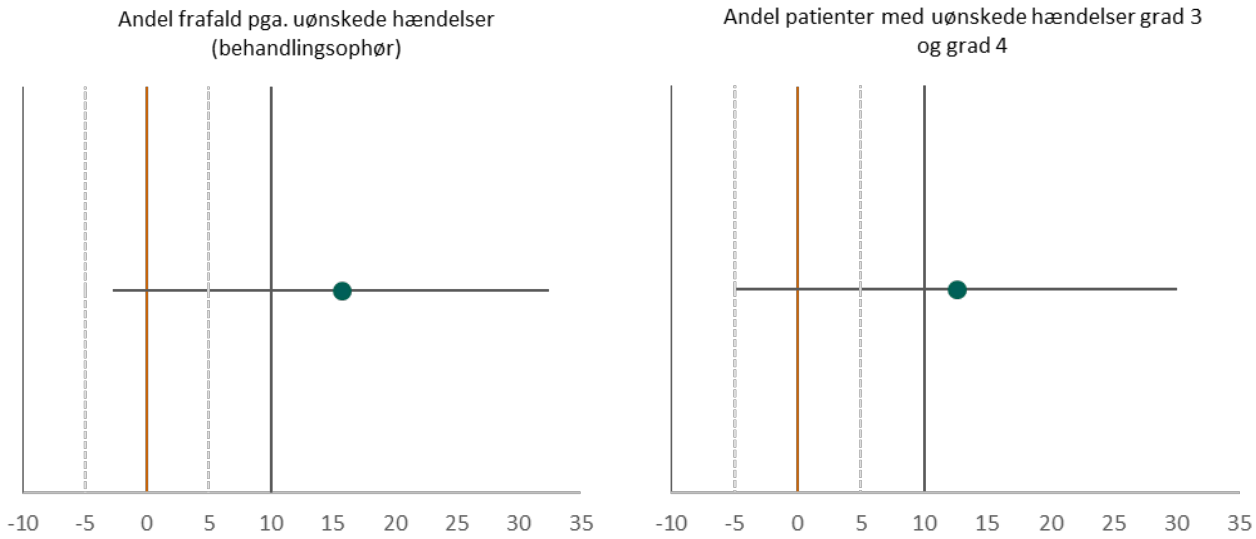
Ansøger har indsendt det efterspurgte data fra den direkte sammenligning med R-Benda i GO29365-studiet.

Andelen, der ophørte behandling, var 31,1 % i polatuzumab vedotin-R-Bendaarmen og 15,4 % i R-Bendaarmen.

Punkestimatet for den absolutte forskel i behandlingsophør tyder på en negativ klinisk relevant effektforskel, da punktestimatet på 15,7 %-point overstiger den mindste klinisk relevante forskel på 10 %-point. Konfidensintervallet indeholder dog ingen forskel (= 0). Derfor kan den foreløbige værdi ikke kategoriseres jf. Medicinrådets metoder. Den absolutte forskel er afbildet i figur 3.

Andelen af patienter, der oplevede ≥ 1 uønsket hændelse af grad 3 og 4, var 84,4 % i polatuzumab-vedotin-R-Bendaarmen og 71,8 % i R-Bendaarmen.

Punktestimatet for den absolutte forskel i andelen af patienter, der oplever ≥ 1 uønsket hændelse af grad 3 og 4, afspejler en negativ klinisk relevant forskel, da punktestimatet på 12,6 %-point overstiger den mindste klinisk relevante forskel på 10 %-point. Den nedre grænse i konfidensintervallet ligger tættere på en positiv klinisk relevant forskel end på en negativ klinisk relevant forskel, og den foreløbige værdi kan derfor ikke kategoriseres. Den absolutte forskel er afbildet i figur 3.



Figur 3. Punktestimat og 95 % konfidensinterval for de absolutte forskelle for uønskede hændelser. De optrukne linjer indikerer den mindste klinisk relevante forskel. De stiplede linjer indikerer grænserne for Medicinrådets kategorier svarende til halvdelen af MKRF.

Den relative effektforskel for behandlingsophør kan ikke kategoriseres, da konfidensintervallet indeholder både negativ og positive værdier. Det samme gør sig gældende for effektforskellen på andelen af patienter, der oplever ≥ 1 uønsket hændelse af grad 3 og 4.

Da ingen af de foreløbige værdier kan kategoriseres, kan den aggregerede værdi for effektmålet uønskede hændelser heller ikke kategoriseres jf. Medicinrådets metoder.

Til den kvalitative gennemgang har ansøger indsendt data for de efterspurgte hændelser. Data er gengivet i tabel 6.

Tabel 6: Data for andelen (%), der oplever udvalgte uønskede hændelser i GO29365.

	Polatuzumab vedotin-R-Benda (n = 45)	R-Benda (n = 39)
Neuropati	40 %	7,7 %
Infektioner	53, 3 %	51,3 %
Grad 3/4	23,1 %	20,5 %
Pneumoni med død til følge	4,4 %	2,6 %
Infusionsrelaterede reaktioner	33,3 %	23,1 %
Immunologiske hændelser	7,1 %	i.o.
i.o.: ikke oplyst		

Neuropati optrådte væsentligt hyppigere hos patienter behandlet med polatuzumab vedotin-R-Benda (40,0 % vs. 7,7 %). Ingen tilfælde af neuropati ansås for at være alvorlige, have død til følge eller medførte

behandlingsophør. Alle neuropatier var grad 1 og 2 i begge arme. Den øgede forekomst af neuropati var forventeligt ud fra fagudvalgets erfaring med andre antistoflægemiddelkonjugater. Vedvarende neuropati kan dog ikke udelukkes, og dette kan være til gene for patienterne i et omfang, som kan påvirke livskvaliteten væsentligt.

Forekomsten af infektioner var ifølge EPAR'en sammenlignelig imellem polatuzumab vedotin-R-Bendaarmen og komparator (53,3 % mod 51,3 %). De fleste hændelser var grad ≥ 3 i begge arme og hyppigheden af alvorlige infektioner var også sammenlignelig mellem arme (28,9 % mod 30,8 %).

Ifølge EPAR'en var forekomsten af infusionsrelaterede reaktioner (inden for 24 timer efter infusion) højere i polatuzumab vedotin-R-Bendaarmen (33,3 % mod 23,1 %).

Vedrørende immunologiske hændelser angives i den endelige ansøgning antistofudvikling overfor polatuzumab vedotin hos 7,1 % (3/42 evaluerbare patienter), hvilket af fagudvalget ikke anses for betydende.

Fagudvalget har suppleret effektmålet uønskede hændelser med en klinisk vurdering af toksiciteten ved behandling med polatuzumab vedotin-R-Benda. Data tyder på en moderat overvægt af toksicitet og behandlingsrelaterede behandlingsophør i polatuzumab vedotin-R-Bendaarmen. Det er uklart, om dette har haft indflydelse på mortaliteten. Ifølge EPAR'en er der dog ikke væsentlig forskel mellem dødsfald forårsaget af uønskede hændelser mellem grupperne. En øget forekomst af grad 3-4 uønskede hændelser og præmaturt behandlingsophør er primært betinget af hæmatologisk toksicitet (neutropeni især). Fagudvalget vurderer, at den observerede hæmatologisk toksicitet var håndterbar, bortset fra at nogle patienter måtte stoppe med behandlingen. I klinisk praksis vil man ofte være lidt mere tålmodig inden behandlingen stoppes – især hvis den ser ud til at virke.

5.1.5 Fagudvalgets konklusion

Fagudvalget vurderer, at den samlede værdi af polatuzumab vedotin sammenlignet med enkeltstofkemoterapi og kombinationskemoterapi til patienter med recidiverende/refraktært diffust storcellet B-cellelymfom, der ikke er kandidater til hæmatopoietisk stamcelletransplantation, ikke kan kategoriseres i henhold til Medicinrådets metoder.

Sammenligningen med R-Benda
For det vigtige effektmål uønskede hændelser antyder data, at polatuzumab vedotin-R-Benda er forbundet med en moderat øget toksicitet, som hovedsageligt er af hæmatologisk karakter. Fagudvalget vurderer, at de hæmatologiske uønskede hændelser er håndterbare.

Der er ikke data for det vigtige effektmål livskvalitet, hvilket bidrager til usikkerhed i vurderingen af lægemidlet, idet det ikke er muligt at afklare, om den potentielt øgede toksicitet, herunder særligt den øgede forekomst af neuropati, påvirker patienternes livskvalitet.

Fagudvalget finder, at effektestimaterne for det kritiske effektmål OS og det vigtige effektmål PFS indikerer, at der kan være en klinisk relevant forskel til fordel for polatuzumab vedotin-R-Benda. Især fremhæves, at effektstørrelserne i polatuzumab vedotin-R-Bendaarmen er bemærkelsesværdigt høje. F.eks. for 2-års OS er effektstørrelsen væsentlig højere, end man ville forvente med nuværende standardbehandling i dansk klinisk praksis. Herudover er der en bemærkelsesværdig høj andel af patienter, som er uden progression efter 2 år.

Fagudvalget finder dog, at der er en række forhold, som mindsker pålideligheden af effektestimaterne betragteligt. Dette inkluderer en ulige fordeling af baselinekarakteristika, herunder særligt forskelle i væsentlige prognostiske variable, som alle falder ud til fordel for polatuzumab vedotin. Sammen med studiets størrelse, der kun inkluderer 40 patienter i hver arm, giver det anledning til væsentlige usikkerheder om effekternes reelle størrelse og usikkerhed om, hvorvidt randomiseringen i studiet er vellykket i forhold til at give sammenlignelige arme. På denne baggrund vurderer fagudvalget, at datagrundlaget samlet set ikke er

pålideligt til at kategorisere den samlede værdi af polatuzumab vedotin. Derfor vurderer fagudvalget, at polatuzumab vedotin i kombination med R-Benda sammenlignet med R-Benda ikke kan kategoriseres i henhold til Medicinrådets metoder.

Sammenligningen med kombinationskemoterapi
Fagudvalget har ikke fundet grundlag for at foretage en kategorisering af polatuzumab vedotin-R-benda på baggrund af de studier, som ansøger har identificeret med kombinationskemoterapi. Fagudvalget finder heller ikke grundlag for at ekstrapolere effekten af polatuzumab vedotin-R-Benda overfor R-Benda til en effekt af polatuzumab vedotin-R-Benda overfor kombinationskemoterapi. Værdien af polatuzumab vedotin-R-Benda overfor kombinationskemoterapi kan derfor ikke kategoriseres jf. Medicinrådets metoder.

6 Andre overvejelser

For at vurdere om studiepopulationen fra GO29365 er sammenlignelig med patienter i dansk klinisk praksis, har fagudvalget efterspurgt data på DLBCL-undertyper fra studiet, som ansøger har leveret.

Fordelingen af DBLCL-undertyper vurderes at være ligeligt fordelt mellem de to behandlingsarme og giver ikke anledning til yderligere overvejelser fra fagudvalget.

7 Relation til behandlingsvejledning

Der er ingen relevant behandlingsvejledning udarbejdet af Medicinrådet.

8 Referencer

1. Dansk Lymfomgruppe. Kliniske retningslinjer for diffust storcellet b-celle-lymfom. 2019.
2. Friedberg JW. Relapsed/refractory diffuse large B-cell lymphoma. I: ASH Education Program Book 20111. 2011. s. 498–505.
3. Green TM, Young KH, Visco C, Xu-Monette ZY, Orazi A, Go RS, et al. Immunohistochemical double-hit score is a strong predictor of outcome in patients with diffuse large B-cell lymphoma treated with rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone. J Clin Oncol. 2012;30(28):3460–7.
4. Copie-Bergman C, Cuillière-Dartigues P, Baia M, Briere J, Delarue R, Canioni D, et al. MYC-IG rearrangements are negative predictors of survival in DLBCL patients treated with immunochemotherapy: A GELA/LYSA study. Blood. 2015;126(22):2466–74.
5. Lenz G, Rutherford SC, Davies A, Zinzani PL, Salles G et al. The Burden of Relapsed/Refractory (R/R) Diffuse Large B-Cell Lymphoma (DLBCL): A Systematic Literature Review (SLR). Blood, 132(Suppl 1), 2241.
6. Sehn LH, Herrera AF, Flowers CR, Kamdar MK, McMillan A, Hertzberg M, et al. Polatuzumab Vedotin in Relapsed or Refractory Diffuse Large B-Cell Lymphoma. J Clin Oncol. 2020;38(2):155–65.
7. Van Den Neste E, Schmitz N, Mounier N, Gill D, Linch D, Trneny M, et al. Outcomes of diffuse large B-cell lymphoma patients relapsing after autologous stem cell transplantation: an analysis of patients included in the CORAL study. Bone Marrow Transplant. 2017;52(2):216–21.
8. Van Den Neste E, Schmitz N, Mounier N, Gill D, Linch D, Trneny M, et al. Outcome of patients with relapsed diffuse large B-cell lymphoma who fail second-line salvage regimens in the International CORAL study. Bone Marrow Transplant. 2016;51(1):51–7.

9 Sammensætning af fagudvalg og kontaktinformation til Medicinrådet

Medicinrådets fagudvalg vedrørende lymfekræft (lymfomer)

Formand	**Indstillet af**
Lars Møller Pedersen Forskningsansvarlig overlæge	Lægevidenskabelige Selskaber og udpeget af Region Hovedstaden
Medlemmer	**Udpeget af**
Jakob Madsen Overlæge	Region Nordjylland
Paw Jensen Ledende overlæge	Region Nordjylland
Peter Kamper Overlæge, ph.d.	Region Midtjylland
Ida Blok Sillesen Afdelingslæge	Region Midtjylland
Jacob Haaber Christensen Overlæge, ph.d.	Region Syddanmark
Dorte Maegaard Tholstrup Afdelingslæge	Region Sjælland
Michael Pedersen Overlæge	Region Hovedstaden
Michael Boe Møller Overlæge	Dansk Patologiselskab
Kathrine Bruun Svan Farmaceut	Dansk Selskab for Sygehusapoteksledelse
Kenneth Skov Afdelingslæge	Dansk Selskab for Klinisk Farmakologi
Jørn Søllingvrå 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

10 Versionslog

Version	**Dato**	***Æ*ndring**
1.1	27. januar 2021	Godkendt af Medicinrådet.

11 Bilag 1: Evidensens kvalitet

11.1 Cochrane, Risk of Bias

Vurdering af risiko for bias ved Cochranes RoB 2.0 assessment tool.

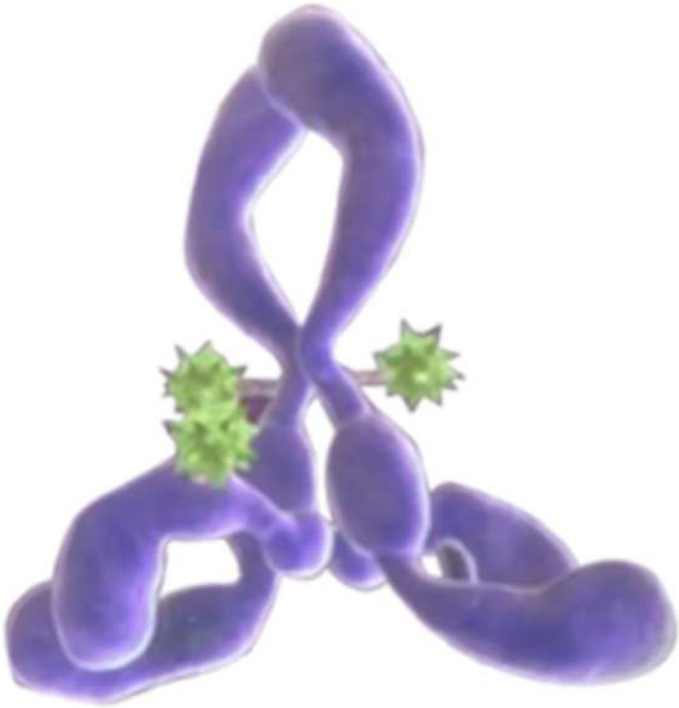
	Risiko for bias i randomiserings-processen	**Risiko for bias grundet afvigelser fra tilsigtet intervention** **(effekt af tildeling til intervention)**	**Manglende data for effektmål**	**Risiko for bias ved indsamlingen af data**	**Risiko for bias ved udvælgelse af resultater der rapporteres**	**Overordnet risiko for bias**
GO29365	*Høj*	*Forbehold*	*Lav*	*Forbehold*	*Forbehold*	*Høj*

11.2 GRADE-profil

Kvalitetsvurdering							Antal patienter		Effekt		Kvalitet (GRADE)	Kritisk / vigtigt
Antal studier	**Studiedesign**	**Risk of bias**	**Inkonsistens**	**Indirekthed**	**Unøjagtighed**	**Andre overvejelser**	**Pola-R-Benda**	**R-Benda**	**Relativ [95 % CI]**	**Absolut 95 % CI]**		
Samlet overlevelse (OS); median overlevelse i antal måneder/andel af patienter, der opnår 2-års overlevelse												
1	Randomiseret forsøg	Alvorlig[c,d]	Alvorlig[a]	Alvorlig[b]	Ikke alvorlig	Ingen	40	40	HR: 0,40 [0,2; 0,7]	7,7 måneder 21,2 %-point	⊕◯◯◯ MEGET LAV	KRITISK
Helbredsorienteret livskvalitet												
0	-	-	-	-	-	-	-	-	-	-	-	VIGTIGT
Progressionsfri overlevelse (PFS); median PFS i antal måneder/andel af patienter, der opnår 2-års progressionsfri overlevelse												
1	Randomiseret forsøg	Alvorlig[d]	Alvorlig[a]	Alvorlig[b]	Ikke alvorlig	Ingen	40	40	HR: 0,38 [0,22; 0,65]	5,5 måneder 19,3 %-point	⊕◯◯◯ MEGET LAV	VIGTIGT
Uønskede hændelser, Andel frafald pga. uønskede hændelser												
1	Randomiseret forsøg	Alvorlig[d,e]	Alvorlig[a]	Alvorlig[b]	Alvorlig[f]	Ingen	14/45 (31 %)	6/39 (15 %)	RR: 2,02 [0,86; 4,75]	15,7 %-point [-2,7; 32,4]	⊕◯◯◯ MEGET LAV	VIGTIGT
Uønskede hændelser, Andel patienter med uønskede hændelser grad 3 og grad 4												
1	Randomiseret forsøg	Alvorlig[d,e]	Alvorlig[a]	Alvorlig[b]	Alvorlig[f]	Ingen	38/45 (84 %)	28/39 (72 %)	RR: 1,18 [0,93; 1,49]	12,6 %-point [-5,0; 30,0]	⊕◯◯◯ MEGET LAV	VIGTIGT

CI: Confidence interval; HR: Hazard ratio; RR: Risk ratio.
a. Der nedgraderes ét niveau for inkonsistens, da der kun foreligger data fra et studie.
b. Der er indirekthed i forhold til den danske population pga. studiets in-/eksklusionskriterier.
c. Der er en del censureringer, som kan påvirke effektestimatet.
d. Risiko for bias i randomiserings-processen.
e. Der er tale om et open-label-studie, som kan påvirke registrering af uønskede hændelser.
f. Der nedgraderes evidensens kvalitet ét niveau pga. unøjagtighed, da usikkerheden om det relative effektestimat kan føre til forskellige konklusioner.

APPLICATION FOR THE ASSESSMENT OF POLIVY (POLATUZUMAB VEDOTIN) IN COMBINATION WITH BENDAMUSTINE AND RITUXIMAB FOR THE TREATMENT OF ADULT PATIENTS WITH RELAPSED/REFRACTORY DIFFUSE LARGE B-CELL LYMPHOMA WHO ARE NOT CANDIDATES FOR HAEMATOPOIETIC STEM CELL TRANSPLANT



Polatuzumab vedotin

Contents

1 Basic information 3
2 Abbreviations 4
3 Summary 5
4 Introduction 7
5 Literature search 10
5.1 Relevant studies 12
5.2 Main characteristics of included studies 13
6 Clinical questions 15
6.1 Clinical question 1 15
6.1.1 Presentation of the relevant studies 15
6.1.2 Results per study 19
6.1.3 Comparative analyses 23
7 References 28
8 Appendices 30
8.1 Literature search 30
8.2 Main characteristics of included studies 36
8.3 Results per study 41

1 Basic information

Table 1. Contact information	
Name	Anette Bøgsted
Title	Scientific Advisor
Area of responsibility	Haematology
Phone	+45 21 21 60 96
E-mail	anette.bogsted@roche.com
Name	Pavika Jain Lyngsie
Title	Value Demonstration Manager
Area of responsibility	Market Access
Phone	+ 45 42 14 29 38
E-mail	pavika.jain@roche.com
Name	Tobias Justesen
Title	Junior Scientific Advisor
Area of responsibility	Haematology
Phone	+ 45 30 23 92 95
E-mail	tobias.justesen@roche.com

Table 2. Overview of the pharmaceutical	
Proprietary name	Polivy®
Generic name	Polatuzumab vedotin
Marketing authorization holder in Denmark	Roche a/s
ATC code	L01XC37
Pharmacotherapeutic group	Other antineoplastic agents, monoclonal antibodies
Active substance(s)	Polatuzumab vedotin
Pharmaceutical form(s)	Powder for concentrate for solution for infusion
Mechanism of action	Polatuzumab vedotin is a CD79b-targeted antibody-drug conjugate that preferentially delivers a potent anti-mitotic agent (monomethyl auristatin E, or MMAE) to B-cells, which results in the killing of malignant B-cells. The molecule consists of MMAE covalently attached to a humanized immunoglobulin G1 monoclonal antibody via a cleavable linker. The monoclonal antibody binds with high affinity and selectivity to CD79b, a cell surface component of the B-cell receptor. CD79b expression is restricted to normal cells within the B-cell lineage (with the exception of plasma cells) and malignant B-cells; it is expressed in > 95% of diffuse large B-cell lymphoma. Upon binding CD79b, polatuzumab vedotin is rapidly internalized and the linker is cleaved by lysosomal proteases to enable intracellular delivery of MMAE. MMAE kills dividing cells by inhibiting cell division and inducing apoptosis.
Dosage regimen	The recommended dose of polatuzumab vedotin is 1.8 mg/kg given every 21 days in combination with bendamustine and rituximab for 6 cycles. Polatuzumab vedotin, bendamustine and rituximab can be administered in any order on Day 1 of each cycle. When administered with polatuzumab vedotin, the recommended dose of

	bendamustine is 90 mg/m^2/day on Day 1 and Day 2 of each cycle and the recommended dose of rituximab is 375 mg/m^2 on Day 1 of each cycle.
Therapeutic indication relevant for assessment (as defined by the European Medicines Agency)	Polatuzumab vedotin in combination with bendamustine and rituximab is indicated for the treatment of adult patients with relapsed/refractory diffuse large B-cell lymphoma (DLBCL) who are not candidates for haematopoietic stem cell transplant.
Other approved therapeutic indications	N/A
Handling	Polatuzumab vedotin should be kept in a refrigerator (2-8 °C) in the outer carton to protect from light and should not be frozen or shaken. If stored correctly, an unopened vial has a shelf life of 2 years.
Will dispensing be restricted to hospitals?	Yes
Combination therapy and/or co-medication	Bendamustine Rituximab
Packaging, types, sizes/number of units, and concentrations	20 mL vial (colorless glass), 1 vial per package, 140mg polatuzumab vedotin
Orphan drug designation	Yes (designated EU/3/18/2013 on 16 April 2018)
Other considerations	N/A

2 Abbreviations

ADC	antibody-drug conjugate
ADR	adverse drug reactions
AE	adverse event
BEAM	carmustine, etoposide, cytarabine, melphalan
BR	bendamustine + rituximab
BG	bendamustine + obinutuzumab
BSC	best supportive care
CMA	Conditional Marketing Authorization
COPE	cyclophosphamide, vincristine, cisplatin, and etoposide
CSR	clinical study report
CR	complete response
CT	computed tomography
CVP	cyclophosphamide, vincristine, and prednisone
DHAP	dexamethasone, cytarabine, and cisplatin
DLBCL	Diffuse Large B-cell Lymphoma
DMC	Danish Medicine Council
DOR	duration of response
ECOG	Eastern Cooperative Oncology Group
EPAR	European Public Assessment Report
EMA	European Medicines Agency
FL	follicular lymphoma
GDP	gemcitabine, dexamethasone, cisplatin
GemOx	gemcitabine and oxaplatin
HRQoL	health-related quality of life
HSCT	haematopoietic stem cell transplant
IRC	Independent Review Committee
ITT	intent-to-treat
Len	lenalidomide
LYFO	Danish National Lymphoma Registry
MMAE	monomethyl auristatin E
N/A	Not applicable
NHL	non-Hodgkin's lymphoma
OS	overall survival
Pola	Polatuzumab vedotin
PET	positron emission tomography
PFS	progression-free survival

PN	peripheral neuropathy
PREBen	pixantrone, rituximab, etoposide, and bendamustine
PRO	patient-reported outcome
R-CHOP	rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone
R-ICE	rituximab + ifosfamide, carboplatin, etoposide
RKKP	National Clinical Registries ("Regionernes Kliniske Kvalitetsudviklingsprogram")
R/R	relapsed/refractory
SAE	serious adverse event
SoC	standard of care
SmPC	summary of Product Characteristics
TNAS	treatment-induced neuropathy assessment scale
2L	second line

3 Summary

This application concerns Polivy® (polatuzumab vedotin) in combination with bendamustine and rituximab (BR) for the treatment of adult patients with relapsed/refractory diffuse large B-cell lymphoma (DLBCL) who are not candidates for haematopoietic stem cell transplant.

Aim: To assess the added clinical value of Polivy® (polatuzumab vedotin) in combination with bendamustine and rituximab compared with bendamustine and GDP, GemOx or ICE in combination with rituximab in adult patients with relapse or refractory diffuse large B-cell lymphoma who are not candidates for haematopoietic stem cell transplant.

Methods: In accordance with the protocol defined by the Danish Medicine Council (DMC) [1], the evaluated outcome measures are:
Critical outcome/s:

- Overall survival (median OS and 2-year OS rate)

Important outcome/s:

- Health related quality of life (SF-36 and FACT-Lym)
- Progression free survival (median PFS and 2-year PFS rate)
- Adverse events (proportion of patients who discontinued treatment due to adverse events and proportion of patients experiencing ≥ 1 grade 3 or 4 adverse events)

As defined in the protocol by the Danish Medicine Council the relevant comparator for the subpopulation of patients suited to single agent chemotherapy is bendamustine and rituximab (BR regimen). For this subpopulation, only one publication [2] was identified and deemed relevant for the comparison of Polivy® (polatuzumab vedotin).

As defined in the protocol by the Danish Medicine Council, the relevant comparators in the subpopulation suited for treatment with a combination chemotherapy is one of three combination chemotherapy regimens (rituximab and GDP/GemOx/ICE). In this subpopulation, all three treatment regimens are considered to be clinically equivalent regimens and the DMC encouraged the applicant to choose the comparator that would yield the optimal basis for a comparison. The full text reading of the relevant studies identified, in the literature search, revealed that R-ICE was the comparator that yielded the best basis for the comparative analysis. However, in a setting of no large or randomized studies with a standard treatment, an indirect trial comparison (ITC) was not possible. For this reason the CORAL EXT-1 [3] and

CORAL EXT-2 [4] studies are relevant publications based on the patient populations and relatively large number of patients (total of 278) for the combination chemotherapy subpopulation.

Results:

1. **For subpopulation of patients suited to single agent chemotherapy:**

Overall survival: Median overall survival was 12.4 months in the polatuzumab vedotin + BR arm and 4.7 months in the BR arm (HR 0.42; CI 0.24-0.75). 2-year overall survival rate was 38.2% (CI 22.5%-53.9%) in the polatuzumab vedotin + BR arm and 17.0% (CI 3.6%-30.4%) in the BR arm.

Health related quality of life: No data on SF-36 or FACT-Lym was available. PRO data was reported on therapy-induced neuropathy scale (TNAS). The mean scores rarely exceeded 3.0 during treatment in the polatuzumab vedotin + BR arm, indicating that overall, patients perceived PN symptoms to be mild. Trends for the BR arm across all items were relatively flat.

Progression free survival: Progression free survival by independent review committee (IRC) was 9.5 months in the polatuzumab vedotin + BR arm and 3.7 months in the BR arm (HR 0.36; CI 0.21-0.63). In the same subpopulation, 2-year progression free survival rate was 31.3% (CI 16.6%-46.5%) in the polatuzumab vedotin + BR arm and 4.9% (CI 0%-13.4%) in the BR arm.

Adverse events: I) the proportion of patients who discontinued treatment due to adverse events was 31.1% (14) in the polatuzumab vedotin + BR group and 15.4% (6) in the BR group. II) the proportion of patients experiencing ≥1 grade 3 or 4 adverse events was 84.4% (38) in the polatuzumab vedotin + BR group and 71.8% (28) in the BR group.

2. **For subpopulation of patients suited to combination chemotherapy:**

Overall survival: The median overall survival was 12.4 months in the polatuzumab vedotin + BR arm compared to 10.0 months in the CORAL EXT-1 population and 4.4 months in the CORAL EXT-2 population. The 2-year overall survival rate was 38.2% in the polatuzumab vedotin + BR arm compared to approximately 30% in the CORAL EXT-1 population and 15.7% in the CORAL EXT-2 population.

Health related quality of life: No data on SF-36, FACT-Lym or other HRQoL measures were collected in neither the CORAL EXT-1 study nor the CORAL EXT-2 study, making a comparative analysis of polatuzumab vedotin + BR and R-ICE impossible.

Progression free survival: No PFS data was collected in neither the CORAL EXT-1 study nor the CORAL EXT-2 study, making a comparative analysis of polatuzumab vedotin + BR and R-ICE impossible.

Adverse events (AEs): No adverse events data was collected in neither the CORAL EXT-1 study nor the CORAL EXT-2 study making a comparative analysis of polatuzumab vedotin + BR and R-ICE impossible.

Conclusion:

The overall purpose for the treatment of patients with relapsed or refractory DLBCL, who are not candidates for stem cell transplant, is to prolong life despite of a serious and life-threatening illness.

In summary, for the single agent chemotherapy subpopulation, the addition of polatuzumab vedotin to BR is associated with an absolute improvement in overall survival of 7.7 months in favor of polatuzumab vedotin + BR and a reduced risk of death by 58%. In the 2-year survival rate an absolute improvement of

21.2% in favor of polatuzumab vedotin + BR was demonstrated. No statistically significant differences were noted regarding the adverse events.

For the combination chemotherapy subpopulation, the patients treated with polatuzumab vedotin + BR had a longer median overall survival in the range of 2.4-8.0 months and a higher 2-year overall survival rate of 8.2-22.5% when compared with regimens in the CORAL EXT-1 and EXT-2 studies based on a naïve indirect comparison.

4 Introduction

Diffuse large B-cell lymphoma

Diffuse large B-cell lymphoma (DLBCL) is the most common histologic subtype of non-Hodgkin lymphoma (NHL), with an incidence of 434 in 2018 [5] and represents approximately 40% of all NHL cases in Denmark [6]. The median age at time of diagnosis is 67 years in Denmark and approximately 60% of patients receiving 1L treatment may be cured [7,8]. The current standard of care for these patients consists of rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP) [9]. Nevertheless, despite the improvements in overall survival (OS) of patients with DLBCL, one-fourth of patients present with either a primary refractoriness to the 1L treatment or relapse after reaching a complete response (CR) [10]. Relapsed or refractory (R/R) DLBCL patients, who are ineligible for haematopoietic stem cell transplant (HSCT), have a poor prognosis with a median OS ranging from 3.4 to 9.0 months [8]. Thus a high unmet medical need continues to exist for patients with R/R DLBCL, as there is limited efficacy and clinical evidence for the chemotherapy regimens currently used for treatment.
In the current Danish guidelines [11] patients with R/R DLBCL are commonly referred to as second line (2L) and third line (3L), given the lines of previous treatment. The primary reason for this is that the literature generally does not distinguish between treatment options for patients with relapsed or refractory disease. In this final application the terms relapse/refractory will be used instead of 2L, 3L and later lines since these terms are used in the European Commission Decision as well as in the Danish Medicine Council protocol.

Current treatment of DLBCL in Denmark

The Danish Lymphoma Group recently updated the national clinical guidelines [11] (February 2019) for the treatment of DLBCL in cooperation with the Danish Multidisciplinary Cancer Groups (DMCG.dk) and the Regions' Clinical Quality Development Program (RKKP).

According to these guidelines there is no single treatment option for patients with R/R DLBCL, who are not candidates for HSCT, as no prior randomized trials have established superiority of one regimen for this population. Patients who are eligible should be offered inclusion in open Danish clinical protocols. Given this, the clinical treatment landscape is fragmented with a number of different chemotherapy regimens being used for this patient population.

The Danish Medicine Council protocol [1] defines two subpopulations: 1) the fit patients, who are often offered a combination of chemotherapy agents e.g. rituximab, gemcitabine, dexamethasone and cisplatin (R-GDP), rituximab, gemcitabine and oxaplatin (R-GemOx) or rituximab, ifosfamide, carboplatin and etoposide (R-ICE), are referred to as the “combined chemotherapy subpopulation”, 2) the relatively frail patients, who are often offered single agent chemotherapy e.g. bendamustine in combination with rituximab (BR), are referred to as the “single agent chemotherapy subpopulation”.

Data from the Danish National Lymphoma Registry (LYFO) database, from the period 2013-2018, revealed that bendamustine +/- rituximab was the most commonly used treatment for patients with R/R DLBCL, who are not candidates for HSCT (though for both the single agent chemotherapy and combined chemotherapy subpopulations). The following distribution of chemotherapy regimens (+/- rituximab) for patients, who are not candidates for HSCT, was seen in the LYFO database: bendamustine 24%, CHOP/COPE 15%, ICE 12%, COP/CVP 8%, PREBen 8%, DHAP 6%, GDP 4%, others 25% [12].

Figure 1. Patient flow diagram

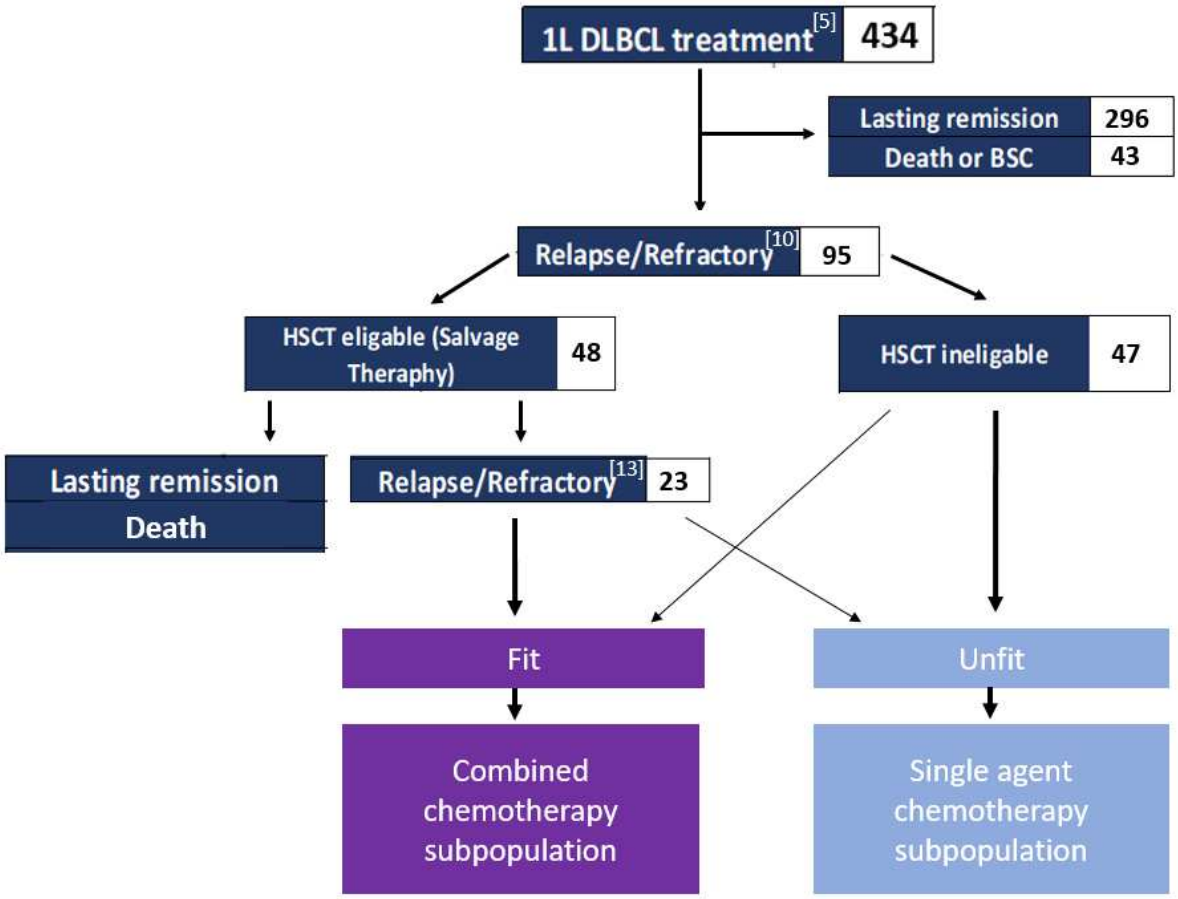


Figure 1. references: [5,10,13]

Rationale for combination therapy in diffuse large B-cell lymphoma

CD79b is a cell surface antigen whose expression is restricted to all mature B cells except plasma cells. It is expressed in a majority of B-cell–derived malignancies, including >95% of DLBCL [14,15]. Antibodies bound to CD79b are rapidly internalized, which makes CD79b ideally suited for targeted delivery of cytotoxic agents [16,17].

Polatuzumab vedotin is a CD79b-targeted antibody-drug conjugate (ADC) delivering a potent anti-mitotic agent, mono-methyl auristatin E (MMAE). MMAE has a mode of action similar to that of vincristine, which is a component of standard chemotherapy (e.g. R-CHOP used for the treatment of lymphoma). Following binding at the cell-surface epitope and internalization of the ADC by the targeted cell, MMAE is released following cleavage of the linker by lysosomal enzymes. MMAE then binds to tubulin and disrupts the microtubule network, resulting in inhibition of cell division and cell growth [18]. This therapeutic approach takes advantage of the specific targeting capability of the antibody and the cytotoxic activity of MMAE and

the increased potency of MMAE compared with vincristine. It has been demonstrated that the addition of polatuzumab vedotin to a standard anti-CD20 antibody i.e. rituximab plus chemotherapy i.e. bendamustine regimen, will provide enhanced efficacy and safety to patients with DLBCL [2]. In addition to this, DLBCL expresses the CD20 antigen, and anti-CD20 therapy (rituximab) has been demonstrated to provide enhanced anti-tumor activity in combination with other agents targeting the disease, leading to increased response rates, PFS and OS, which led to acceptance of rituximab as a standard component in initial therapy [19-22].

Rationale for the combination of polatuzumab vedotin with bendamustine and rituximab in the treatment of DLBCL

It has been demonstrated that the addition of polatuzumab vedotin to a standard anti-CD20 antibody i.e. rituximab plus bendamustine regimen will provide enhanced efficacy to patients with R/R DLBCL. Furthermore, for transplant ineligible patients with R/R DLBCL, there is no universally established standard of care (SoC) regimen used as no prior randomized trials have been able to establish the superiority of one regimen over another for this patient population, making no regimen an obvious choice as backbone therapy for polatuzumab vedotin. In the phase Ib/II clinical study [2] BR was selected to partner with polatuzumab vedotin to avoid potential overlapping peripheral neuropathy that may be seen with platinum-based therapies.

Rationale for bendamustine + rituximab and rituximab + ifosfamide + carboplatin + etoposide (ICE) as comparators

The BR regimen is defined in the Danish Medicine Council protocol [1] as the relevant comparator in the “single agent chemotherapy subpopulation”. In line with this, data from the LYFO database from the period 2013-2018 revealed that bendamustine +/- rituximab is the most commonly used treatment (administered to 24%) for patients with R/R DLBCL who are not candidates for HSCT.

R-ICE is classified in the Danish Medicine Council protocol as one of three options (rituximab and GDP/GemOx/ICE) in the “combination chemotherapy subpopulation”. The full text reading of the relevant studies, following the literature search as defined by the MR, revealed that R-ICE was the comparator that yielded the best basis for the comparative analysis, however, in a setting of no large or randomised studies with a common comparator. Which makes an adjusted indirect trial comparison (ITC) impossible.

The CORAL EXT-1 [3] and CORAL EXT-2 [4] studies are observational follow-up studies based on the CORAL study [23], but they include a relatively large number of patients (total of 278). The patient populations in the two studies are similar to the “combined chemotherapy subpopulation” defined in the Danish Medicine Council protocol, although it is not directly comparable. The treatment regimens in the CORAL EXT-1 and EXT-2 studies are somewhat fragmented with ICE +/- R being the most commonly used regimen (17-19%). ICE +/- R is considered a representative treatment regimen for both the CORAL EXT-1 and EXT-2 studies, due to the fact that the overall survival data did not differ significantly according to the type of treatment, making all the regimens equal.

Furthermore, data from the LYFO database from the period 2013-2018 revealed that ICE +/- rituximab was the third most commonly used treatment (12%) for patients with R/R DLBCL, who are not candidates for HSCT, although these data are for both the single agent chemotherapy and combined chemotherapy subpopulations. GDP +/- rituximab at 4% and GemOx +/- rituximab listed among others (i.e. less than 4%). The Danish Medicine Council did not suggest CHOP/COPE (15%) as a comparator, which is why we do not consider it.

5 Literature search

The literature search is based on the, in the protocol [1], defined search criteria for both MEDLINE (using PubMed) and CENTRAL (using the Cochrane Library).

After removal of any duplicates, two employees independent of each other screened all references on title level and abstract level according to established in and exclusion criteria (see table 6) in a reference management tool, and full text references were selected for review. In case of uncertainty as to whether a reference by title and abstract level met the criteria for entry and exit, these references were selected for full text review. In the event of any disagreement, it was agreed that a third party (medical peer) would be involved. Then full text references were read by Scientific Advisor. Excluded full text references with justification appears in a separate appendix (see Appendices, table 7). The full searches and selection appears in the PRISMA flow diagram (see Appendices).

Hand-searched literature included the CORAL EXT-1 and CORAL EXT-2 studies.

Searched literature is included in the PRISMA flow diagram (Appendices).

Search date: Searches were made on January 7, 2020 in both MEDLINE (via PubMed) and in CENTRAL (via Cochrane Library).

Search period covered: 1978 to 2020.

Databases and search strategy

The search strategies for MEDLINE and CENTRAL were according to the DMR protocol, Version 1.0.

Search Builder MEDLINE:

History

Download history Clear histor

Search	Add to builder	Query	Items found	Time
#15	Add	Search (((((("Lymphoma, Large B-Cell, Diffuse"[mh]) OR ((diffuse[tiab] AND (large cell[tiab] OR large-cell[tiab] OR b-cell[tiab] OR b cell[tiab] OR histiocytic[tiab]) AND lymphoma*[tiab]) OR DLBCL[tiab]))) AND ((((((((("gemcitabine-oxaliplatin regimen" [nm] OR ("gemcitabine" [nm] AND "Oxaliplatin"[mh]))) OR (gemox[tiab] OR gem-ox[tiab] OR R-gemox[tiab] OR (gemcitabin*[tiab] AND (oxaliplatin*[tiab] OR Eloxatin*[tiab] OR ACT078[tiab] OR ACT-078[tiab]))))) OR ("GDP protocol" [nm] OR ("gemcitabine" [nm] AND "Dexamethasone"[mh] AND "Cisplatin"[mh]))) OR (GDP[tiab] OR RGDP[tiab] OR R-GDP[tiab] OR (gemcitabin*[tiab] AND dexamethason*[tiab] AND (cisplatin*[tiab] OR cis-platin*[tiab])))) OR ("ICE protocol 1"[nm] OR "ICE protocol 2"[nm] or "ICE protocol 3"[nm] or "ICE protocol 4"[nm] or "ICE protocol 5"[nm] or "ICE protocol 6"[nm] OR ("Ifosfamide"[mh] AND "Carboplatin"[mh] AND "Etoposide"[mh]))) OR (((iphosphamid*[tiab] OR isophosphamid*[tiab] OR isofosfamid*[tiab]) AND Carboplat*[tiab] AND (eposi*[tiab] OR etopos*[tiab] OR VP-16*[tiab] OR VP16[tiab])) OR R-ICE[tiab] OR RICE[tiab])) OR "polatuzumab vedotin" [nm]) OR (polatuzumab[tiab] OR Polivy[tiab])))) NOT (("case reports"[pt] OR "comment"[pt] OR "editorial"[pt] OR "guideline"[pt] OR "systematic review"[pt] OR "review"[pt]))	71	11:00:19
#14	Add	Search ("case reports"[pt] OR "comment"[pt] OR "editorial"[pt] OR "guideline"[pt] OR "systematic review"[pt] OR "review"[pt])	5719100	10:58:44
#13	Add	Search ((("Lymphoma, Large B-Cell, Diffuse"[mh]) OR ((diffuse[tiab] AND (large cell[tiab] OR large-cell [tiab] OR b-cell[tiab] OR b cell[tiab] OR histiocytic[tiab]) AND lymphoma*[tiab]) OR DLBCL[tiab]))) AND ((((((((("gemcitabine-oxaliplatin regimen" [nm] OR ("gemcitabine" [nm] AND "Oxaliplatin"[mh]))) OR (gemox[tiab] OR gem-ox[tiab] OR R-gemox[tiab] OR (gemcitabin*[tiab] AND (oxaliplatin*[tiab] OR Eloxatin*[tiab] OR ACT078[tiab] OR ACT-078[tiab]))))) OR ("GDP protocol" [nm] OR ("gemcitabine" [nm] AND "Dexamethasone"[mh] AND "Cisplatin"[mh]))) OR (GDP[tiab] OR RGDP[tiab] OR R-GDP[tiab] OR (gemcitabin*[tiab] AND dexamethason*[tiab] AND (cisplatin*[tiab] OR cis-platin*[tiab])))) OR ("ICE protocol 1"[nm] OR "ICE protocol 2"[nm] or "ICE protocol 3"[nm] or "ICE protocol 4"[nm] or "ICE protocol 5"[nm] or "ICE protocol 6"[nm] OR ("Ifosfamide"[mh] AND "Carboplatin"[mh] AND "Etoposide"[mh]))) OR (((iphosphamid*[tiab] OR isophosphamid*[tiab] OR isofosfamid*[tiab]) AND Carboplat*[tiab] AND (eposi*[tiab] OR etopos*[tiab] OR VP-16*[tiab] OR VP16[tiab])) OR R-ICE[tiab] OR RICE[tiab])) OR "polatuzumab vedotin" [nm]) OR (polatuzumab[tiab] OR Polivy[tiab]))	104	10:58:17
#12	Add	Search (((((((("gemcitabine-oxaliplatin regimen" [nm] OR ("gemcitabine" [nm] AND "Oxaliplatin"[mh]))) OR (gemox[tiab] OR gem-ox[tiab] OR R-gemox[tiab] OR (gemcitabin*[tiab] AND (oxaliplatin*[tiab] OR Eloxatin*[tiab] OR ACT078[tiab] OR ACT-078[tiab]))))) OR ("GDP protocol" [nm] OR ("gemcitabine" [nm] AND "Dexamethasone"[mh] AND "Cisplatin"[mh]))) OR (GDP[tiab] OR RGDP[tiab] OR R-GDP[tiab] OR (gemcitabin*[tiab] AND dexamethason*[tiab] AND (cisplatin*[tiab] OR cis-platin*[tiab])))) OR ("ICE protocol 1"[nm] OR "ICE protocol 2"[nm] or "ICE protocol 3"[nm] or "ICE protocol 4"[nm] or "ICE protocol 5"[nm] or "ICE protocol 6"[nm] OR ("Ifosfamide"[mh] AND "Carboplatin"[mh] AND "Etoposide"[mh]))) OR (((iphosphamid*[tiab] OR isophosphamid*[tiab] OR isofosfamid*[tiab]) AND Carboplat*[tiab] AND (eposi*[tiab] OR etopos*[tiab] OR VP-16*[tiab] OR VP16[tiab])) OR R-ICE[tiab] OR RICE[tiab])) OR "polatuzumab vedotin" [nm]) OR (polatuzumab[tiab] OR Polivy[tiab])	68477	10:55:58
#11	Add	Search (polatuzumab[tiab] OR Polivy[tiab])	62	10:51:33
#10	Add	Search "polatuzumab vedotin" [nm]	3	10:51:20
#9	Add	Search (((iphosphamid*[tiab] OR isophosphamid*[tiab] OR isofosfamid*[tiab]) AND Carboplat*[tiab] AND (eposi*[tiab] OR etopos*[tiab] OR VP-16*[tiab] OR VP16[tiab])) OR R-ICE[tiab] OR RICE[tiab])	52056	10:51:07
#8	Add	Search ("ICE protocol 1"[nm] OR "ICE protocol 2"[nm] or "ICE protocol 3"[nm] or "ICE protocol 4"[nm] or "ICE protocol 5"[nm] or "ICE protocol 6"[nm] OR ("Ifosfamide"[mh] AND "Carboplatin"[mh] AND "Etoposide"[mh]))	642	10:50:54
#7	Add	Search (GDP[tiab] OR RGDP[tiab] OR R-GDP[tiab] OR (gemcitabin*[tiab] AND dexamethason*[tiab] AND (cisplatin*[tiab] OR cis-platin*[tiab])))	14731	10:50:41
#6	Add	Search ("GDP protocol" [nm] OR ("gemcitabine" [nm] AND "Dexamethasone"[mh] AND "Cisplatin"[mh]))	51	10:49:43
#5	Add	Search (gemox[tiab] OR gem-ox[tiab] OR R-gemox[tiab] OR (gemcitabin*[tiab] AND (oxaliplatin*[tiab] OR Eloxatin*[tiab] OR ACT078[tiab] OR ACT-078[tiab])))	917	10:49:29
#4	Add	Search ("gemcitabine-oxaliplatin regimen" [nm] OR ("gemcitabine" [nm] AND "Oxaliplatin"[mh]))	513	10:49:11
#3	Add	Search ("Lymphoma, Large B-Cell, Diffuse"[mh]) OR ((diffuse[tiab] AND (large cell[tiab] OR large-cell [tiab] OR b-cell[tiab] OR b cell[tiab] OR histiocytic[tiab]) AND lymphoma*[tiab]) OR DLBCL[tiab])	28035	10:48:29
#2	Add	Search ((diffuse[tiab] AND (large cell[tiab] OR large-cell[tiab] OR b-cell[tiab] OR b cell[tiab] OR histiocytic[tiab]) AND lymphoma*[tiab]) OR DLBCL[tiab])	17293	10:48:00
#1	Add	Search "Lymphoma, Large B-Cell, Diffuse"[mh]	19151	10:47:44

Search Builder CENTRAL

View fewer lines | Print

#1	[mh "Lymphoma, Large B-Cell, Diffuse"]	Limits	349
#2	((diffuse AND (large cell OR large-cell OR b-cell OR b cell OR histiocytic) AND lymphoma*) OR DLBCL):ti,ab,kw	Limits	1594
#3	#1 OR #2	Limits	1594
#4	(gemox OR gem-ox OR R-gemox OR (gemcitabin* AND ([mh "Oxaliplatin"] OR oxaliplatin* OR Eloxatin* OR ACT078 OR ACT-078))):ti,ab,kw	Limits	465
#5	(GDP OR RGDP OR R-GDP OR (gemcitabin* AND (dexamethason* OR [mh "Dexamethasone"]) AND ([mh "Cisplatin"] cisplatin* OR cis-platin*))):ti,ab,kw	Limits	285
#6	[mh "Ifosfamide"] AND [mh "Carboplatin"] AND [mh "Etoposide"]	Limits	75
#7	(((iphosphamid* OR isophosphamid* OR isofosfamid*) AND Carboplat* AND (eposi* OR etopos* OR VP-16* OR VP16)) OR R-ICE OR RICE):ti,ab,kw	Limits	1848
#8	(polatuzumab OR Polivy):ti,ab,kw	Limits	49
#9	#4 OR #5 OR #6 OR #7 OR #8	Limits	2696
#10	#3 AND #9	Limits	98
#11	("conference abstract" OR review):pt	Limits	184426
#12	NCT*:au	Limits	147666
#13	("clinicaltrials.gov" OR trialsearch):so	Limits	277326
#14	#11 or #12 or #13	Limits	461867
#15	#10 NOT #14	Limits	21

5.1 Relevant studies

Table 3. Relevant studies included in the assessment					
Reference (title, *author, journal, year*)	Trial name	NCT number	Dates of study (start and expected completion date)	Relevant for clinical question	Relevant for comparator subpopulation
Polatuzumab Vedotin in Relapsed or Refractory Diffuse Large B-Cell Lymphoma, *Laurie H. Sehn et al., Journal of Clinical Oncology, 2019* [2]	GO29365	02257567	October 2014 - December 2019 (primary completion date)	1	Single agent chemotherapy subpopulation
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 E et al., Bone Marrow Transplantation, 2017* [3]	CORAL EXT-1	00137995	The CORAL study (June 2003 - October 2008) [13]	1	Combined chemotherapy subpopulation
Outcome of patients with relapsed diffuse large B-cell lymphoma who fail second-line salvage regimens in the International CORAL study, *Van Den Neste E et al., Bone Marrow Transplantation, 2016* [4]	CORAL EXT-2	00137995	The CORAL study (June 2003 - October 2008) [13]	1	Combined chemotherapy subpopulation

5.2 Main characteristics of included studies

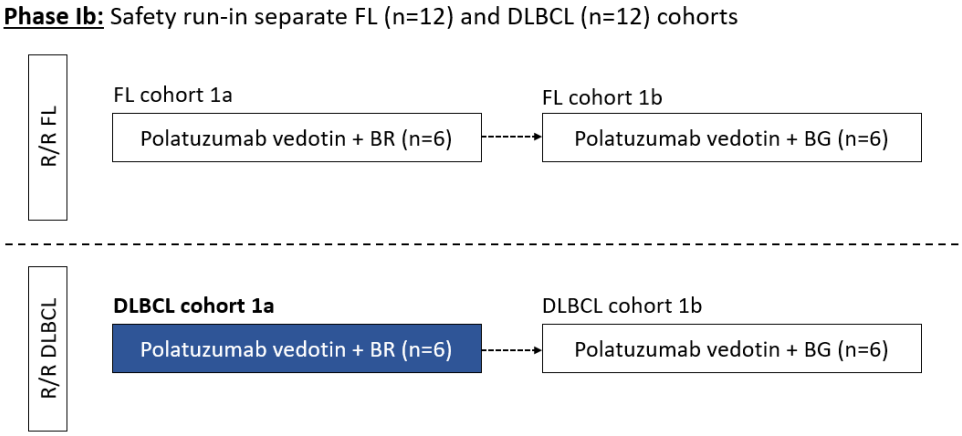
The application includes data from a total of 3 selected relevant clinical studies. The in-depth main characteristics of each of the included studies are tabulated in the appendix (only data from cohort 1a, arm C and D of the GO29365 study are tabulated).

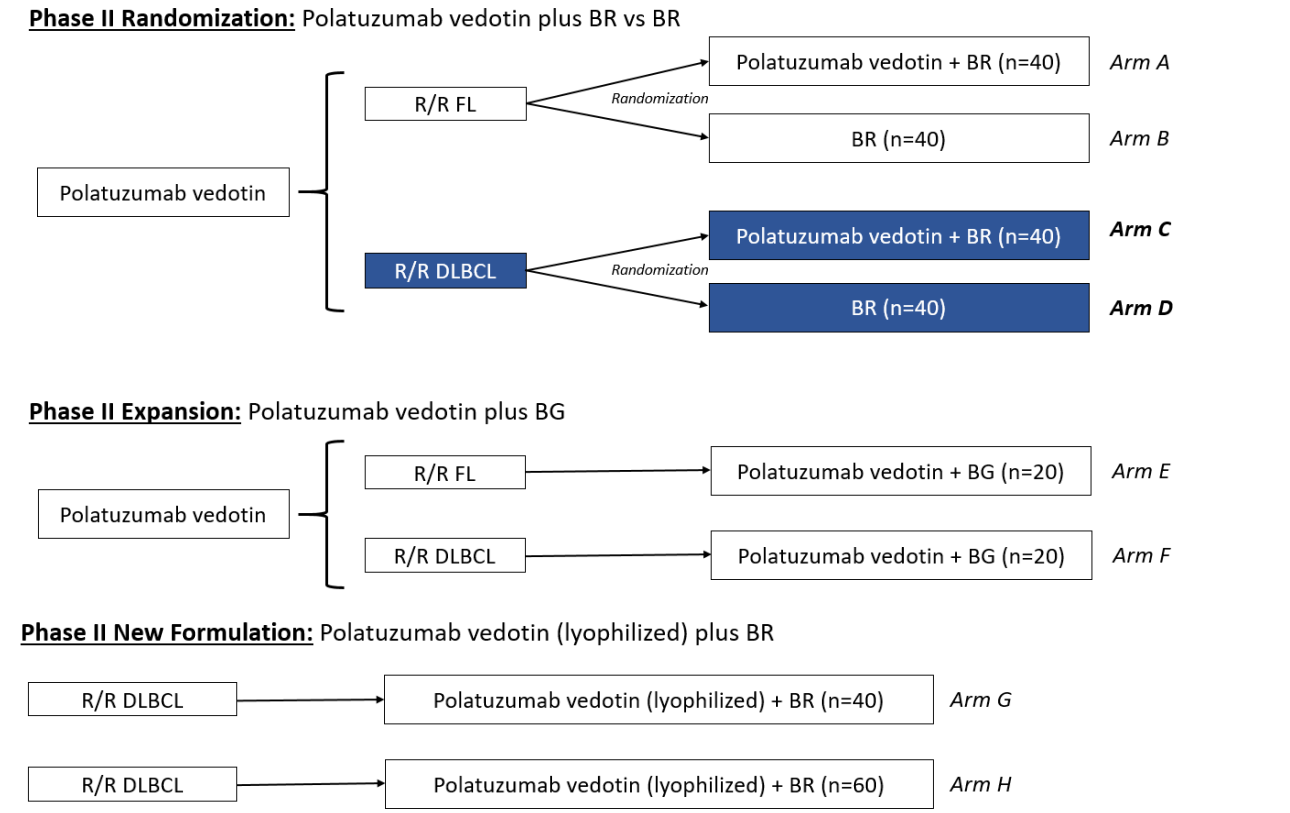
Single agent chemotherapy subpopulation

- Study including polatuzumab vedotin and bendamustine + rituximab:

GO29365 is a phase Ib/II, open-label, international, multicenter clinical trial assessing the efficacy and safety of polatuzumab vedotin in patients ≥18 years with R/R DLBCL or follicular lymphoma (FL), who are not candidates for HSCT. Patients with FL are not relevant for this application and will not be further described. The phase Ib safety run-in included 6 polatuzumab vedotin + BR treated patients and 6 polatuzumab vedotin + bendamustine and obinutuzumab (BG) treated patients. The phase II portion included an expansion cohort evaluating polatuzumab vedotin + BG (20 patients), a randomly assigned cohort (80 patients) where patients were randomized 1:1 to receive polatuzumab vedotin plus BR or BR alone and a new formulation cohort where all patients received polatuzumab vedotin (lyophilized) plus BR. The randomization of patients in the randomly assigned cohort was stratified by duration of response to prior therapy (≤12 months vs. >12 months).

Figure 2. Overview of the GO29365 study – R/R DLBCL and R/R FL patients





Tumor responses were assessed on the basis of physical examinations, CT scans, PET-CT scans and bone marrow examinations using the modified Lugano 2014 response criteria [24]. PET-CT scans were obtained at screening, at an interim response assessment after cycle 3 of study treatment and at the primary response assessment at the end of treatment (defined as 6 to 8 weeks after cycle 6 Day 1 or last dose of study medication) [25].

The patient-reported outcome (PRO) objective for the study was to assess and quantify the symptomatic burden and personal tolerability of peripheral neuropathy (PN). The patients' self-assessments of their experience with PN were captured using the novel validated therapy-induced neuropathy scale known as the TNAS [26], which is designed to capture multiple neuropathy-related symptoms, to be brief enough for repeated administrations, to be highly sensitive and reliable, and to demonstrate good content validity [27]. TNAS v1.0 consists of an 11-item questionnaire that assesses the severity of neuropathy-related symptoms in the last 24 hours [28]. Each item is scored on a 0-10 scale, with 0 being the symptom is not present, and 10 being the symptom is as bad as the patient can imagine.

Completion of the TNAS was scheduled weekly over the course of study treatment. Following the study treatment period, the TNAS was to be completed once per week for the first 2 months, then once per month for the next 10 months. However, less than 50% of patients filled the questionnaire and participation decreased further over time and less than 25% of the few compliant patients continued this assessment after week 29 in the polatuzumab vedotin + BR arm [26]. The PRO analyses included patients in the intent-to-treat population, and as PN in the study is assumed to be specific to polatuzumab vedotin, data from polatuzumab vedotin + BG and polatuzumab + BR arms were pooled across the phase Ib and phase II stages to maximize the sample size available for analyses given the extent of missing data [25].

Combined chemotherapy subpopulation

Studies including ICE and rituximab:
The CORAL study was a phase III, multicentre, randomised trial that compared the efficacy of R-ICE or R-DHAP, followed by HSCT with or without rituximab maintenance in patients aged 18–65 years with relapsed DLBCL [13,23]. In total, between July 2003 and June 2008, 477 patients were randomly assigned to R-ICE (n = 243) or R-DHAP (n = 234) [3]. CORAL EXT-1 and CORAL EXT-2 are two observational studies following two separate sub-groups of patients from the CORAL study.

CORAL EXT-1 focuses on the 75 patients who relapsed after HSCT and were candidates for a third-line regimen. Third-line therapy consisted of ICE +/-R (17.3%), DHAP +/- R (24%), gemcitabine-containing (28%), CHOP-like (13.3%) and miscellaneous regimens (17.3%). Overall survival data did not differ significantly according to the type of treatment [3].

CORAL EXT-2 focuses on the 203 patients who failed second-line salvage regimens and could not proceed to the scheduled HSCT, and due to this were candidates for a third-line regimen. Among the 203 patients, 170 (83.7%) had been removed from the CORAL salvage strategy with R-DHAP/ICE for an event characterized as “treatment failure”, 19 (9.4%) for treatment toxicity, 1 (0.5%) for major protocol violation and 13 (6.4%) for various other reasons. Third-line therapy consisted of ICE +/-R, DHAP-like and gemcitabine-containing regimens were given to 18.5%, 18% and 13.8% of the patients, respectively, miscellaneous regimen were given to 31.9% of the patients (53; of these, unknown regimen in 37 patients). Overall survival data did not differ significantly according to the type of treatment [4].

6 Clinical questions

6.1 Clinical question 1

What is the value of polatuzumab vedotin in combination with bendamustine and rituximab compared with bendamustine, GDP, GemOx or ICE in combination with rituximab in adult patients with relapse or refractory diffuse large B-cell lymphoma, who are not candidates for haematopoietic stem cell transplant?

6.1.1 Presentation of the relevant studies

The GO29365 study
The application is based on the patients treated with polatuzumab vedotin plus BR or BR in the phase Ib safety run-in and the randomized phase II portion of the GO29365 study of patients with R/R DLBCL. The phase Ib safety run-in with polatuzumab vedotin plus BG (bendamustine and obinutuzumab) and the phase II expansion cohort is not relevant for this application due to the fact that the patients are treated with polatuzumab vedotin plus BG. Data for the phase II new formulation cohort is not published at the time of writing.

CORAL EXT-1
An observational study that follows a sub-group of patients from the CORAL study. It includes 75 patients who relapsed after HSCT and were candidates for a third-line regimen.

CORAL EXT-2
An observational study that follows a sub-group of patients from the CORAL study. It includes 203 patients who failed second-line salvage regimens and could not proceed to the scheduled HSCT and due to this were candidates for a third-line regimen.

Table 4 illustrates the differences and similarities in study characteristics.

Table 5 illustrates the differences and similarities in patient characteristics.

Table 4. Study and outcome characteristics of the studies used to answer the clinical question 1

Study	**GO29365**	**CORAL EXT-1**	**CORAL EXT-2**
Reference	**[29]**	**[3]**	**[4]**
Geography	Australia, Canada, Czechia, France, Germany, Hungary, Italy, Republic of Korea, Netherlands, Spain, Turkey, United Kingdom, and the United States of America	The CORAL study [13]: Australia, Belgium, Czechia, Finland, Germany, Israel, Sweden, Switzerland, United Kingdom, and the United States of America	The CORAL study [13]: Australia, Belgium, Czechia, Finland, Germany, Israel, Sweden, Switzerland, United Kingdom, and the United States of America
Study period	October 2014 - December 2019 (Primary completion date)	The CORAL study (June 2003 - October 2008) The CORAL EXT-1 study is following the CORAL study	The CORAL study (June 2003 - October 2008) The CORAL EXT-2 study is following the CORAL study
Design	International, multicenter, open-label, phase Ib/II trial	Observational follow-up study on a sub-group of patients from the CORAL study	Observational follow-up study on a sub-group of patients from the CORAL study
Median follow-up, months	22.3	32.8	30.1
Population (Inclusion criteria)	• Histologically confirmed relapsed or refractory DLBCL • At least one bi-dimensionally measurable lesion on imaging scan defined as >1.5 centimeters (cm) in its longest dimension • Life expectancy of at least 24 weeks • Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2 Additional eligibility criteria are listed in "Main characteristics"	• Histologically confirmed relapsed or refractory DLBCL • Relapsed after HSCT and were candidates for a third-line regimen Eligibility criteria of the CORAL study are listed at clinicaltrials.gov, NCT 00137995	• Histologically confirmed relapsed or refractory DLBCL • Failed to proceed to BEAM (carmustine, etoposide, cytarabine, and melphalan) + HSCT and were candidates for a third-line regimen Eligibility criteria of the CORAL study are listed at clinicaltrials.gov, NCT 00137995
Intervention	**Polivy®** (polatuzumab vedotin) 1.8mg/kg IV on Day 2 of cycle 1 and Day 1 of subsequent cycles, up to 6 cycles. Bendamustine 90mg/m^2 IV on Days 2 and 3 of cycle 1 and then Days 1 and 2 of subsequent cycles, and rituximab 375/m^2 IV on Day	ICE-like (ifosfamide, carboplatin and etoposide +/- rituximab) DHAP-like Gemcitabine-containing CHOP-like Miscellaneous regimens	ICE-like (ifosfamide, carboplatin and etoposide +/- rituximab) DHAP-like Gemcitabine-containing Dexa-BEAM CHOP-like

Table 4. Study and outcome characteristics of the studies used to answer the clinical question 1			
Study	**GO29365**	**CORAL EXT-1**	**CORAL EXT-2**
	1 of each cycle, both up to 6 cycles. Each cycle is 21 days		Miscellaneous regimens
Comparator	Bendamustine 90mg/m^2 IV on Days 2 and 3 of cycle 1 and then Days 1 and 2 of subsequent cycles, and rituximab 375/m^2 IV on Day 1 of each cycle, both up to 6 cycles. Each cycle is 21 days	N/A	N/A
Definition of outcomes			
Overall survival	Time from the date of randomization and treatment assignment until death	Time from the date of relapse after HSCT until death	Time from the date the patient was declared as having failed CORAL induction until death
Health related quality of life	TNAS	N/A	N/A
Progression free survival	Based on PET-CT or CT assessed by independent review committee	N/A	N/A
Adverse events	The National Cancer institute Common Terminology Criteria for Adverse Events (version 4.03) was used to assess and grade all adverse events (AEs) throughout the study. All AEs, including serious AEs (SAEs), were reported from cycle 1 Day 1 until 90 days after last dose of study drug regardless of relationship to treatment.	N/A	N/A

Table 5. Baseline characteristics of the studies used to answer the clinical question 1

Study	GO29365			CORAL	
Population	**Phase Ib safety run-in** Polatuzumab vedotin + BR (DLBCL cohort 1a) n = 6	**Phase II randomized** Polatuzumab vedotin + BR (Arm C) n = 40	BR (Arm D) n = 40	**CORAL EXT-1** ITT population n = 75	**CORAL EXT-2** ITT population n = 203
Median age, years (range)	65 (58-79)	67.0 (33-86)	71.0 (30 – 84)	56.1 (20.9-67.7)	***at CORAL inclusion*** 55.0 (19.0-65.0)
≥ 65 years	N/A	23 (57.5)	26 (65.0)	N/A	N/A
Female sex, n (%)	2 (33.3)	12 (30.0)	15 (27.5)	24 (32)	79 (38.9)
ECOG performance status score at baseline, n (%)					
0-1	6 (100.0)	33 (82.5)	31 (77.5)	N/A	N/A
2	0	6 (15.0)	8 (20.0)		
WHO 2016 Classification (central pathology review)‡, n (%)					***GC/non-GC algorithm, n = 102[!] (%)***
DLBCL, NOS	6 (100.0)	38 (95.0)	40 (100.0)	N/A	
ABC	4 (66.7)	19 (47.5)	19 (47.5)		Non-GC 54 (52.9)
GCB	1 (16.7)	15 (37.5)	17 (42.5)		GC 48 (47.1)
Burkitt lymphoma	0	1 (2.5)	0		
Follicular lymphoma	0	1 (2.5)	0		
International Prognostic Index score, n (%)	***at enrollment***	***at enrollment***	***at enrollment***		***at CORAL failure***
0	0	0	0		
1	1 (16.7)	9 (22.5)	3 (7.5)		
2	3 (50.0)	9 (22.5)	8 (20.0)		
3	2 (33.3)	13 (32.5)	12 (30.0)		
4	0	8 (20.0)	12 (30.0)		
5	0	1 (2.5)	5 (12.5)		
0-2	4 (66.7)	18 (45)	11 (27.5)	48 (71.6)	
>2	2 (33.3)	22 (55)	29 (72.5)	19 (28.4)	
0-1	1 (16.7)	9 (22.5)	3 (7.5)		35 (30.4)
2-3	5 (83.3)	22 (55.0)	20 (50.0)		60 (52.2)
4-5	0	9 (22.5)	17 (42.5)		20 (17.4)
Ann Arbor stage III/IV, n (%)	4 (66.7)	34 (85.0)	36 (90.0)	N/A	N/A
Stratification factor DOR of last treatment ≤ 12 months, n (%)	5 (83.3)	32 (80.0)	33 (82.5)	N/A	N/A
Prior stem cell transplant, n (%)	0	10 (25.)	6 (15.0)	75 (100)	0
Lines of prior therapy, n (%)					
1 line	2 (33.3)	11 (27.5)	12 (30.0)	0	0
2 lines	4 (66.7)	11 (27.5)	9 (22.5)	75 (100)	203 (100)
≥3 lines	0	18 (45.0)	19 (47.5)	0	0
Median no. lines (range)	2 (1-2)	2 (1-7)	2 (1-5)		

ABC = activated B-cell-like; GC = germinal center; GCB = germinal center B-cell like;
‡Central pathology review incorporated results of NanoString cell of origin when available.
! Number of patients for whom information was available.

6.1.2 Results per study

Single agent chemotherapy subpopulation

GO29365

The population in the study is representative of the population seen in Danish practice based upon expert statements from Danish haematologists.

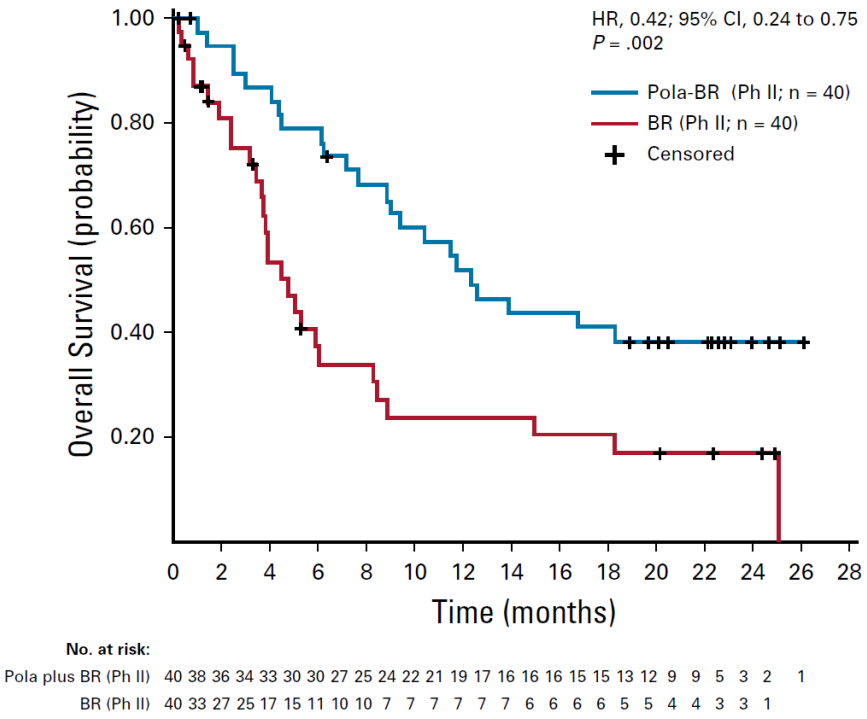
The results for each outcome relevant for the clinical question are briefly presented in this section. For further descriptions, absolute and relative risk calculations and data sources see appendix table 11.

Overall survival (OS)

Median overall survival was 12.4 months in the polatuzumab vedotin + BR arm and 4.7 months in the BR arm (HR 0.42; CI 0.24-0.75). In the same population 2-year overall survival rate was 38.2% (CI 22.5%-53.9%) in the polatuzumab vedotin + BR arm and 17.0% (CI 3.6%-30.4%) in the BR arm.

Below is provided the Kaplan-Meier curves of the overall survival of polatuzumab vedotin combined with BR compared with BR (figure 3) [2].

Figure 3. Overall survival



Overall, efficacy results for the as-treated DLBCL population (according to central pathology review, excluding the 2 patients with FL or Burkitt's lymphoma) were similar to those of the intent-to-treat population [2].

Health related quality of life (HRQoL)

No patient-reported outcome (PRO) data on SF-36 or FACT-Lym was collected in the GO29365 study. However, the PRO objective for the study was to assess and quantify the symptomatic burden and personal

tolerability of peripheral neuropathy using the treatment-induced neuropathy scale (TNAS). These PRO data are still awaiting publication and are only available in the clinical study report [25].

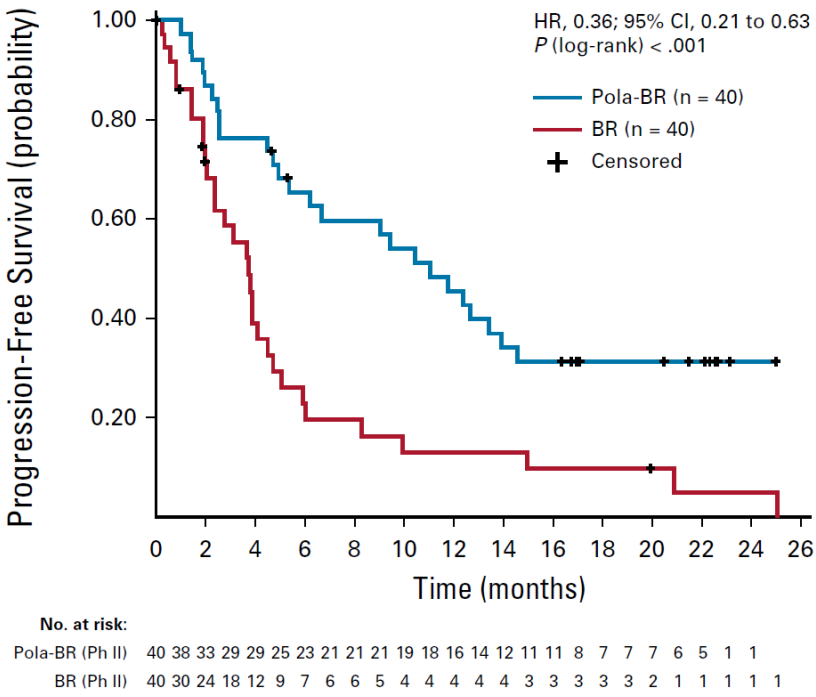
Mean scores for individual TNAS items were low (≤1.5) at the beginning of treatment in both the polatuzumab vedotin + BR and BR arms. By end of treatment with polatuzumab vedotin + BR the severity of peripheral neuropathy symptoms was rated as low, with the highest means observed for numbness/tingling in hands/feet, although still ≤2. The mean scores rarely exceeded 3.0 during treatment, indicating that overall, patients perceived PN symptoms to be mild. Trends for the BR arm across all items were relatively flat [25].

Progression free survival (PFS) assessed by independent review committee

Progression free survival by independent review committee (IRC) was 9.5 months in the polatuzumab vedotin + BR arm and 3.7 months in the BR arm (HR 0.36; CI 0.21-0.63). In the same population 2-year progression free survival rate was 31.3% (CI 16.6%-46.5%) in the polatuzumab vedotin + BR arm and 4.9% (CI 0%-13.4%) in the BR arm.

Below is provided the Kaplan-Meier curves of the progression free survival of polatuzumab vedotin combined with BR compared with BR only (figure 4) [2].

Figure 4. Progression free survival - assessed by independent review committee



Adverse events

The safety-evaluable population consisted of 45 patients in the polatuzumab vedotin + BR group (DLBCL cohort 1a and arm C) and 39 patients in the BR group (arm D). One patient in each group did not receive the study treatment, and so was excluded from the safety-evaluable population. The adverse events are presented according to the three subheadings requested in the DMC protocol.

I) Proportion of patients who discontinued treatment due to adverse events

31.1% (14) of the polatuzumab vedotin + BR group and 15.4% (6) of the patients in the BR group discontinued any treatment due to adverse events. In 12/14 cases polatuzumab vedotin, bendamustine and rituximab were all discontinued while in two cases only bendamustine was discontinued. Cytopenia (neutropenia and thrombocytopenia) were the most frequent causes of discontinuation.

The number for the BR group is taken from the EPAR [26], due to the fact that there is listed a wrong number in the article by Sehn et al. [2] concerning discontinuation of any treatment due to AEs. The number found in the EPAR is the same as in the CSR [25].

II) Proportion of patients experiencing ≥ 1 grade 3 or 4 adverse events

84.4% (38) of the patients in the polatuzumab vedotin + BR group and 71.8% (28) of the patients in the BR group experienced one or more grade 3-4 adverse events.

III) Narrative of the adverse events profile focused on a number of adverse events of special interest specified by the Danish Medicine Council Protocol

Neuropathy

Peripheral neuropathy (PN) is identified as a general risk for antibody-drug conjugates that delivers MMAE, including polatuzumab vedotin. In the polatuzumab vedotin + BR group the overall incidence was 40% (18/45 patients) [26]. 6 of these patients had grade 2 events, while no grade 3 events or above were observed. 10 of the 18 patients who had a PN event during treatment with polatuzumab vedotin plus BR had a history of prior PN, and of these, 8 patients had ongoing grade 1 PN at baseline [25]. Most events (11/18) resolved in the polatuzumab vedotin + BR group, while 7 were unresolved, mainly grade 1. In the BR group the overall incidence of PN events was 7.7% (3/39) [26].

Infections

The incidence of all infectious events was similar in the polatuzumab + BR and BR groups (53.3% vs 51.3%) [26], and so was the incidence of grade 3 to 4 infections and infestations (23.1% vs 20.5%) [2]. In the polatuzumab vedotin + BR group, 4 patients (8.9%) experienced fatal events, including pneumonia (2), meningoencephalitis herpetic (1), and sepsis (1). In the BR group, 4 patients (10.3%) experienced fatal events, including sepsis (2), pneumonia (1), and septic shock (1). Six opportunistic infections were reported in 4 patients (8.9%) in the polatuzumab + BR group: herpetic encephalitis (1 patient), cerebral toxoplasmosis, cytomegalovirus (CMV), and pneumonia (in the same patient), CMV infection (reported twice in the same patient), and pneumocystis jiroveci pneumonia (1 patient). 3 of these patients died due to opportunistic infection. In the BR group, opportunistic infections were reported in 2 patients: CMV infection and pulmonary mycosis [26].

Infusion-related reactions

The incidence of infusion-related reactions (related AEs during or within 24 hours of infusion) was 33.3% in the polatuzumab vedotin group and 23.1% in the BR group [25].

Immunological events

In the polatuzumab vedotin + BR group the incidence of treatment-emergent (sum of treatment-induced and treatment-enhanced) anti-drug antibodies (ADA) to polatuzumab vedotin was 7.1% (3/42 ADA evaluable patients). Baseline prevalence of ADAs was 4.6% (2/42 ADA evaluable patients). Both patients with a positive ADA result at baseline were treatment unaffected [25]. No identifiable relationship between an ADA response and reported AEs was observed. However, due to the limited number of anti-polatuzumab vedotin antibody positive patients to date, no conclusions can be drawn concerning a potential effect of

immunogenicity on safety at this time [26]. In addition, the emergence of ADAs to polatuzumab vedotin did not appear to impact efficacy with ongoing long-term responses despite development of ADAs [25].

Combined chemotherapy subpopulation

CORAL EXT-1

The results for each outcome relevant for the clinical question are briefly presented in this section. For further descriptions and data sources, see appendix table 12.

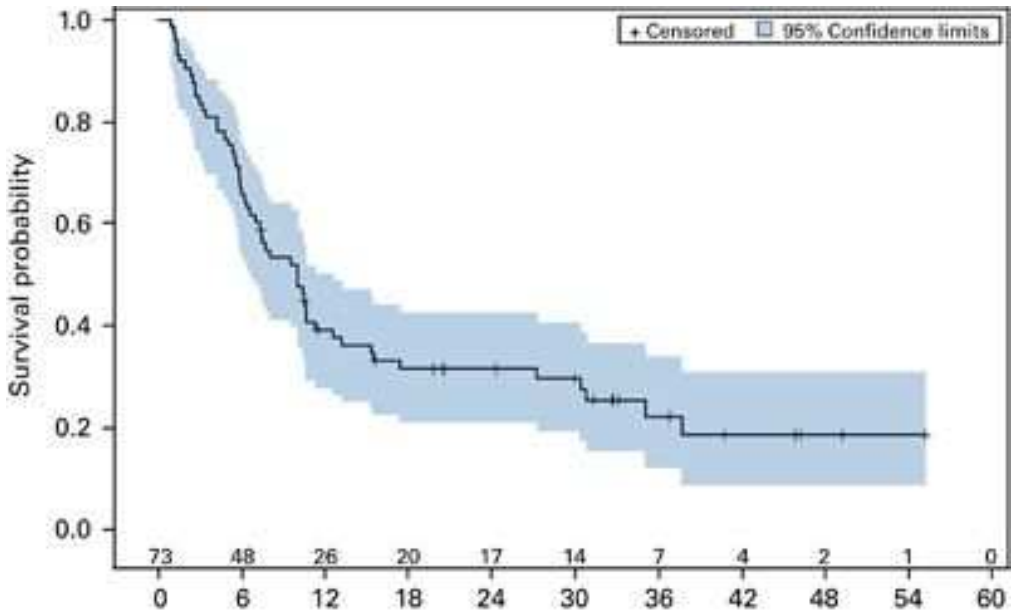
Overall survival

The median overall survival in the ITT population of 75 patients was 10.0 months. 2-year overall survival rate was not reported in the study, but we estimate it to be approximately 30% based on the Kaplan-Meier overall survival curve. This is in line with the estimation made by the Danish Medicine Council, that was reported in two assessment reports [30,31]. Supporting this, the CORAL EXT-1 study reported an estimated 1-year overall survival rate of 39.1%.

No statistically significant difference in OS was found between the different types of treatment.

Below is provided the Kaplan-Meier curves of the overall survival of the patients in the ITT population (figure 5) [3].

Figure 5. Overall survival in the ITT population



Health related quality of life (HRQoL)

No PRO data was collected in the CORAL EXT-1 study.

Progression free survival (PFS)

No data on progression free survival was reported for the reason that PFS results after the third-line treatment were anticipated to be too unreliable.

Adverse events

No data on adverse events was collected.

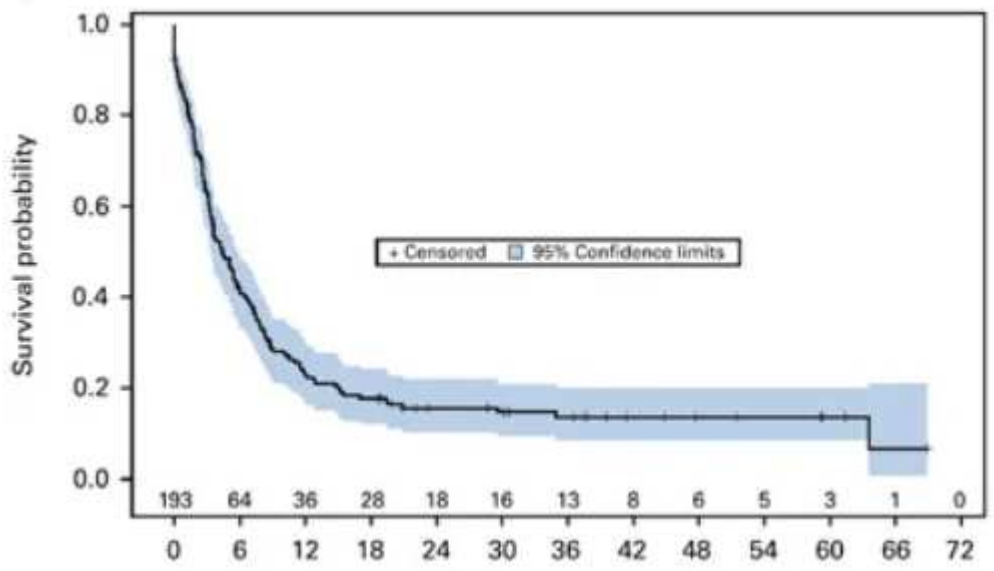
CORAL EXT-2

The results for each outcome relevant for the clinical question are briefly presented in this section. For further descriptions and data sources, see appendix table 13.

Overall survival

In the ITT population of 203 patients, median overall survival was 4.4 months. The 2-year overall survival rate was 15.7% in the same population. No statistically significant difference in OS was found between the different types of treatment. Below is provided the Kaplan-Meier curves of the overall survival of the patients in the ITT population (figure 6) [4].

Figure 6. Overall survival in the ITT population



Health related quality of life (HRQoL)

No PRO data was collected in the CORAL EXT-2 study.

Progression free survival (PFS)

No data on progression free survival was reported for the reason that PFS results after the third-line treatment were anticipated to be too unreliable.

Adverse events

No data on adverse events was collected.

6.1.3 Comparative analyses

The comparative analysis of data for polatuzumab vedotin + BR vs BR in the single agent chemotherapy subpopulation is based on data from the GO29365 study, while the comparative analysis of polatuzumab vedotin + BR vs R-ICE in the combined chemotherapy subpopulation is based on the CORAL EXT-1 and CORAL

EXT-2 studies. This is in alignment with the clinical question 1. For further descriptions, absolute and relative risk calculations and data sources see appendix table 11-13.

Due to the lack of head-to-head comparative trials, an indirect trial comparison of polatuzumab vedotin + BR and a regimen for the combined chemotherapy subpopulation was proposed by the Danish Medicine Council. However, an adjusted indirect comparison was not possible due to the lack of a common regimen/control, and therefore polatuzumab vedotin + BR vs R-ICE was only compared in a naïve indirect comparison.

Single agent chemotherapy subpopulation

Overall survival (OS) – critical outcome

In the GO29365 study median overall survival was 12.4 months in the polatuzumab vedotin + BR arm and 4.7 months in the BR arm. Yielding an absolute improvement of 7.7 months in favor of polatuzumab vedotin + BR.

The proportion of patients alive after 2 years was 38.2% in the polatuzumab vedotin + BR arm and 17.0% in the BR arm, which is an absolute improvement in the 2-year survival rate of 21.2% in favor of polatuzumab vedotin + BR.

Regarding the relative difference between polatuzumab vedotin + BR and BR, the hazard ratio of (HR 0.42; CI 0.24-0.75; p value 0.002) means a statistically significant relative risk reduction in the polatuzumab vedotin + BR arm.

In conclusion, polatuzumab vedotin + BR shows improvements greater than the normative minimal clinically relevant difference, defined in the Danish Medicine Council protocol [1], in both median overall survival and 2-year overall survival rate. Furthermore, it shows a relative reduction in the risk of death of 58% compared to BR in the single agent chemotherapy subpopulation. This indicates that polatuzumab vedotin + BR results in a great added value in overall survival according to the Danish Medicine Council Manual [32] and protocol [1].

Health related quality of life (HRQoL) – important outcome

No data on SF-36 or FACT-Lym was available for the comparative analysis for polatuzumab vedotin + BR and BR, though some TNAS data was available for polatuzumab vedotin + BR and BR. These TNAS data will be narratively compared.

Polatuzumab vedotin + BR resulted in higher scores in the severity of the peripheral neuropathy symptoms than the BR regimen. However, by the end of treatment the highest means observed was for numbness/tingling in hands/feet, although still ≤2 (range 0-10, 0 being no symptoms). Furthermore, the mean scores rarely exceeded 3.0 during treatment, indicating that overall, patients perceived PN symptoms to be mild.

Since no data on SF-36 or FACT-Lym was available, polatuzumab vedotin + BR cannot be categorized in regards to health-related quality of life.

Progression free survival (PFS) – important outcome

In the GO29365 study progression free survival, assessed by an independent review committee (IRC), was 9.5 months in the polatuzumab vedotin + BR arm and 3.7 months in the BR arm. Yielding an absolute improvement of 5.8 months in favor of polatuzumab vedotin + BR.

The proportion of patients alive and without progression after 2 years (IRC) was 31.3% in the polatuzumab vedotin + BR arm and 4.9% in the BR arm, which is an absolute improvement in the 2-year progression free survival rate of 26.4% in favor of polatuzumab vedotin + BR.

Regarding the relative difference in PFS (IRC) between polatuzumab vedotin + BR and BR, the hazard ratio of (HR 0.36; CI 0.21-0.63; p value <0.001) means a statistically significant relative risk reduction in the polatuzumab vedotin + BR arm.

When comparing polatuzumab vedotin + BR with BR, the polatuzumab vedotin arm shows improvements much greater than the normative minimal clinically relevant differences (MCRD) in 2-year progression free survival rate, while the improvement in median PFS is almost equivalent to the normative MCRD. Furthermore, it shows a relative reduction in the risk of progression or death of 64% compared to BR. This indicates that polatuzumab vedotin + BR results in a great added value in progression free survival according to the Danish Medicine Council Manual [32] and protocol [1].

Adverse events (AEs) – important outcome

The comparative analysis of polatuzumab vedotin + BR versus BR is based on the safety-evaluable population in the GO29365 study, which consisted of 45 patients in the polatuzumab vedotin + BR group (DLBCL cohort 1a and arm C) and 39 patients in the BR group (arm D).

I) Proportion of patients who discontinued treatment due to adverse events

The proportion of patients who discontinued any treatment due to adverse events was 31.1% in the polatuzumab vedotin + BR group and 15.4% in the BR group. In the setting of longer treatment exposure in the polatuzumab vedotin + BR group, this is a statistically insignificant absolute difference of 15.7% (CI -2.7 to 32.4; p value 0.09) between the two treatment regimes.

In relative terms, polatuzumab vedotin + BR results in an increased relative risk of 2.02 (CI 0.86 to 4.75) of patients discontinuing any treatment due to adverse events compared to BR, however statistically insignificant (p value 0.011).

In conclusion, polatuzumab vedotin + BR is associated with a higher proportion of patients who discontinued treatment due to adverse events than BR, however statistically insignificant in terms of both absolute and relative differences. This indicates that the added value polatuzumab vedotin + BR regarding discontinuation due to adverse events cannot be categorized according to the DMC Manual [32] and protocol [1].

II) Proportion of patients experiencing ≥ 1 grade 3 or 4 adverse events

The proportion of patients experiencing one or more treatment-related grade 3 to 4 adverse events was 84.4% in the polatuzumab vedotin + BR group and 71.8% in the BR group. This is a statistically insignificant absolute difference in grade 3 to 4 adverse events of 12.6% (CI -5.0 to 30.0; p value 0.16) between the two treatment regimes.

In relative terms, polatuzumab vedotin + BR results in an increased relative risk of 1.18 (CI 0.93, 1.49) of patients experiencing grade 3 to 4 adverse reactions compared to BR, however statistically insignificant (p value 0.17).

In conclusion, polatuzumab vedotin + BR is associated with a higher proportion of patients experiencing ≥ 1 grade 3 or 4 adverse events than BR, however insignificant in terms of both absolute and relative differences. This indicates that the added value of polatuzumab vedotin + BR regarding grade 3 or 4 adverse events cannot be categorized according to the DMC Manual [32]and protocol [1].

III) Narrative of the adverse events profile focused on a number of adverse events of special interest specified by the Danish Medicine Council Protocol

Neuropathy

The proportion of patients experiencing peripheral neuropathy was 40% in the polatuzumab vedotin + BR group and 7.7% in the BR group, which is an absolute difference of 32.3%. The grade of the PN events should be taken into account when evaluating the higher incidence in the polatuzumab vedotin + BR group, where data showed that only 6/18 patients had grade 2 events and no grade 3 events or above were observed. By the end of treatment, most PN events (11/18) in the polatuzumab vedotin + BR group had resolved, which is of great importance for the patients. The 7 unresolved events were mainly grade 1. These data are reflected in the TNAS data which indicated that overall, patients perceived PN symptoms to be mild.

Infections

The incidence of all infectious events and the incidence of grade 3 to 4 infections were similar in the polatuzumab + BR and BR groups (53.3% vs 51.3% and 23.1% vs 20.5%, respectively). However, in both cases the incidence was higher in the polatuzumab vedotin + BR group (2.2% and 2.6%, respectively). 6 opportunistic infections were reported in 4 patients (8.9%) in the polatuzumab + BR group, while 2 opportunistic infections were reported in 2 patients in the BR group.

Infusion-related reactions

The incidence of infusion-related reactions (related AEs during or within 24 hours of infusion) was 10.2% higher in the polatuzumab vedotin group (33.3%) compared to the BR group (23.1%).

Immunological events

The low incidence of ADAs in patients receiving polatuzumab vedotin suggests that the immunogenicity potential is low, and this is not unexpected given that the mechanism of action of polatuzumab vedotin is to target and kill B cells. There appeared to be no impact of ADAs on polatuzumab vedotin pharmacokinetics.
In terms of safety, based on the current data, there is no identifiable relationship between ADA-positivity and reported AEs. In addition, the emergence of ADAs to polatuzumab vedotin did not appear to impact efficacy with ongoing long-term responses despite development of ADAs [25].

Combined chemotherapy subpopulation

Overall survival (OS) – critical outcome

The median overall survival was 12.4 months in the polatuzumab vedotin + BR arm compared to 10.0 months in the CORAL EXT-1 population and 4.4 months in the CORAL EXT-2 population. This yields an absolute improvement of 2.4 and 8.0 months (CORAL EXT-1 and CORAL EXT-2, respectively) in favor of polatuzumab vedotin + BR.

The 2-year overall survival rate was 38.2% in the polatuzumab vedotin + BR arm compared to approximately 30% in the CORAL EXT-1 population and 15.7% in the CORAL EXT-2 population. This yields an absolute improvement of 8.2% and 22.5% (CORAL EXT-1 and CORAL EXT-2, respectively) in favor of polatuzumab vedotin + BR.

When comparing polatuzumab vedotin + BR with R-ICE (and the equivalent regimens in the CORAL EXT-1 and EXT-2 studies) in the combined chemotherapy subpopulation, the patients treated with polatuzumab vedotin + BR had a longer median overall survival in the range of 2.4-8.0 months and a higher 2-year overall survival rate of 8.2%-22.5%. These data indicates that polatuzumab + BR results in a relevant improvement in overall

survival, however the improvement cannot be categorized due to the nature of the naïve indirect comparison.

Health related quality of life (HRQoL) – important outcome

No data on SF-36, FACT-Lym or other HRQoL measures was collected in neither the CORAL EXT-1 study nor the CORAL EXT-2 study making a comparative analysis of polatuzumab vedotin + BR and R-ICE impossible.

Progression free survival (PFS) – important outcome

No PFS data was collected in neither the CORAL EXT-1 study nor the CORAL EXT-2 study making a comparative analysis of polatuzumab vedotin + BR and R-ICE impossible.

Adverse events (AEs) – important outcome

No adverse events data was collected in neither the CORAL EXT-1 study nor the CORAL EXT-2 study making a comparative analysis of polatuzumab vedotin + BR and R-ICE impossible.

Other considerations

Currently, there is only vial size available of Polivy (140mg). A smaller vial size (30mg), is expected to be made available in Q3 2020. The large vial size is suitable for the standard dosing regimen for an adult up to 78kg. Although, it is expected there are very few patients over 78kg in Denmark, the limited patient numbers does not facilitate vial sharing. For this reason, there is potentially significant waste associated for patients whose weight are above 78kg. For this reason, Roche is offering a waste agreement to all treatment centers where wastage of product will be financially compensated. For further information, please feel free to contact Roche.

There is increased focus on real life efficacy of treatment. As Polivy's EMA approval was based on phase II trial data, we at Roche believe is necessary to follow up and ensure efficacy in Denmark is comparable to efficacy in the clinical trial. For this reason, we are currently exploring the possibility to implement a pay for performance model for Polivy, which would ensure that only patients who have an increased overall survival compared to current treatment pay for Polivy. The agreement is in ongoing discussion with National Clinical Registries (RKKP), Amgros and clinical experts in Denmark.

7 References

1. Medicinrådets protokol for vurdering af polatuzumab vedotin i kombination med bendamustin og rituximab til behandling af diffust storcellet B-cellelymfom (Version 1.0). 2019.
2. Sehn LH, Herrera AF, Flowers CR, et al. Polatuzumab Vedotin in Relapsed or Refractory Diffuse Large B-Cell Lymphoma. J Clin Oncol. 2020;38(2):155-165.
3. Van Den Neste E, Schmitz N, Mounier N, et al. Outcomes of diffuse large B-cell lymphoma patients relapsing after autologous stem cell transplantation: an analysis of patients included in the CORAL study. Bone Marrow Transplant. 2017;52(2):216-221.
4. Van Den Neste E, Schmitz N, Mounier N, et al. Outcome of patients with relapsed diffuse large B-cell lymphoma who fail second-line salvage regimens in the International CORAL study. Bone Marrow Transplant. 2016;51(1):51-57.
5. Den landsdækkende LYFO database. Malignt Lymfom og CLL - National årsrapport. 2018.

.

6. Arboe B, El-Galaly TC, Clausen MR, et al. The Danish National Lymphoma Registry: Coverage and Data Quality. PLoS One. 2016;11(6):e0157999.
7. Sehn LH, Gascoyne RD. Diffuse large B-cell lymphoma: optimizing outcome in the context of clinical and biologic heterogeneity. Blood. 2015;125(1):22-32.
8. Lenz G, Rutherford SC, Davies A, et al. The Burden of Relapsed/Refractory (R/R) Diffuse Large B-Cell Lymphoma (DLBCL): A Systematic Literature Review (SLR). Blood. 2018;132.
9. Friedberg JW. Relapsed/refractory diffuse large B-cell lymphoma. Hematology Am Soc Hematol Educ Program. 2011;2011:498-505.
10. Arboe B, Olsen MH, Gorlov JS, et al. Treatment intensity and survival in patients with relapsed or refractory diffuse large B-cell lymphoma in Denmark: a real-life population-based study. Clin Epidemiol. 2019;11:207-216.
11. Dansk Lymfom Gruppe (DLG). Kliniske retningslinjer - Diffust storcellet B-celle lymfom (Version 1.0). 2019.
12. Dansk Lymfom Gruppe (DLG). Udtræk fra LYFO database 2013-2018
13. The CORAL study. 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. ClinicalTrials.gov Identifier: NCT00137995. 2003-2008.
14. Dornan D, Bennett F, Chen Y, et al. Therapeutic potential of an anti-CD79b antibody-drug conjugate, anti-CD79b-vc-MMAE, for the treatment of non-Hodgkin lymphoma. Blood. 2009;114(13):2721-2729.
15. Pfeifer M, Zheng B, Erdmann T, et al. Anti-CD22 and anti-CD79B antibody drug conjugates are active in different molecular diffuse large B-cell lymphoma subtypes. Leukemia. 2015;29(7):1578-1586.
16. Polson AG, Yu SF, Elkins K, et al. Antibody-drug conjugates targeted to CD79 for the treatment of non-Hodgkin lymphoma. Blood. 2007;110(2):616-623.
17. Polson AG, Calemine-Fenaux J, Chan P, et al. Antibody-drug conjugates for the treatment of non-Hodgkin's lymphoma: target and linker-drug selection. Cancer Res. 2009;69(6):2358-2364.
18. Doronina SO, Toki BE, Torgov MY, et al. Development of potent monoclonal antibody auristatin conjugates for cancer therapy. Nat Biotechnol. 2003;21(7):778-784.
19. Coiffier B. Rituximab in the treatment of diffuse large B-cell lymphomas. Semin Oncol. 2002;29(1S2):30-35.
20. Coiffier B, Feugier P, Mounier N, et al. Long-term results of the GELA study comparing R-CHOP and CHOP chemotherapy in older patients with diffuse large B-cell lymphoma show good survival in poor-risk patients. Journal of Clinical Oncology. 2007;25(18).
21. Coiffier B, Thieblemont C, Van Den Neste E, et al. Long-term outcome of patients in the LNH-98.5 trial, the first randomized study comparing rituximab-CHOP to standard CHOP chemotherapy in

DLBCL patients: a study by the Groupe d'Etudes des Lymphomes de l'Adulte. Blood. 2010;116(12):2040-2045.

22. Habermann TM, Weller EA, Morrison VA, et al. Rituximab-CHOP versus CHOP alone or with maintenance rituximab in older patients with diffuse large B-cell lymphoma. Journal of Clinical Oncology. 2006;24(19):3121-3127.

23. Gisselbrecht C, Glass B, Mounier N, et al. Salvage regimens with autologous transplantation for relapsed large B-cell lymphoma in the rituximab era. J Clin Oncol. 2010;28(27):4184-4190.

24. Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. J Clin Oncol. 2014;32(27):3059-3068.

25. Roche. CSR (Clinical Study Report) of GO29365. 2019.

26. Committee for Medicinal Products for Human Use (CHMP). European Public Assessment Report (EPAR) - Polivy. Procedure No. EMEA/H/C/004870/0000. 2019.

27. Mendoza TR, Wang XS, Williams LA, et al. Measuring Therapy-Induced Peripheral Neuropathy: Preliminary Development and Validation of the Treatment-Induced Neuropathy Assessment Scale. J Pain. 2015;16(10):1032-1043.

28. Thomas SK, Mendoza TR, Vichaya EG, et al. Validation of the chemotherapy-induced neuropathy assessment scale. Journal of Clinical Oncology. 2012;30(15).

29. Study GO29365. A Study of Polatuzumab Vedotin (DCDS4501A) in Combination With Rituximab or Obinutuzumab Plus Bendamustine in Participants With Relapsed or Refractory Follicular or Diffuse Large B-Cell Lymphoma. ClinicalTrials.gov Identifier: NCT02257567.

30. Medicinrådet. Medicinrådets vurdering af klinisk merværdi for axicabtagene ciloleucel til behandling af diffust storcellet B-celle-lymfom (version 1.1). 2019.

31. Medicinrådet. Medicinrådets vurdering af klinisk merværdi for tisagenlecleucel til behandling af diffust storcellet B-celle-lymfom (version 1.1). 2019.

32. Medicinrådet. Håndbog for Medicinrådets proces og metode vedr. nye lægemidler og indikationsudvidelser (version 2.4). .

33. Roche data on file. 2020.

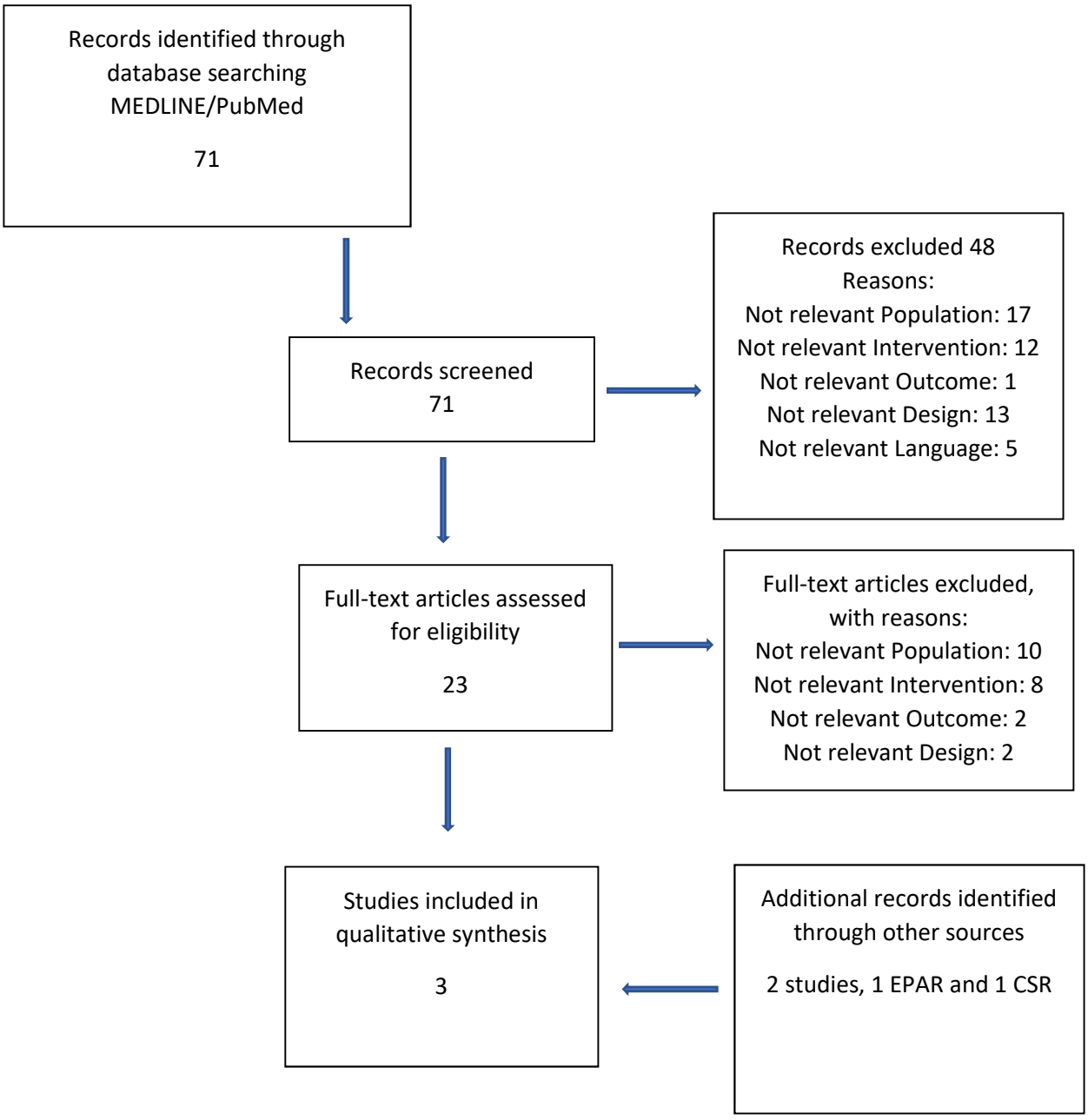
34. Roche Registration GmbH, MAH Core Submission Dossier PTJA06, https://eunethta.eu/ptja06

8 Appendices

8.1 Literature search

Table 6. Inclusion and exclusion criteria		
	Inclusion criteria	**Exclusion criteria**
Population	Adult patients with relapsed/refractory diffuse large cell B-cell lymphoma, who are not candidates for haematopoietic stem cell transplant	Other types of populations than the demanded ones
Intervention	Polatuzumab vedotin in combination with rituximab and bendamustine	Other types of intervention than the demanded ones
Comparators	Single Agent Chemotherapy: • Bendamustine (70 mg/m^2 or 90 mg/m^2 Day 1-2) and rituximab (375 mg/m^2 Day 1) Combination chemotherapy: • GDP and rituximab (375 mg/m^2 Day 1) • GemOx and rituximab (375 mg/m^2 Day 1) • ICE and rituximab (375 mg/m^2 Day 1) Studies that can be used for an indirect comparison of polatuzumab vedotin, bendamustine and rituximab with GDP or GemOx or ICE in combination with rituximab.	
Outcomes	At least one relevant for the protocol (OS, PFS, AE, HRQoL)	Outcome(s) out of PICO, other types of populations than the demanded
Design	Prospective, randomized clinical trials Retrospective, observational studies Full text only	Review articles Conference abstract
Language	English, Scandinavian	Other language
Publication date (Date limits)	N/A	N/A
Human/animal	Human only	Veterinary (not human)

PRISMA Flow Diagram MEDLINE via PubMed



PRISMA Flow Diagram CENTRAL via Cochrane Library

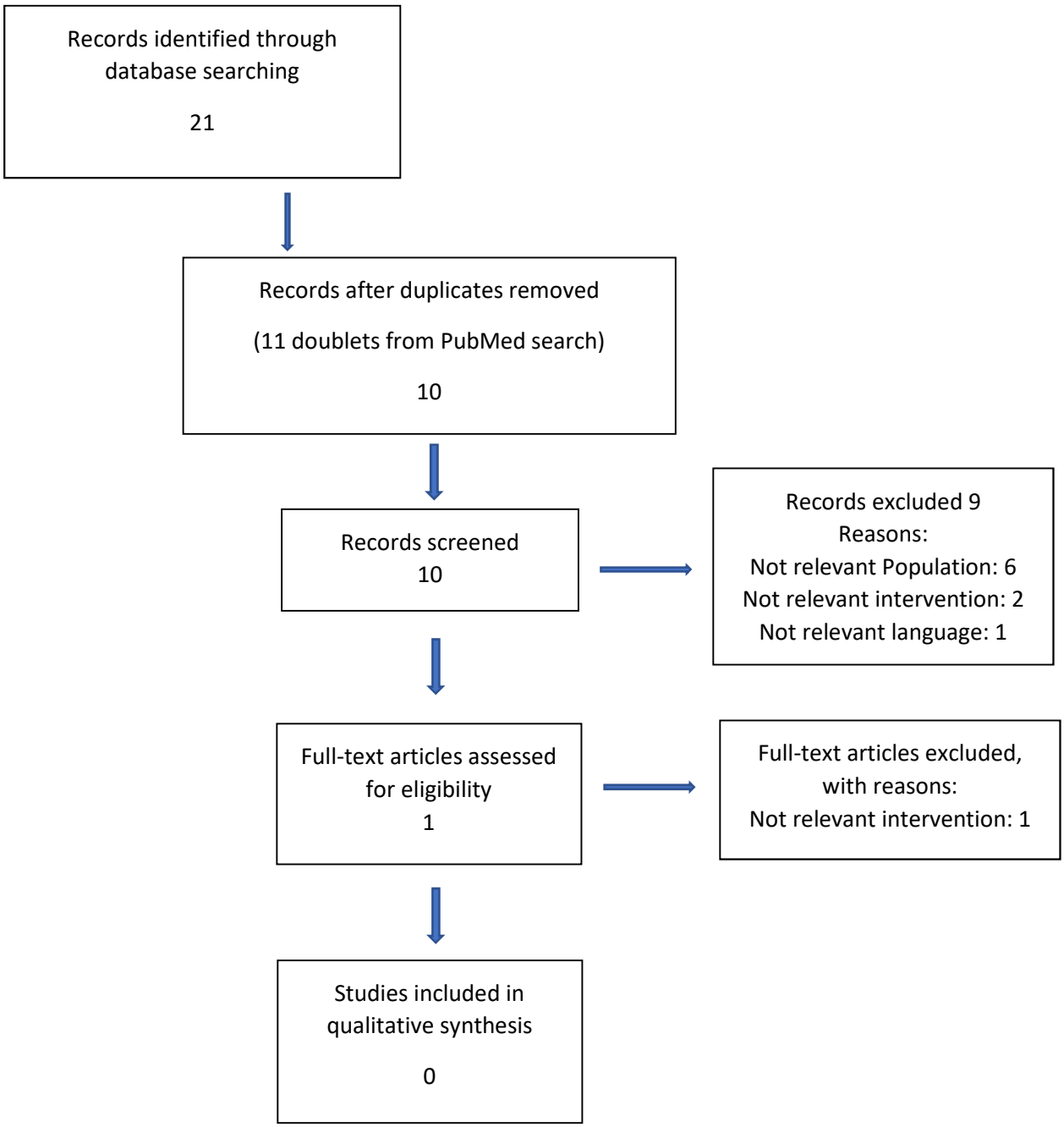


Table 7. Overview of excluded full text articles				
Author	Journal and year	Title	Reason	Search
Yamasaki, S. et al	Kurume Med J 2019	Rituximab-Mediated Complement-Dependent Cytotoxicity Enhanced by Gemcitabine in Older Patients with Previously Rituximab-Treated Diffuse Large B-Cell Lymphoma: Study Protocol	Outcome: No outcome, only trial design	PubMed
Shingleton, J. R. et al	J Clin Oncol 2019	Polatuzumab Vedotin: Honing in on Relapsed or Refractory Diffuse Large B-Cell Lymphoma	Outcome: Associated content to article - no outcome data	PubMed
Morschhauser, F. et al.	Lancet Haematol 2019	Polatuzumab vedotin or pinatuzumab vedotin plus rituximab in patients with relapsed or refractory non-Hodgkin lymphoma: final results from a phase 2 randomized study (ROMULUS)	Intervention: Bendamustine not included as IMP	PubMed and Cochrane
Ionescu-Ittu, R. et al	J Comp Eff Res 2019	Second-line rituximab-bendamustine versus rituximab-gemcitabine-oxaliplatin in diffuse large B-cell lymphoma in the real world	Intervention: R-GEMOX - not chosen as comparator *and Real world study n = 702; R-Benda n=32; R-GemOx n=10*	PubMed
No authors listed	Cancer Discovery 2019	Polatuzumab Vedotin Approved for DLBCL	Design: Review	PubMed
Turki, A. T. et al	Oncol Res Treat 2018	R-ICE Chemotherapy with or without Autologous Transplantation for Elderly Patients with Relapsed or Refractory Aggressive B-Cell Lymphomas	Population: 53% DLBCL, 35% Transformed FL, 12% unknown aggressive B-cell	PubMed
Moccia, A. A. et al	Leuk Lymphoma 2017	Gemcitabine, dexamethasone, and cisplatin (GDP) is an effective and well-tolerated salvage therapy for relapsed/refractory diffuse large B-cell lymphoma and Hodgkin lymphoma	Population: Patients eligible for stem cell transplantation	PubMed
Czuczman, M. S. et al.	Clin Cancer Res 2017	A Phase 2/3 Multicenter, Randomized, Open-Label Study to Compare the Efficacy and Safety of Lenalidomide Versus Investigator's	Intervention: Investigators choice was single agent CT not valid as	PubMed and Cochrane

		Choice in Patients with Relapsed or Refractory Diffuse Large B-Cell Lymphoma	comparator in protocol	
Jo, J. C. et al.	Asia Pac J Clin Oncol 2016	Biweekly dose-dense gemcitabine-oxaliplatin and dexamethasone for relapsed/refractory aggressive non-Hodgkin lymphoma: A multicenter, single-arm, phase II trial	Population: Patients eligible for stem cell transplantation and population mixed of DLBCL other NHL and outcome not specified for DLBCL	PubMed
Pfeifer, M. et al.	Leukemia 2015	Anti-CD22 and anti-CD79B antibody drug conjugates are active in different molecular diffuse large B-cell lymphoma subtypes	Intervention: Not including bendamustine	PubMed and Cochrane
Palanca-Wessels, M. C. et al.	Lancet Oncol 2015	Safety and activity of the anti-CD79B antibody-drug conjugate polatuzumab vedotin in relapsed or refractory B-cell non-Hodgkin lymphoma and chronic lymphocytic leukaemia: a phase 1 study	Intervention: Not including bendamustine	PubMed
Mounier, N. et al	Haematologica 2013	Rituximab plus gemcitabine and oxaliplatin in patients with refractory/relapsed diffuse large B-cell lymphoma who are not candidates for high-dose therapy. A phase II Lymphoma Study Association trial	Intervention: R-GEMOX - not chosen as comparator	PubMed
Hou, Y. et al.	Med Oncol 2012	Rituximab, gemcitabine, cisplatin, and dexamethasone in patients with refractory or relapsed aggressive B-cell lymphoma	Population: R/R (NHL), 60% DLBCL, 40% FL and outcome for DLBCL is not specified	PubMed
Aribi, M. et al.	J Cancer Res Ther 2010	Gemcitabine and treatment of diffuse large B-cell lymphoma in relapsed or refractory elderly patients: a prospective randomized trial in Algeria	Intervention: Rituximab not included in GDP regime	PubMed and Cochrane
Kim, K. H. et al.	Korean J Intern Med 2009	Gemcitabine, etoposide, cisplatin, and dexamethasone in patients with refractory or relapsed non-Hodgkin's lymphoma	Population: Patient eligible for stem cell transplantation	PubMed
Lopez, A. et al.	Eur J Haematol 2008	GEMOX-R regimen is a highly effective salvage regimen in patients with refractory/relapsing	Intervention: R-GEMOX - not chosen as comparator	PubMed

		diffuse large-cell lymphoma: a phase II study		
Simpson, L. et al.	Leuk Lymphoma 2007	Effectiveness of second line salvage chemotherapy with ifosfamide, carboplatin, and etoposide in patients with relapsed diffuse large B-cell lymphoma not responding to cis-platinum, cytosine arabinoside, and dexamethasone	Population: Patient eligible for stem cell transplantation	PubMed
El Gnaoui et al.	Ann Oncol 2007	Rituximab, gemcitabine and oxaliplatin: an effective salvage regimen for patients with relapsed or refractory B-cell lymphoma not candidates for high-dose therapy	Population: The majority (72%) had diffuse large B-cell lymphoma.	PubMed
Hagberg, H. et al.	Ann Oncol 2006	Randomized phase III study of R-ICE versus R-DHAP in relapsed patients with CD20 diffuse large B-cell lymphoma (DLBCL) followed by high-dose therapy and a second randomization to maintenance treatment with rituximab or not: an update of the CORAL study	Design: Symposium article; no outcomes on PFS or OS	PubMed and Cochrane
Jerkeman, M. et al	Eur J Haematol 2004	ICE (ifosfamide, carboplatin, etoposide) as second-line chemotherapy in relapsed or primary progressive aggressive lymphoma--the Nordic Lymphoma Group experience	Population: Patients eligible for stem cell transplantation	PubMed
Crump, M. et al	Cancer 2004	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)	Population: Patients eligible for stem cell transplantation	PubMed
Hertzberg, M. S. et al	Ann Oncol 2003	Outpatient-based ifosfamide, carboplatin and etoposide (ICE) chemotherapy in transplant-eligible patients with non-Hodgkin's lymphoma and Hodgkin's disease	Population: Patients eligible for stem cell transplantation	PubMed

8.2 Main characteristics of included studies

Table 8. Main study characteristics of the GO29365 study	
Trial name	A study of Polatuzumab Vedotin (DSDS4501A) in Combination With Rituximab or Obinutuzumab Plus Bendamustine in Participants With Relapsed or Refractory Follicular or Diffuse Large B-Cell Lymphoma
NCT number	02257567
Objective	The main purpose of this study is to evaluate efficacy, safety, and pharmacokinetics of polatuzumab vedotin administered with bendamustine and rituximab compared with bendamustine and rituximab in adult participants with relapsed or refractory diffuse large B-cell lymphoma. *(Patients with follicular lymphoma are not relevant for this application and will not be described)*
Publications – title, *author, journal, year*	Polatuzumab Vedotin in Relapsed or Refractory Diffuse Large B-Cell Lymphoma, *Laurie H. Sehn et al., Journal of Clinical Oncology, 2019* [2]
Study type and design	GO29365 is an International, multicenter, open-label, phase Ib/II clinical trial which included participants with relapsed or refractory diffuse large B-cell lymphoma who are 18 years or older. Participants in the randomly assigned cohort were randomized in a 1:1 ratio to receive either polatuzumab vedotin plus bendamustine and rituximab or bendamustine and rituximab only.
Follow-up time	Median follow-up was 22.3 months (data cutoff: April 30, 2018)
Population (inclusion and exclusion criteria)	**Inclusion criteria:** • Histologically confirmed relapsed or refractory DLBCL • If the participant has received prior bendamustine, response duration must have been greater than (>) 1 year (for participants who have relapse disease after a prior regimen) • At least one bi-dimensionally measurable lesion on imaging scan defined as >1.5 centimeters (cm) in its longest dimension • Life expectancy of at least 24 weeks • Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2 • Adequate hematological function unless inadequate function is due to underlying disease **Exclusion criteria:** • Contraindication to bendamustine, rituximab, or obinutuzumab • Treatment with radiotherapy, chemotherapy, immunotherapy, immunosuppressive therapy, or any investigational agent for the purposes of treating cancer within 2 weeks prior to Cycle 1 Day 1

	• Completion of autologous stem cell transplant (SCT) within 100 days prior to Cycle 1 Day 1 • Prior allogeneic SCT • Eligibility for autologous SCT • Grade 3b follicular lymphoma • History of transformation of indolent disease to DLBCL • Primary or secondary CNS lymphoma • Current Grade >1 peripheral neuropathy All criteria are listed at clinicaltrials.gov
Intervention	**Polatuzumab vedotin plus bendamustine and rituximab arm:** Polatuzumab vedotin at a dose of 1.8 mg/kg, administered intravenously, on day 2 of cycle 1, then on day 1 of each subsequent cycle for up to 6 cycles. Bendamustine at a dose of 90 mg per square meter of body-surface area, administered intravenously, on days 2 and 3 of cycles 1, then on days 1 and 2 of each subsequent cycle up to 6 cycles. Rituximab at a standard dose of 375 mg per square meter of body-surface area, administered intravenously, on day 1 of each subsequent cycle for up to 6 cycles. **Bendamustine and rituximab arm:** Bendamustine at a dose of 90 mg per square meter of body-surface area, administered intravenously, on days 2 and 3 of cycles 1, then on days 1 and 2 of each subsequent cycle up to 6 cycles. Rituximab at a standard dose of 375 mg per square meter of body-surface area, administered intravenously, on day 1 of each subsequent cycle for up to 6 cycles.
Baseline characteristics	See table 5. – Characteristics of cohort 1a and the randomized cohort.
Primary and secondary endpoints	Primary outcome measures: • Percentage of Participants with Complete Response (CR) According to Modified Lugano Criteria as Measured by PET/CT Scan and Determined by Independent Review Committee (IRC) Secondary outcome measures: • Percentage of Participants with Adverse Events • Progression free survival (IRC-assessed) by PET-CT or CT alone Exploratory outcome measures: • Overall survival All primary and secondary endpoints are described at clinicaltrials.gov
Method of analysis	The safety-evaluable population comprised patients who received ≥1 dose of any study treatment. One patient in both the polatuzumab + BR and the BR group did not receive the study treatment and so was excluded from the safety-evaluable population. Efficacy analyses were performed based on the intent-to-treat principle (i.e., all

	randomly assigned patients were analyzed according to their treatment assignment at the time of randomization). The intent-to-treat population included all patients with DLBCL by investigator/site pathology. Response rates were reported as percentages with associated 95% Clopper–Pearson (i.e., exact binomial) CIs. Time-to event end points, including DOR, PFS, and OS, were summarized as median survival time estimated using Kaplan–Meier methodology with 95% Greenwood's CIs. Differences in response rate and time-to-event end points between the pola-BR and BR arms were compared for exploratory purposes and reported as absolute differences and hazard ratios (HRs) using stratified Wilson and Cox regression methods, respectively.
Subgroup analyses	Post hoc analyses of a number of clinical and biological subgroups were performed (not full list): age groups <65 or ≥65, sex, race, baseline ECOG PS 0-1 or ≥2, ABC or GCB.

Table 9. Main study characteristics of the CORAL EXT-1 study

Trial name	R-ICE Versus R-DHAP in Patients Aged 18-65 With Relapse Diffuse Large B-cell Lymphoma
NCT number	00137995
Objective	Investigate the outcome and prognostic factors in the group of patients that relapsed after BEAM/HSCT in the CORAL study.
Publications – title, *author, journal, year*	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 E et al., Bone Marrow Transplantation, 2017 [*3]
Study type and design	CORAL EXT-1 is a retrospective, observational study, which included participants more than 18 of age with DLBCL from the CORAL study (randomized phase 3 study), who relapsed after HSCT, and due to this were candidates for a third-line regimen. Patient characteristics at relapse, response to third-line treatment and OS data were retrospectively collected.
Follow-up time	Median follow-up was 32.8 months (range 24.3-45.8 months)
Population (inclusion and exclusion criteria)	**Inclusion criteria:** • Histologically confirmed relapsed or refractory DLBCL • Relapsed after HSCT and were candidates for a third-line regimen Eligibility criteria of the CORAL study are listed at clinicaltrials.gov, NCT 00137995
Intervention	**ICE-like** Ifosfamide, carboplatin and etoposide +/- rituximab **DHAP-like** **Gemcitabine-containing**

	Mostly combined with vinorelbine, oxaliplatin, dacarbazine or cyclophosphamide **CHOP like** **Miscellaneous regimens** Including lenalidomide, vincristine, bleomycin, fludarabine, bendamustine, in monotherapy or in various combinations *No data on dose and frequency of administration are available*
Baseline characteristics	See table 5.
Primary and secondary endpoints	N/A
Method of analysis	The Kaplan–Meier method was used to estimate the OS. The Wilcoxon's signed-rank test or X^2-test was used to compare the patient characteristics. Cox regression analysis was used to calculate the hazard ratio (HR) between different patient categories. All reported P-values are two-sided, and P-values <0.05 were considered significant.
Subgroup analyses	Subgroup analyses of the following prognostic factors were performed: tertiary IPI at second relapse, disease-free interval after HSCT, response to third-line therapy, and transplantation.

Table 10. Main study characteristics of the CORAL EXT-2 study

Trial name	R-ICE Versus R-DHAP in Patients Aged 18-65 With Relapse Diffuse Large B-cell Lymphoma
NCT number	00137995
Objective	Investigate the outcome and prognostic factors in the group of patients who did not proceed to HSCT in the CORAL study and who were candidates for a third-line regimen.
Publications – title, *author, journal, year*	Outcome of patients with relapsed diffuse large B-cell lymphoma who fail second-line salvage regimens in the International CORAL study, *Van Den Neste E et al., Bone Marrow Transplantation, 2016* [4]
Study type and design	CORAL EXT-2 is a retrospective, observational study, which included participants more than 18 of age with DLBCL from the CORAL study (randomized phase 3 study) who failed to proceed to BEAM+HSCT, and due to this were candidates for a third-line regimen. Patient characteristics at relapse, response to third-line treatment and OS data were retrospectively collected.
Follow-up time	Median follow-up was 30.1 months
Population (inclusion and exclusion criteria)	**Inclusion criteria:** • Histologically confirmed relapsed or refractory DLBCL

	• Failed to proceed to BEAM+HSCT and were candidates for a third-line regimen Eligibility criteria of the CORAL study are listed at clinicaltrials.gov, NCT 00137995
Intervention	**ICE-like** Isofosfamide, carboplatin and etoposide +/- rituximab **DHAP-like** **Gemcitabine-containing** Mostly combined with vinorelbine, oxaliplatin, dacarbazine or cyclophosphamide **Dexa-BEAM** **CHOP like** **Miscellaneous regimens** Including lenalidomide, vincristine, bleomycin, fludarabine, bendamustine, in monotherapy or in various combinations *No data on dose and frequency of administration are available*
Baseline characteristics	See table 5.
Primary and secondary endpoints	N/A
Method of analysis	The Kaplan–Meier method was used to estimate OS. Wilcoxon's signed rank test or the χ2 test was used to compare patient characteristics. Cox regression analysis was used to calculate the hazard ratio (HR) between different patient categories. All reported P-values are two-sided, and P<0.05 was considered significant. Progression-free survival (PFS) and event-free survival (EFS) after third-line treatment were not taken into account because it was anticipated that these results would be less reliable, and the initial CORAL report showed that over 90% of deaths were lymphoma-related.
Subgroup analyses	A sub-analysis was performed on patients who were removed from the CORAL study for no response to first salvage therapy. Subgroup analyses of a number of prognostic factors were performed as well.

8.3 Results per study

Table 11. Results from the GO29365 study

Trial name: **A study of Polatuzumab Vedotin (DSDS4501A) in Combination With Rituximab or Obinutuzumab Plus Bendamustine in Participants With Relapsed or Refractory Follicular or Diffuse Large B-Cell Lymphoma**

Results published in:

1) Polatuzumab Vedotin in Relapsed or Refractory Diffuse Large B-Cell Lymphoma, *Laurie H. Sehn et al., Journal of Clinical Oncology, 2019* [2]
2) European Public Assessment Report (EPAR) CHMP [26]
3) Exact numbers from Roche data on file [33]
4) Manual calculations
5) Medcalc calculations using: https://www.medcalc.org/calc/comparison_of_proportions.php
6) Medcalc calculations using: https://www.medcalc.org/calc/relative_risk.php

NCT number: 02257567

Overall survival (1)

				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation
Outcome	Study arm	N	Result (95% CI)	Difference	95% CI	*P* value	Hazard ratio	95% CI	*P* value	
Median overall survival, months	Polatuzumab + bendamustine and rituximab	40	12.4 (9.0–not evaluable) months(1)	7.7 (4)			0.42(1)	0.24-0.75	0.0023	Probability of survival is estimated from Kaplan–Meier method with 95% Greenwoods confidence intervals. Difference in time-to-event end points were reported as hazard ratios (HRs) using Cox regression methods.
	Bendamustine and rituximab	40	4.7 (3.7–8.3) months(1)							
2-year overall survival rate, %	Polatuzumab + bendamustine and rituximab	40	38.2% (22.5-53.9) (3)	21.2 (4)			N/A			Survival rates are based on Kaplan-Meier estimator.
	Bendamustine and rituximab	40	17.0% (3.6-30.4) (3)							

Health-related quality of life

Outcome	Study arm	N	Result	Estimated absolute difference in effect: Difference	95% CI	*P* value	Estimated relative difference in effect: Relative risk	95% CI	*P* value	Description of methods used for estimation
Average change from baseline in SF-36 until end of treatment	Polatuzumab + bendamustine and rituximab	40	N/A							
	Bendamustine and rituximab	40	N/A							
Average change from baseline in SF-36 until end of follow-up	Polatuzumab + bendamustine and rituximab	40	N/A							
	Bendamustine and rituximab	40	N/A							
Average change from baseline in FACT-Lym until end of treatment	Polatuzumab + bendamustine and rituximab	40	N/A							
	Bendamustine and rituximab	40	N/A							
Average change from baseline in FACT-Lym until end of follow-up	Polatuzumab + bendamustine and rituximab	40	N/A							
	Bendamustine and rituximab	40	N/A							
Progression free survival – assessed by independent review committee										
Outcome	Study arm	N	Result (95% CI)	Estimated absolute difference in effect: Difference	95% CI	*P* value	Estimated relative difference in effect: Hazard ratio	95% CI	*P* value	Description of methods used for estimation
Median progression free survival, months	Polatuzumab + bendamustine and rituximab	40	9.5 (6.2-13.9) [1]	5.8[4]			0.36[1]	0.21-0.63	*<0.001*	P value estimated by log-rank.
	Bendamustine and rituximab	40	3.7 (2.1-4.5) [1]							

2-year progression free survival rate, %	Polatuzumab + bendamustine and rituximab	40	31.3% (16.6-46.5) [3]	26.4[4]			N/A			
	Bendamustine and rituximab	40	4.9% (0-13.4) [3]							
Adverse events										
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation
Outcome	Study arm	N	Result (n)	Difference	95% CI	*P* value	Relative risk	95% CI	*P* value	
Proportion of patients who discontinued any treatment due to adverse events, %	Polatuzumab + bendamustine and rituximab	45	31.1% (14) [x]	15.7[5]	(-)2.7-32.4	*0.09*	2.02[6]	0.86-4.75	*0.11*	The values P-BR and BR is listed from x , table 45, page 145. Colon: Patients with AE leading to any study drug discontinuation [34]. The absolute difference is calculated using the "N-1" Chi-squared test*. The 95% confidence interval is calculated according to the recommended method** The relative risk, its standard error and the 95% confidence interval are calculated according to standard methods.***
	Bendamustine and rituximab	39	15.4% (6) [x]							
Proportion of patients experiencing ≥ 1 grade 3 or 4 adverse events	Polatuzumab + bendamustine and rituximab	45	84.4% (38) [2]	12.6[5]	(-)5.0-30.0	*0.16*	1.18[6]	0.93-1.49	*0.17*	The absolute difference is calculated using the "N-1" Chi-squared test*. The 95% confidence interval is calculated according to the recommended method** The relative risk, its standard error and the 95% confidence interval are calculated according to standard methods.***
	Bendamustine and rituximab	39	71.8% (28) [2]							

* Campbell I (2007) Chi-squared and Fisher-Irwin tests of two-by-two tables with small sample recommendations. Statistics in Medicine 26:3661-3675, Richardson JTE (2011) The analysis of 2 x 2 contingency tables - Yet again. Statistics in Medicine 30:890 ** Altman DG, Machin D, Bryant TN, Gardner MJ (Eds) (2000) Statistics with confidence, 2nd ed. BMJ Books. (p. 49) *** Altman DG (1991) Practical statistics for medical research. London: Chapman and Hall.

Table 12. Results from the CORAL EXT-1 study

Trial name:	**R-ICE Versus R-DHAP in Patients Aged 18-65 With Relapse Diffuse Large B-cell Lymphoma** Results published in: 1) 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 E et al., Bone Marrow Transplantation, 2017* [3]
NCT number:	00137995

Overall survival (1)

				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation
Outcome	Study arm	N	Result (95% CI)	Difference	95% CI	*P* value	Hazard ratio	95% CI	*P* value	
Median overall survival, months	ITT population	75	10.0 (N/A)							
2-year overall survival rate, %	ITT population	75	Approx.. 30% (N/A)							Estimated from the Kaplan-Meier overall survival curve. It is in line with the estimations made by the Danish Medicine Council [30,31].

Health-related quality of life

				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation
Outcome	Study arm	N	Result	Difference	95% CI	*P* value	Relative risk	95% CI	*P* value	
Average change from baseline in SF-36 until end of treatment	ITT population	75	N/A							

Average change from baseline in SF-36 until end of follow-up	ITT population	75	N/A						
Average change from baseline in FACT-Lym until end of treatment	ITT population	75	N/A						
Average change from baseline in FACT-Lym until end of follow-up	ITT population	75	N/A						
Progression free survival									
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Hazard ratio	95% CI	*P* value	
Median progression free survival, months	ITT population	75	N/A							
2-year progression free survival rate, %	ITT population	75	N/A							
Adverse events										
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation
Outcome	Study arm	N	Result (n)	Difference	95% CI	*P* value	Relative risk	95% CI	*P* value	
Proportion of patients who discontinued any treatment due to adverse events, %	ITT population	75	N/A							

Proportion of patients experiencing ≥ 1 grade 3 or 4 adverse events	ITT population	75	N/A							

Table 13. Results from the CORAL EXT-2 study

Trial name:	**R-ICE Versus R-DHAP in Patients Aged 18-65 With Relapse Diffuse Large B-cell Lymphoma** Results published in: 1) Outcome of patients with relapsed diffuse large B-cell lymphoma who fail second-line salvage regimens in the International CORAL study, *Van Den Neste E et al., Bone Marrow Transplantation, 2016* [4]
NCT number:	00137995

Overall survival (1)

				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation
Outcome	Study arm	N	Result (95% CI)	Difference	95% CI	*P* value	Hazard ratio	95% CI	*P* value	
Median overall survival, months	ITT population	203	4.4 (N/A)							
2-year overall survival rate, %	ITT population	203	15.7% (N/A)							Survival rates are based on Kaplan-Meier estimator.

Health-related quality of life

				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation
Outcome	Study arm	N	Result	Difference	95% CI	*P* value	Relative risk	95% CI	*P* value	
Average change from baseline in SF-36 until end of treatment	ITT population	203	N/A							

Average change from baseline in SF-36 until end of follow-up	ITT population	203	N/A					
Average change from baseline in FACT-Lym until end of treatment	ITT population	203	N/A					
Average change from baseline in FACT-Lym until end of follow-up	ITT population	203	N/A					
Progression free survival								
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Hazard ratio	95% CI	*P* value	
Median progression free survival, months	ITT population	203	N/A							
2-year progression free survival rate, %	ITT population	203	N/A							
Adverse events										
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation
Outcome	Study arm	N	Result (n)	Difference	95% CI	*P* value	Relative risk	95% CI	*P* value	
Proportion of patients who discontinued any treatment due to adverse events, %	ITT population	203	N/A							

Proportion of patients experiencing ≥ 1 grade 3 or 4 adverse events	ITT population 203 N/A			

Medicinrådet har på rådsmødet d. 26/08 2020 diskuteret vurderingsrapporten vedr. polatuzumab vedotin til patienter med DLBCL og har i den forbindelse efterspurgt yderligere data på lægemidlet (tillæg til den endelige ansøgning) fra Roche.

Sekretariatet har efterspurgt opdaterede tabeller samt rå data fra den seneste Clinical Study Report. Den seneste Clinical Study Report (CSR) er dateret Juni 2020.

Alle data i dette tillæg er på nuværende tidspunkt ikke publicerede og skal derfor blændes.

Tillægget indeholder som følger:

<u>Tabeller med opdaterede data på Arm C, D samt nye data på Arm G, H samt G+H (poolet)</u>

- Baseline karakteristika for Arm G og H samt G+H (side 3-4)
- Opdaterede effektdata for Arm C og D (side 5,7)
- Effektdata fra Arm G, H samt G+H (side 5,7,8)

<u>Rå data fra CSR på Arm C, D, G, H samt G+H (poolet)</u>

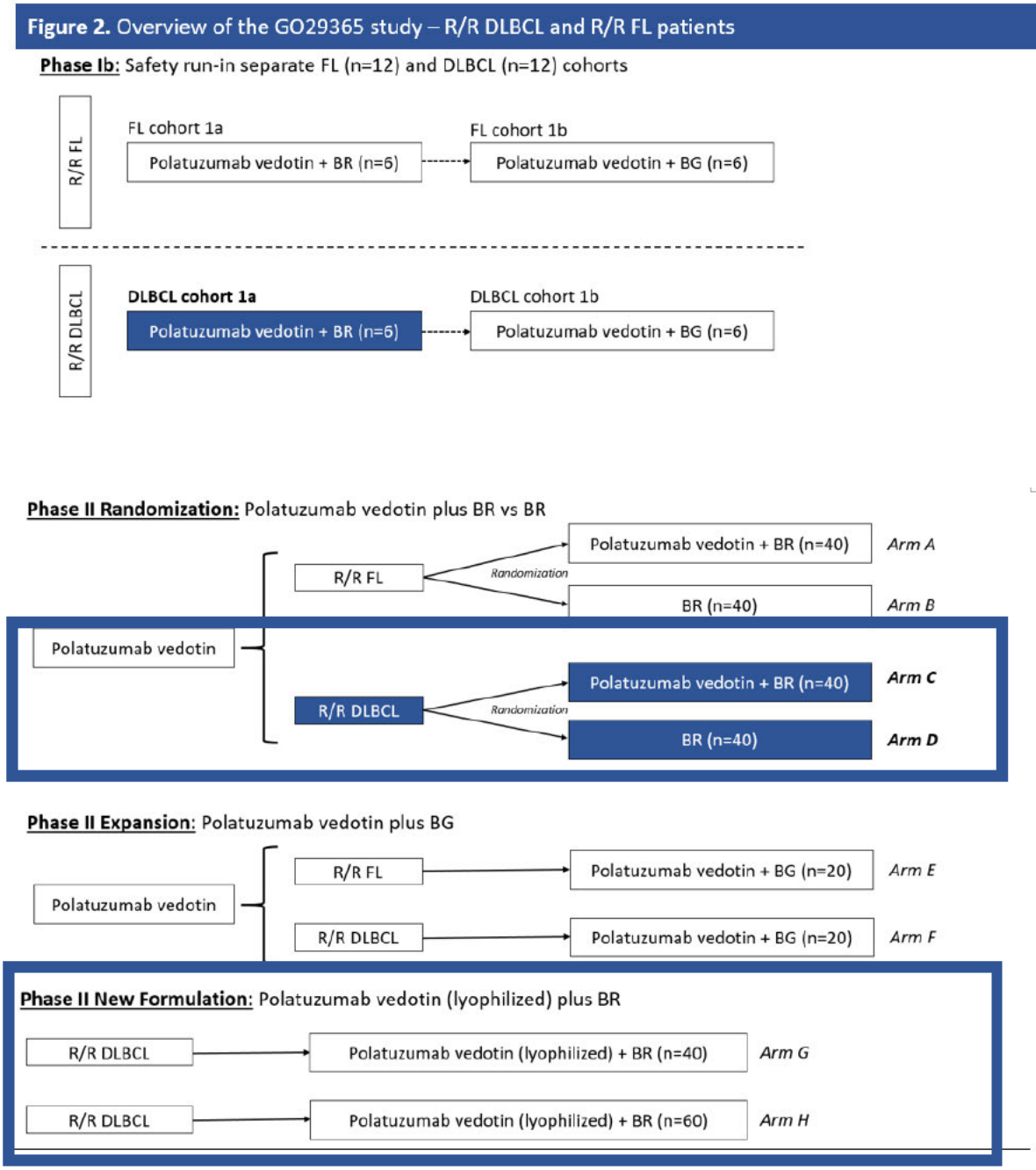
- Baseline karakteristika for Arm G og H samt G+H (side 10-11)
- Information om opfølgningsdata, OS og PFS (side 12)
- Median OS arm C, D, G, H samt G+H (side 13)
- 2-year overall survival rate, % arm C & D (side 14)
- OS Kaplan-Meier Kurve arm C, D, G, H samt G+H, extract fra 5. marts 2020 (side 15-16)
- PFS Kaplan-Meier Kurve arm C, D, G, H samt G+H, extract fra 5. marts 2020 (side 17-18)
- Median PFS arm C, D, G, H samt G+H (side 19)
- 2-year progression free survival rate % arm C & D (side 20)
- Proportion of patients who discontinued any treatment due to adverse events, % arm G og H (side 21)

<u>Follow up i den seneste Clinical Study Report (CSR) Juni 2020 er:</u>

- For kohorte arm 1a, arm C og arm D (42.2 – 42.9 mdr) (side 22)
- For arm G (19.4 mdr), , arm H (8.8 mdr), arm G+H (9.7 mdr) (side 23)
- Generel information om censureringer (side 24)

Tillægget indeholder data på Arm C, D, G, H samt G+H (poolet):

Figure 2. Overview of the GO29365 study – R/R DLBCL and R/R FL patients



Tillæg til endelig ansøgning vedrørende polatuzumab vedotin til patienter med DLBCL – indsendt til Medicinrådets sekretariat 16. september 2020

Note: Tal med grå farve er gengivetfra Tabel 5 i den endelige ansøgning. Tal med sort farve er opdaterede data stammer fra CSR Tabel 13 side 117 eller CSR side 184 eller hvor % andelen er udregnet jf noter i tabellen

Baseline karakteristika for DLBCL cohort 1a, Arm C, D, G, H samt G&H						
Study	**GO29365**			**Lyo Pola+BR**		
Population	**Phase Ib safety run-in Polatuzumab vedotin + BR (DLBCL cohort 1a) n = 6**	**Phase II randomized**		**Phase II Lyophilized Formulation Cohort**		
		Polatuzumab vedotin + BR (Arm C) n = 40	**BR (Arm D) n = 40**	**Polatuzumab vedotin + BR (Arm G) n=42**	**Polatuzumab vedotin + BR (Arm H) n=64**	**Total (Arm G+H) n= 106**
Median age, years (range)	65 (58-79)	67.0 (33-86)	71.0 (30 – 84)	[redacted]	[redacted]	[redacted]
≥ 65 years	N/A	23 (57.5)	26 (65.0)	[redacted]	[redacted]	[redacted]
Female sex, n (%)	2 (33.3)	12 (30.0)	15 (27.5)	[redacted]	[redacted]	[redacted]
ECOG performance status score at baseline, n (%)						
0-1	6 (100.0)	33 (82.5)	31 (77.5)	[redacted]	[redacted]	[redacted]
2	0	6 (15.0)	8 (20.0)	[redacted]	[redacted]	[redacted]
WHO 2016 Classification (central pathology review)‡ n (%)	6 (100.0)	38 (95.0)	40 (100.0)	[redacted]	[redacted]	[redacted]
ABC	4 (66.7)	19 (47.5)	19 (47.5)	[redacted]	[redacted]	[redacted]
GCB	1 (16.7)	15 (37.5)	17 (42.5)	[redacted]	[redacted]	[redacted]
Burkitt lymphoma	0	1 (2.5)	0	[redacted]	[redacted]	[redacted]
Follicular lymphoma	0	1 (2.5)	0	[redacted]	[redacted]	[redacted]
DLBCL, NOS	0	0	0	[redacted]	[redacted]	[redacted]
DLBCL+EBV, NOS	0	0	0	[redacted]	[redacted]	[redacted]
DLBCL, High grade with rearrangements	0	0	0	[redacted]	[redacted]	[redacted]
T-cell/Histiocyte-rich Large B-cell lymphoma						
International Prognostic Index score, n (%) at study entry	*adderet fra tabel 5 (final ansøgning)*	*adderet fra tabel 5 (final ansøgning*	*adderet fra tabel 5 (final ansøgning)*	NA	NA	*CSR s. 184 - % andel udregnet*
<3	4 (66.7)	18 (45.0)	11 (27.5)			[redacted]
>=3	2 (33.3)	22 (55.0)	29 (72.5).			[redacted]
<4	0	31 (77,5)	23 (57.5)			[redacted]
>=4	0	9 (22.5)	17 (42.5)			[redacted]
Bulky disease (>= 7.5 cm)	1 (16.7)	10 (25.0)	15 (37.5)	[redacted]	[redacted]	[redacted]
Ann Arbor stage III/IV, n (%)	4 (66.7)	34 (85.0)	36 (90.0)	NA	NA	NA
Stratification factor DOR of last treatment ≤ 12 months, n (%)	5 (83.3)	32 (80.0)	33 (82.5)	NA	NA	*fra opdateret CSR s. 184 - % andel udregnet* [redacted]
Prior stem cell transplant, n (%)	0	10 (25.0)	6 (15.0)	NA	NA	[redacted]

Baseline karakteristika for DLBCL cohort 1a, Arm C, D, G, H samt G&H fortsat

Study	**GO29365**			**Lyo Pola+BR**		
Population	**Phase Ib safety run-in Polatuzumab vedotin + BR (DLBCL cohort 1a) n = 6**	**Phase II randomized**		**Phase II Lyophilized Formulation Cohort**		
		Polatuzumab vedotin + BR (Arm C) n = 40	**BR (Arm D) n = 40**	**Polatuzumab vedotin + BR (Arm G) n=42**	**Polatuzumab vedotin + BR (Arm H) n=64**	**Total (Arm G+H) n= 106**
Lines of prior therapy, n (%)	*adderet fra tabel 5 (final ansøgning)*	*adderet fra tabel 5 (final ansøgning)*				*fra opdateret CSR s. 184 - % andel udregnet*
1 line	2 (33.3)	11 (27.5)	12 (30.0)	NA	NA	[redacted]
≥2 lines	4 (66.7)	29 (72.5)	28(70)			
Median no. lines (range)	2 (1-2)	2 (1-7)	2 (1-5)	NA	NA	[redacted]

ABC = activated B-cell-like; GC = germinal center; GCB = germinal center B-cell like;
‡Central pathology review incorporated results of NanoString cell of origin when available.
! Number of patients for whom information was available.

Oprindelig Table 11. Results from the GO29365 study plus opdaterede data fra CSR dateret juni 2020 for Arm G, H samt G+H

Trial name: A study of Polatuzumab Vedotin (DSDS4501A) in Combination With Rituximab or Obinutuzumab Plus Bendamustine in Participants With Relapsed or Refractory Follicular or Diffuse Large B-Cell Lymphoma Tekst i grå farve er ikke ændret i forhold til den finale ansøgning **NE = not evaluable**

Results published in:

1) **Polatuzumab Vedotin in Relapsed or Refractory Diffuse Large B-Cell Lymphoma, Laurie H. Sehn et al., Journal of Clinical Oncology, 2019 [2]**
2) **European Public Assessment Report (EPAR) CHMP [26]**
3) **Exact numbers from Roche data on file [33]**
4) **Manual calculations**
5) **Medcalc calculations using: https://www.medcalc.org/calc/comparison_of_proportions.php**
6) **Medcalc calculations using: https://www.medcalc.org/calc/relative_risk.php**
7) [redacted]

NCT number: 02257567

Overall survival (1, 6)

Outcome	Study arm	N	Result (95% CI)	Estimated absolute difference in effect: Difference	95% CI	*P* value	Estimated relative difference in effect: Hazard ratio	95% CI	*P* value	Updated arm C and D	Lyo pola +BR Study arm G n = 42 Result (95% CI)	Lyo pola +BR Study arm H n = 64 Result (95% CI)	Lyo pola +BR Study arm G+H n = 106 Result (95% CI)
Median overall survival, months	Polatuzumab + bendamustine and rituximab (Arm C)	40	12.4 (9.0–NE) months(1)	7.7 (4) 7,7(7)			0.42(1) [redacted]	0.24-0.75	0.0023	[redacted]	[redacted]	[redacted]	[redacted]
	Bendamustine and rituximab (Arm D)	40	4.7 (3.7–8.3) months(1)							[redacted]			
2-year overall survival rate, %	Polatuzumab + bendamustine and rituximab	40	38.2% (22.5-53.9) (3)	21.2 (4) 21.2(7)			N/A			[redacted]	NE	NE	NE
	Bendamustine and rituximab	40	17.0% (3.6-30.4) (3)							[redacted]			

	Health-related quality of life										
				Estimated absolute difference in effect			Estimated relative difference in effect			Updated arm C and D	Lyo pola +BR Study arm G n = 42	Lyo pola +BR Study arm H n = 64	Lyo pola +BR Study arm G+H n = 106
Outcome	Study arm	N	Result	Difference	95% CI	*P* value	Relative risk	95% CI	*P* value				
Average change from baseline in SF-36 until end of treatment	Polatuzumab + bendamustine and rituximab	40	N/A										
	Bendamustine and rituximab	40	N/A										
Average change from baseline in SF-36 until end of follow-up	Polatuzumab + bendamustine and rituximab	40	N/A										
	Bendamustine and rituximab	40	N/A										
Average change from baseline in FACT-Lym until end of treatment	Polatuzumab + bendamustine and rituximab	40	N/A										
	Bendamustine and rituximab	40	N/A										
Average change from baseline in FACT-Lym until end of follow-up	Polatuzumab + bendamustine and rituximab	40	N/A										
	Bendamustine and rituximab	40	N/A										
	Progression free survival – assessed by independent review committee												

Outcome	Study arm	N	Result (95% CI)	Estimated absolute difference in effect: Difference	95% CI	*P* value	Estimated relative difference in effect: Hazard ratio	95% CI	*P* value	Updated arm C and D	Lyo pola +BR Study arm G n = 42 Result (95% CI)	Lyo pola +BR Study arm H n = 64 Result (95% CI)	Lyo pola +BR Study arm G+H n = 106 Result (95% CI)
Median progression free survival, months	Polatuzumab + bendamustine and rituximab	40	9.5 (6.2-13.9) [1]	5.8[4]			0.36[1]	0.21-0.63	*<0.001*				
	Bendamustine and rituximab	40	3.7 (2.1-4.5) [1]	5,5[7]									
2-year progression free survival rate, %	Polatuzumab + bendamustine and rituximab	40	31.3% (16.6-46.5) [3]	26.4[4]			N/A				NE	NE	NE
	Bendamustine and rituximab	40	4.9% (0-13.4) [3]	19,3[7]									

Outcome	Study arm	N	Result (n)	Estimated absolute difference in effect			Estimated relative difference in effect			Updated arm C and D	Lyo pola +BR Study arm G n = 42	Lyo pola +BR Study arm H n = 64	Lyo pola +BR Study arm G+H n = 106
				Difference	95% CI	*P* value	Relative risk	95% CI	*P* value				
Proportion of patients who discontinued any treatment due to adverse events, %	Polatuzumab + bendamustine and rituximab	45	31.1% (14) [1]	15.7[5]	(-)2.7-32.4	*0.09*	2.02[6]	0.86-4.75	*0.11*		[redacted]	[redacted]	[redacted]
	Bendamustine and rituximab	39	15.4% (6) [2]										
Proportion of patients experiencing ≥ 1 grade 3 or 4 adverse events	Polatuzumab + bendamustine and rituximab	45	84.4% (38) [2]	12.6[5]	(-)5.0-30.0	*0.16*	1.18[6]	0.93-1.49	*0.17*		NE	NE	NE
	Bendamustine and rituximab	39	71.8% (28) [2]										

* Campbell I (2007) Chi-squared and Fisher-Irwin tests of two-by-two tables with small sample recommendations. Statistics in Medicine 26:3661-3675, Richardson JTE (2011) The analysis of 2 x 2 contingency tables - Yet again. Statistics in Medicine 30:890 ** Altman DG, Machin D, Bryant TN, Gardner MJ (Eds) (2000) Statistics with confidence, 2nd ed. BMJ Books. (p. 49) *** Altman DG (1991) Practical statistics for medical research. London: Chapman and Hall.

CLINICAL STUDY REPORT

Primary CSR Study Report GO29365: A Phase Ib/II study evaluating the safety, tolerability, and anti-tumor activity of polatuzumab vedotin (DCDS4501A) in combination with rituximab (R) or obinutuzumab (G) plus bendamustine (B) in relapsed or refractory follicular or diffuse large B-cell lymphoma. Report No. 1100670, June 2020.

Study Sponsor(s)	F. Hoffmann-La Roche Ltd.
Principal Investigator and Affiliation: Dr. Laurie Sehn BCCA BC Cancer Centre for Lymphoid Cancer 600 West 10th Avenue, Vancouver, British Columbia, V5Z 4E6 Canada	**Study Dates:** First Patient Enrolled: 15 October 2014 Data cut-off: 2 January 2020 Last patient Enrolled: (Arms G and H) 9 July 2019
Trial Phase: Ib/II	**Indication:** Relapsed or refractory B-cell non-Hodgkin's Lymphoma

Clinical Study Report Approval Date: See electronic signature below

Date and Time(UTC)	Reason for Signing	Name
16-Jun-2020 17:38:49	Company Signatory	Qiu, Jiaheng (quij)

Baseline karakteristika for Arm G og H samt G+H - CSR side 117

Table 13 Summary of Demographics and Baseline Characteristics, Lyophilized Cohort (Arms G and H, Intent-to-Treat Patients)

Summary of Demographics and Baseline Characteristics, Lyo Pola+BR Arm G and H, Intent-to-Treat Patients
Protocol: GO29365

	Lyo Pola+BR (Arm G) (N=42)	Lyo Pola+BR (Arm H) (N=64)	Lyo Pola+BR (Total) (N=106)
Age (yr)			
n	42	64	106
Mean (SD)	65.7 (13.9)	66.2 (12.3)	67.2 (13.0)
Median	68.0	71.5	70.0
25th-75th	58.0 - 75.0	65.5 - 75.5	64.0 - 75.0
Min - Max	27 - 94	24 - 91	24 - 94
Age group (yr)			
n	42	64	106
18 - 40	3 (7.1%)	3 (4.7%)	6 (5.7%)
41 - 64	12 (28.6%)	11 (17.2%)	23 (21.7%)
>= 65	27 (64.3%)	50 (78.1%)	77 (72.6%)
Sex			
n	42	64	106
Male	25 (59.5%)	27 (42.2%)	52 (49.1%)
Female	17 (40.5%)	37 (57.8%)	54 (50.9%)
Race			
n	42	64	106
Asian	1 (2.4%)	7 (10.9%)	8 (7.5%)
Black or African American	0	1 (1.6%)	1 (0.9%)
White	33 (78.6%)	50 (78.1%)	83 (78.3%)
Unknown	8 (19.0%)	6 (9.4%)	14 (13.2%)
Ethnicity			
n	42	64	106
Hispanic or Latino	1 (2.4%)	2 (3.1%)	3 (2.8%)
Not Hispanic or Latino	35 (83.3%)	52 (81.3%)	87 (82.1%)
Not Stated	5 (11.9%)	8 (12.5%)	13 (12.3%)
Unknown	1 (2.4%)	2 (3.1%)	3 (2.8%)
Weight (kg) at baseline			
n	42	64	106
Mean (SD)	76.34 (17.01)	72.00 (22.01)	73.72 (20.20)
Median	75.65	67.45	70.00
25th-75th	63.50 - 88.00	56.60 - 80.00	60.00 - 82.70
Min - Max	41.9 - 117.6	39.0 - 178.1	39.0 - 178.1
Height (cm) at baseline			
n	42	63	105
Mean (SD)	167.67 (10.79)	164.07 (9.50)	165.51 (10.14)
Median	167.50	165.00	166.00
25th-75th	160.00 - 174.90	157.40 - 170.10	158.00 - 171.50
Min - Max	146.5 - 192.0	144.7 - 182.8	144.7 - 192.0
ECOG score at baseline			
n	42	64	106
0	12 (28.6%)	18 (28.1%)	30 (28.3%)
1	27 (64.3%)	35 (54.7%)	62 (58.5%)
2	3 (7.1%)	11 (17.2%)	14 (13.2%)
Bulky disease at baseline			
n	42	64	106
Yes	11 (26.2%)	17 (26.6%)	28 (26.4%)
No	31 (73.8%)	47 (73.4%)	78 (73.6%)
Primary Reason for Stem Cell Transplant Ineligibility			
n	42	63	105
Age	17 (40.5%)	29 (46.0%)	46 (43.8%)
Co-Morbidities	0	4 (6.3%)	4 (3.8%)
Failed Prior Transplant	6 (14.3%)	7 (11.1%)	13 (12.4%)
Insufficient Response To Salvage Therapy	15 (35.7%)	15 (23.8%)	30 (28.6%)
Other	1 (2.4%)	7 (11.1%)	8 (7.6%)
Performance Status	3 (7.1%)	1 (1.6%)	4 (3.8%)
WHO2016 DLBCL Status (Central Review)			
n	42	62	104
DLBCL, NOS: ABC	21 (50.0%)	29 (46.8%)	50 (48.1%)
DLBCL, NOS: GBC	15 (35.7%)	27 (43.5%)	42 (40.4%)
DLBCL, NOS	2 (4.8%)	1 (1.6%)	3 (2.9%)
DLBCL + EBV, NOS	2 (4.8%)	1 (1.6%)	3 (2.9%)
DLBCL, High-Grade with Rearrangements	2 (4.8%)	3 (4.8%)	5 (4.8%)
T-CELL/HISTIOCYTE-RICH LARGE B-CELL LYMPHOMA	0	1 (1.6%)	1 (1.0%)

Cutoff Date: 02JAN2020
SDTMv Zipfile Date 06MAR2020 Generated Based on CRF Extract on 05MAR2020.
Program:root/clinical_studies/RO5541077/CDPT7898/GO29365/data_analysis/PRIMARY_CSR/prod/program/t_dm_bsch.sas
Output:root/clinical_studies/RO5541077/CDPT7898/GO29365/data_analysis/PRIMARY_CSR/prod/output/t_dm_bsch_LERDLGH_IT.out
18MAR2020 2:39
Page 2 of 2

Baseline karakteristika for Arm G og H samt G+H - CSR side 184

Baseline Characteristics for Arm G+H Lyo Pola+BR SAMT responsdata – medtaget til at afdække baseline karakteristika for bl.a. IPI

	Lyophilized Arm G+H (n=106)		
	N	**Complete response, n (%)**	**(95% CI)**
Lines of Prior Anti-Lymphoma Therapy			
1 prior line, n	37	18 (48.6%)	(32.54, 64.75)
2 or more prior lines, n	69	24 (34.8%)	(23.54, 46.02)
IPI at study entry			
<3, n	36	16 (44.4%)	(28.21, 60.68)
≥3, n	70	26 (37.1%)	(25.82, 48.46)
IPI at study entry			
<4, n	77	34 (44.2%)	(33.06, 55.25)
≥4, n	29	8 (27.6%)	(11.32, 43.85)
WHO2016 DLBCL Status (Central Review)			
ABC, n	50	19 (38.0%)	(24.55, 51.45)
GCB, n	42	18 (42.9%)	(27.89, 57.82)
DLBCL, NOS[a], n	3	2 (66.7%)	(3.32, 100.00)
EBV+ DLBCL, NOS, n	3	1 (33.3%)	(0.00, 86.68)
High-Grade B-Cell Lymphoma, with MYC and BCL2 and/or BCL6 rearrangements, n	5	1 (20.0%)	(0.00, 55.06)
T-Cell/Histiocyte-Rich Large B-Cell Lymphoma, n	1	0 (0.0%)	(0.00, 0.00)
Unknown, n	2	1 (50.0%)	(0.00, 100.00)
Duration of Response to Prior Anti-Lymphoma Therapy			
>12 months, n	14	10 (71.4%)	(47.76, 95.09)
≤12 months, n	92	32 (34.8%)	(25.05, 44.51)
Extranodal Involvement at Study Entry			
Yes, n	66	24 (36.4%)	(24.76, 47.97)
No, n	40	18 (45.0%)	(29.58, 60.42)
Prior Bone Marrow Transplant			
Yes, n	17	10 (58.8%)	(35.43, 82.22)
No, n	89	32 (36.0%)	(25.99, 45.92)

Information om opfølgningsdata fra CSR :

Consistent with the results at the primary analysis (CCOD: 30 April 2018), at the new CCOD of 2 January 2020, the median overall survival was 12.4 months (95% CI: 9.0, 32.0 months) in patients in the pola+BR arm compared to 4.7months (95% CI: 3.7, 8.3) in the BR arm; 24-month OS was 38.2% (95% CI: 22.5, 53.9) in the pola□BR arm and 17.0% (95% CI: 3.6, 30.4) in the BR arm.

Secondary efficacy endpoints remained in general consistent with those observed at the time of primary analysis (30 April 2018), demonstrating consistent treatment effect favoring the pola+ BR arm compared to the BR arm for BOR (IRC and Investigator assessed) and IRC-assessed DOR and PFS

PFS as determined by IRC was increased in patients treated with pola+BR compared to BR (stratified HR : 0.38; 95% CI: 0.22, 0.65) with median PFS being over two-fold higher (9.2 months [95% CI: 6.0 months, 13.9 months] vs. 3.7months [95% CI: 2.1 months, 4.5 months]) – Sensitivity analysis for PFS assessing the impact of new therapy given prior to progression showed that for pola+BR the median PFS was 10.4 months (95% CI: 4.9 months, 32.0 months) compared to 3.7 months (95% CI 2.0 months, 4.5 months) for BR

Exploratory time-to-event (TTE) analyses with a longer follow-up continued to demonstrate consistent treatment effect favoring the pola/BR arm compared to the BR arm for investigator assessed DOR, PFS, EFS, and OS: – Median PFS by investigator was over three-fold the duration in patients treated with pola/BR (7.5 months [95% CI: 4.9 months, 17.0 months]) compared to BR (2.0 months [95% CI: 1.5months, 3.7 months]) (stratified HR:0.33; 95% CI: 0.20, 0.56).

The risk of death was reduced by 58% in patients treated with pola+BR compared to BR (stratified HR: 0.42; 95% CI: 0.24, 0.73). Median overall survival was extended to 12.4 months (95% CI: 9. months 0, 32.0 months) in the pola+BR arm, from 4.7 months (95% CI: 3.7 months, 8.3 months) in the BR arm. The treatment effect for survival was consistently observed across of subgroups of patients with R/R DLBCL tested.

Median OS arm C, D, G, H samt G+H - CSR side 128

Study Phase	Randomized Phase		Expansion Phase*	Phase II Lyophilized Cohort		
Treatment and Arm	BR Phase II Arm D	Pola+BR Phase II Arm C	Pola+BG Phase II Arm F	Phase II Arm G	Phase II Arm H	Phase II Arm G+H
Sample size	n=40	n=40	n=21	n=42	n=64	n=106
HR (95% CI)	0.3 (0.2, 0.6)		–	–	–	–
EFS (INV assessed)						
Patients with event, n (%)	38 (95.0%)	31 (77.5%)	–	35 (83.3%)	39 (60.9%)	74 (69.8%)
median EFS, months (95% CI)	2.0 (1.5, 3.1)	6.2 (4.0, 11.1)	–	4.9 (2.0, 7.0)	4.9 (4.6, 6.9)	4.9 (4.4, 6.6)
HR (95% CI)	0.3 (0.2, 0.5)		–	–	–	–
OS						
Patients with event, n (%)	29 (72.5%)	26 (65.0%)	17 (81.0%)	27 (64.3%)	24 (37.5%)	51 (48.1%)
median OS, months (95% CI)	4.7 (3.7, 8.3)	[redacted]	9.3 (4.4, 30.2)	9.2 (5.4, 14.2)	NE (8.3, NE)	[redacted] (8.3, 14.2)
HR (95% CI)	0.4 (0.2, 0.7)		–	–	–	–

2-year overall survival rate, % arm C & D - CSR side 149

Table 25 Overall Survival in Patients with R/R DLBCL Treated with Pola+BR or BR (Randomized Phase II; ITT Population) (cont.)

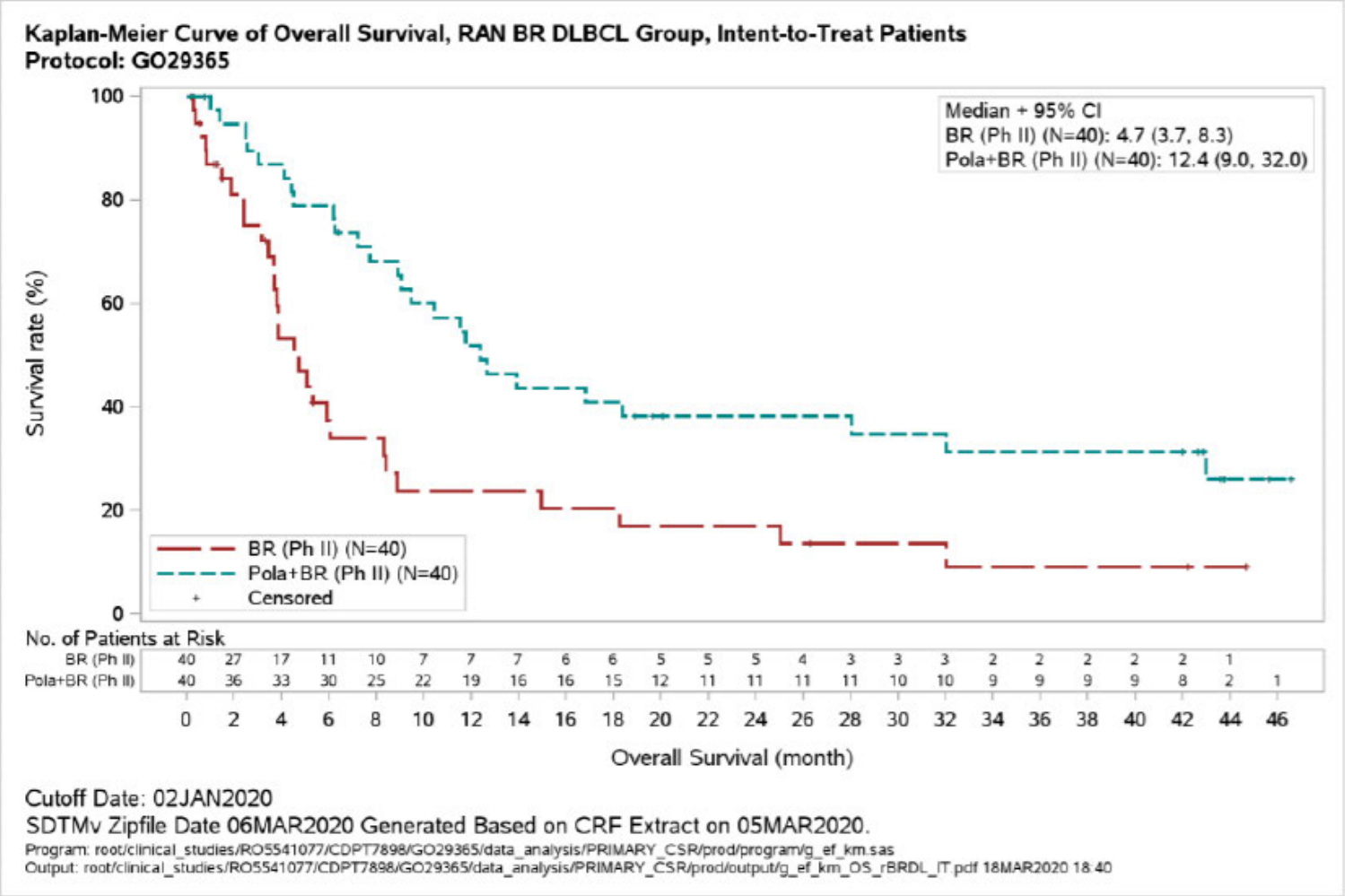
	BR (Ph II) (N=40)		Pola+BR (Ph II) (N=40)
12 months duration			
Patients remaining at risk	7		19
Event Free Rate (%)	23.78		51.85
95% CI	(8.76, 38.81)		(35.79, 67.92)
Difference in Event Free Rate		-28.07	
95% CI		(-50.07, -6.07)	
p-value (Z-test)		0.0124	
18 months duration			
Patients remaining at risk	6		15
Event Free Rate (%)	20.39		40.94
95% CI	(6.11, 34.67)		(25.09, 56.79)
Difference in Event Free Rate		-20.55	
95% CI		(-41.88, 0.79)	
p-value (Z-test)		0.0590	
24 months duration			
Patients remaining at risk	5		11
Event Free Rate (%)	16.99		38.21
95% CI	(3.63, 30.35)		(22.54, 53.88)
Difference in Event Free Rate		-21.22	
95% CI		(-41.81, -0.62)	
p-value (Z-test)		0.0435	

Stratification factors: Duration of Response to Prior Therapy, IXRS (<=12/>12 months).
* Censored at time of data cut off, ^ Censored and event at time of data cut off.
95% CI for rates were constructed using Clopper-Pearson method. 95% CI for median time were constructed using Brookmeyer and Crowley.
Cutoff Date: 02JAN2020
SDTMv Zipfile Date 06MAR2020 Generated Based on CRF Extract on 05MAR2020.

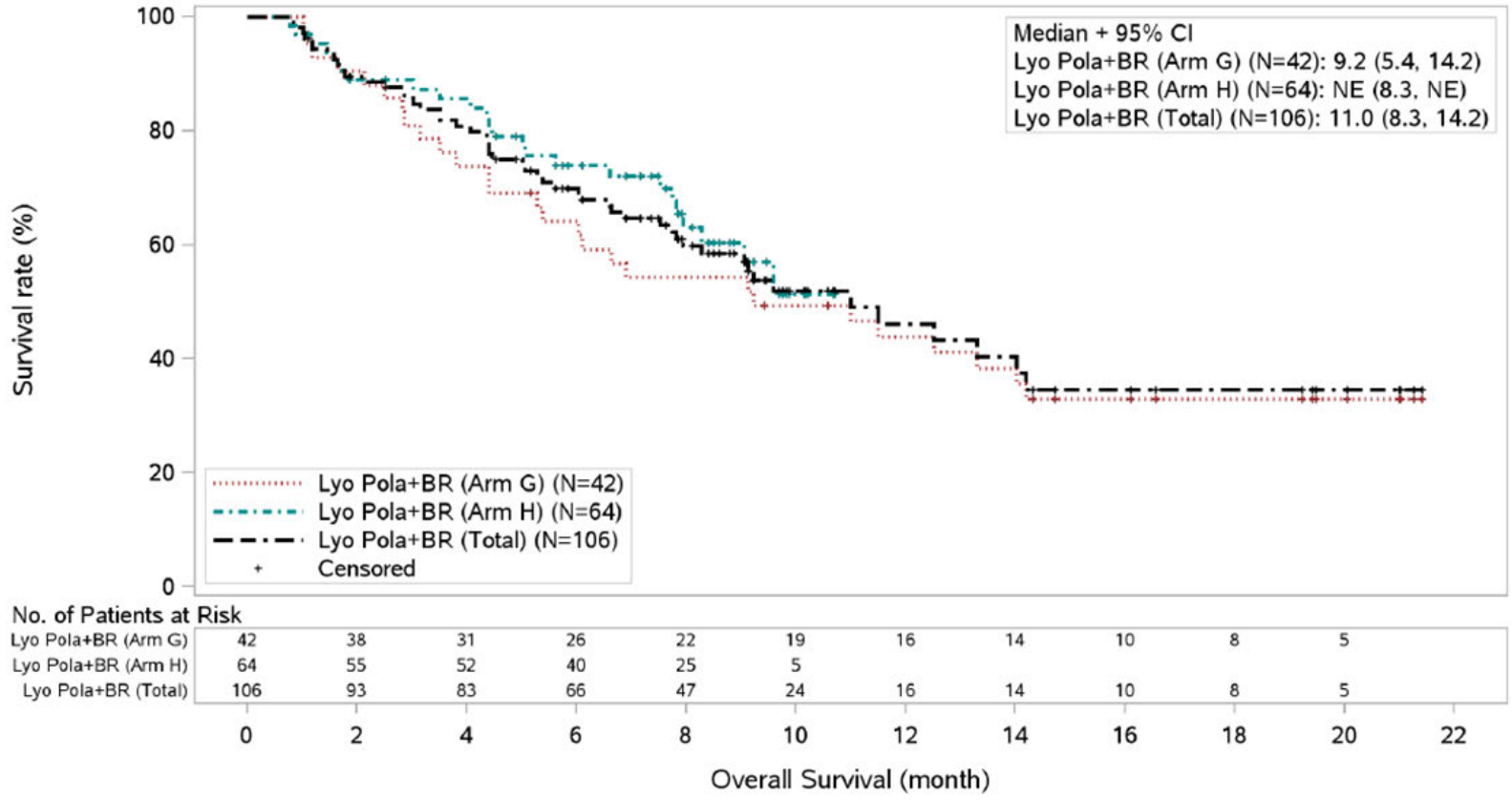
Program:
root/clinical_studies/RO5541077/CDPT7898/GO29365/data_analysis/PRIMARY_CSR/prod/program/t_ef_tte.sas
Output:
root/clinical_studies/RO5541077/CDPT7898/GO29365/data_analysis/PRIMARY_CSR/prod/output/t_ef_tte_OS_rBRDL_IT.out
18MAR2020 18:28

A K-M plot of OS for patients with R/R DLBCL treated with pola+BR compared to BR in the randomized Phase II portion of Study GO29365 is shown in Figure 3.

Figure 3 Kaplan-Meier Plot of Overall Survival in Patients with R/R DLBCL Treated with Pola+BR or BR (Randomized Phase II; ITT Population)

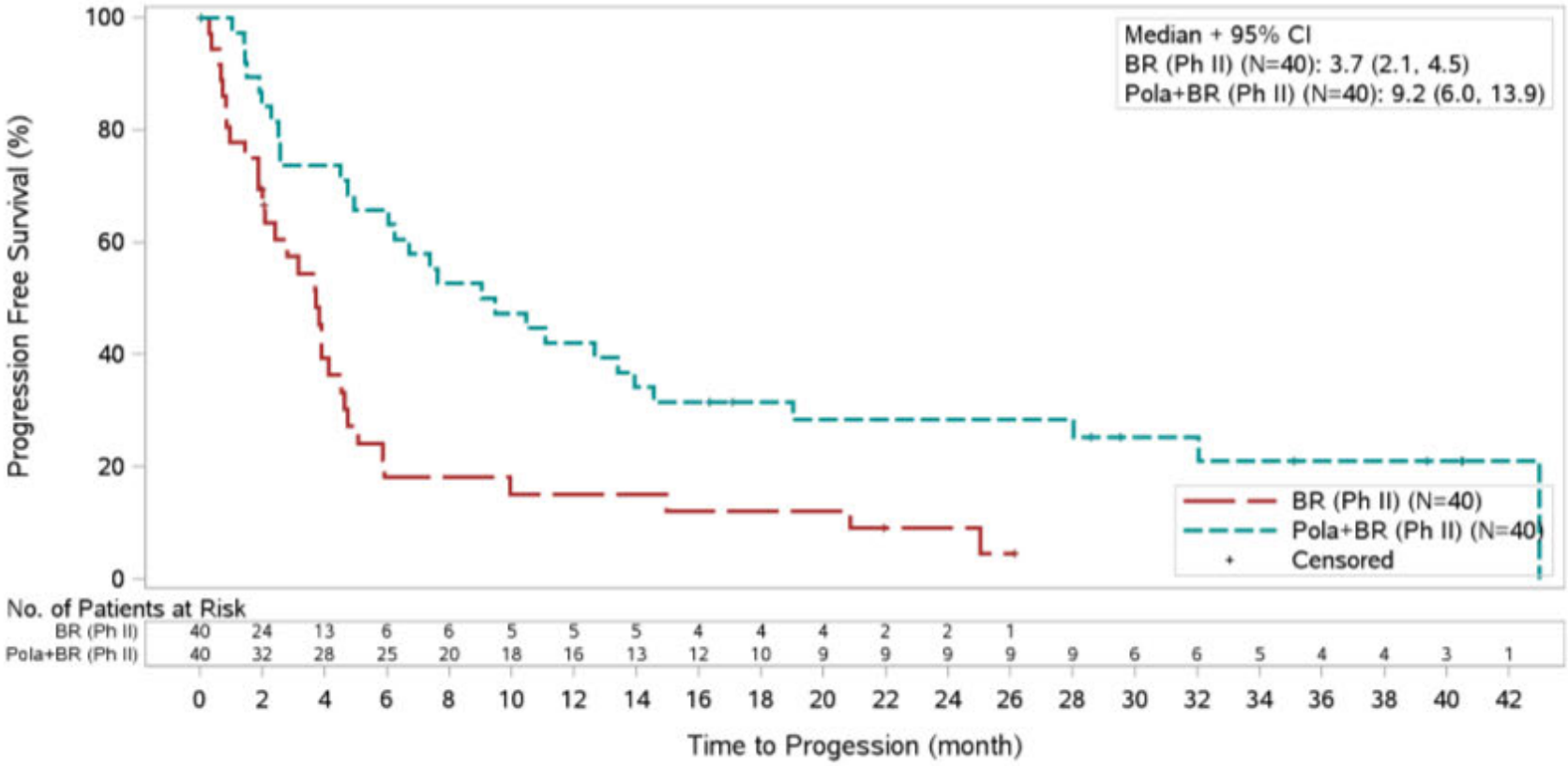


Kaplan-Meier Curve of Overall Survival, Lyo Pola+BR Arm G and H, Intent-to-Treat Patients
Protocol: GO29365



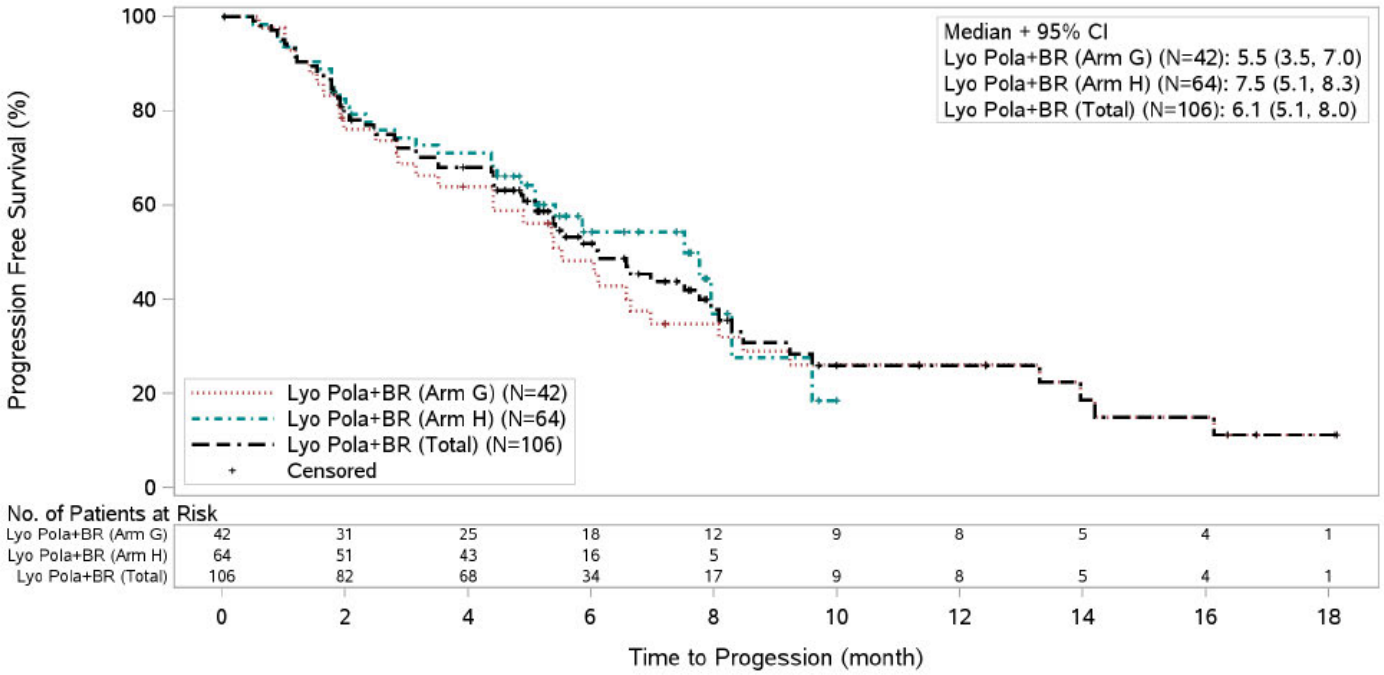
Cutoff Date: 02JAN2020
SDTMv Zipfile Date 06MAR2020 Generated Based on CRF Extract on 05MAR2020.
Program: root/clinical_studies/RO5541077/CDPT7898/GO29365/data_analysis/PRIMARY_CSR/prod/program/g_ef_km.sas
Output: root/clinical_studies/RO5541077/CDPT7898/GO29365/data_analysis/PRIMARY_CSR/prod/output/g_ef_km_OS_LBRDLGH_IT.pdf 18MAR2020 18:41

Kaplan-Meier Curve of Progression-Free Survival by IRC, RAN BR DLBCL Group, Intent-to-Treat Patients
Protocol: GO29365



Tumor assessment result is based on PET-CT whenever it is available and valid and uses CT only result if PET-CT result is missing.
Cutoff Date: 02JAN2020
SDTMv Zipfile Date 06MAR2020 Generated Based on CRF Extract on 05MAR2020.
Program: root/clinical_studies/RO5541077/CDPT7898/GO29365/data_analysis/PRIMARY_CSR/prod/program/g_ef_km.sas
Output: root/clinical_studies/RO5541077/CDPT7898/GO29365/data_analysis/PRIMARY_CSR/prod/output/g_ef_km_PFSIRC3_rBRDL_IT.pdf 18MAR2020 18:42

Kaplan-Meier Curve of Progression-Free Survival by IRC, Lyo Pola+BR Arm G and H, Intent-to-Treat Patients
Protocol: GO29365



No. of Patients at Risk

Lyo Pola+BR (Arm G)	42	31	25	18	12	9	8	5	4	1
Lyo Pola+BR (Arm H)	64	51	43	16	5					
Lyo Pola+BR (Total)	106	82	68	34	17	9	8	5	4	1

0 2 4 6 8 10 12 14 16 18

Time to Progession (month)

Tumor assessment result is based on PET-CT whenever it is available and valid and uses CT only result if PET-CT result is missing.
Cutoff Date: 02JAN2020
SDTMv Zipfile Date 06MAR2020 Generated Based on CRF Extract on 05MAR2020.
Program: root/clinical_studies/RO5541077/CDPT7898/GO29365/data_analysis/PRIMARY_CSR/prod/program/g_ef_km.sas
Output: root/clinical_studies/RO5541077/CDPT7898/GO29365/data_analysis/PRIMARY_CSR/prod/output/g_ef_km_PFSIRC3_LBRDLGH_IT.pdf 18MAR2020 18:43

Median PFS arm C, D, G, H samt G+H - CSR side 127

Study Phase	Randomized Phase		Expansion Phase*	Phase II Lyophilized Cohort		
Treatment and Arm	BR Phase II Arm D	Pola+BR Phase II Arm C	Pola+BG Phase II Arm F	Phase II Arm G	Phase II Arm H	Phase II Arm G+H
Sample size	n=40	n=40	n=21	n=42	n=64	n=106
BOR by PET-CT or CT (CR/PR) (INV assessed)						
n (%)	13 (32.5%)	28 (70.0%)	11 (52.4%)	22 (52.4%)	44 (68.8%)	66 (62.3%)
95% CI for response rate (Clopper-Pearson)	18.6, 49.1	53.5, 83.4	29.8, 74.3	36.4, 68.0	55.9, 79.8	52.3, 71.5
Δ (95% CI) (Wilson)	37.5 (15.6, 54.7)		–	–	–	–
DOR (IRC assessed)						
Patients with event, n (%)	8 (80.0%)	17 (68.0%)	6 (66.7%)	12 (60.0%)	10 (25.0%)	22 (36.7%)
median DOR, months (95% CI)	10.2 (4.0, 19.6)	10.9 (5.7, 40.7	25.8 (9.7, NE)	6.2 (3.9, 12.1)	5.9 (5.4, 7.8)	6.2 (5.4, 11.6)
HR (95% CI)	0.6 (0.3, 1.4)		–	–	–	–
DOR (INV assessed)						
Patients with event, n (%)	11 (84.6%)	20 (71.4%)	9 (81.8%)	14 (63.6%)	14 (31.8%)	28 (42.4%)
median DOR, months (95% CI)	4.07 (2.6, 12.7)	12.7 (5.8, 27.9)	16.1 (2.8, 27.9)	5.3 (4.8, 12.1)	6.2 (3.9, NE)	5.9 (4.8, 11.6)
HR (95% CI)	0.4 (0.2, 0.9)		–	–	–	–
PFS (IRC assessed)						
Patients with event, n (%)	32 (80.0%)	30 (75.0%)	17 (81.0%)	33 (78.6%)	31 (48.4%)	64 (60.4%)
median PFS, months (95% CI)	3.7 (2.1, 4.53)	[redacted]	5.9 (3.2, 11.9)	5.5 (3.5, 7.0)	7.5 (5.1, 8.3)	[redacted]
HR (95% CI)	0.4 (0.2, 0.7)		–	–	–	
PFS (INV assessed)						
Patients with event, n (%)	35 (87.5%)	30 (75.0%)	18 (85.7%)	34 (81.0%)	34 (53.1%)	68 (64.2%)
median PFS, months (95% CI)	2.0 (1.5, 3.7)	7.5 (4.9, 17.0)	5.1 (2.1, 18.2)	4.9 (2.0, 6.7)	5.9 (4.9, 8.2)	[redacted]

2-year progression free survival rate, % by ICR 24 month duration patient remaining at risk - Arm C og D - CSR side 1313

Summary of Progression-Free Survival by IRC, RAN BR DLBCL Group, Intent-to-Treat Patients
Protocol: GO29365

	BR (Ph II) (N=40)		Pola+BR (Ph II) (N=40)
12 months duration			
Patients remaining at risk	5		16
Event Free Rate (%)	15.13		42.11
95% CI	(2.95, 27.30)		(26.41, 57.80)
Difference in Event Free Rate		-26.98	
95% CI		(-46.84, -7.12)	
p-value (Z-test)		0.0078	
18 months duration			
Patients remaining at risk	4		10
Event Free Rate (%)	12.10		31.58
95% CI	(1.01, 23.19)		(16.80, 46.36)
Difference in Event Free Rate		-19.48	
95% CI		(-37.95, -1.00)	
p-value (Z-test)		0.0388	
24 months duration			
Patients remaining at risk	2		9
Event Free Rate (%)	9.08		28.42
95% CI	(0.00, 18.85)		(13.88, 42.96)
Difference in Event Free Rate		-19.35	
95% CI		(-36.87, -1.83)	
p-value (Z-test)		0.0304	

Stratification factors: Duration of Response to Prior Therapy, IXRS (<=12/>12 months).
* Censored at time of data cut off, ^ Censored and event at time of data cut off.
95% CI for rates were constructed using Clopper-Pearson method. 95% CI for median time were constructed using Brookmeyer and Crowley.
Tumor assessment result is based on PET-CT when available and valid and uses CT only result if PET-CT result is NE or missing.
Cutoff Date: 02JAN2020
SDTMv Zipfile Date 06MAR2020 Generated Based on CRF Extract on 05MAR2020.

Program: root/clinical_studies/RO5541077/CDPT7898/GO29365/data_analysis/PRIMARY_CSR/prod/program/t_ef_tte.sas
Output: root/clinical_studies/RO5541077/CDPT7898/GO29365/data_analysis/PRIMARY_CSR/prod/output/t_ef_tte_PFSIRC3_rBRDL_IT.out
18MAR2020 18:11

Proportion of patients who discontinued any treatment due to adverse events, % - CSR side 106

Table 6 Summary of Patient Disposition - Treatment Withdrawal in Lyophilized Cohort (Arms G and H, Safety Evaluable Patients)

Summary of Patient Disposition - Treatment Withdrawal, Lyo Pola+BR Arm G and H, Safety-Evaluable Patients
Protocol: GO29365

Status	Lyo Pola+BR (Arm G) (N=42)	Lyo Pola+BR (Arm H) (N=64)	Lyo Pola+BR (Total) (N=106)
Completed Polatuzumab Vedotin	18 (42.9%)	30 (46.9%)	48 (45.3%)
Completed Bendamustine	18 (42.9%)	31 (48.4%)	49 (46.2%)
Completed Rituximab or Obinutuzumab	18 (42.9%)	30 (46.9%)	48 (45.3%)
Discontinued Polatuzumab Vedotin	24 (57.1%)	33 (51.6%)	57 (53.8%)
ADVERSE EVENT	7 (16.7%)	9 (14.1%)	16 (15.1%)
DEATH	2 (4.8%)	1 (1.6%)	3 (2.8%)
OTHER	2 (4.8%)	1 (1.6%)	3 (2.8%)
PHYSICIAN DECISION	0	1 (1.6%)	1 (0.9%)
PROGRESSIVE DISEASE	12 (28.6%)	19 (29.7%)	31 (29.2%)
WITHDRAWAL BY SUBJECT	1 (2.4%)	2 (3.1%)	3 (2.8%)
Discontinued Bendamustine	24 (57.1%)	33 (51.6%)	57 (53.8%)
ADVERSE EVENT	7 (16.7%)	9 (14.1%)	16 (15.1%)
DEATH	2 (4.8%)	1 (1.6%)	3 (2.8%)
OTHER	2 (4.8%)	1 (1.6%)	3 (2.8%)
PHYSICIAN DECISION	0	1 (1.6%)	1 (0.9%)
PROGRESSIVE DISEASE	12 (28.6%)	19 (29.7%)	31 (29.2%)
WITHDRAWAL BY SUBJECT	1 (2.4%)	2 (3.1%)	3 (2.8%)
Discontinued Rituximab or Obinutuzumab	24 (57.1%)	33 (51.6%)	57 (53.8%)
ADVERSE EVENT	7 (16.7%)	9 (14.1%)	16 (15.1%)
DEATH	2 (4.8%)	1 (1.6%)	3 (2.8%)
OTHER	2 (4.8%)	1 (1.6%)	3 (2.8%)
PHYSICIAN DECISION	0	1 (1.6%)	1 (0.9%)
PROGRESSIVE DISEASE	12 (28.6%)	19 (29.7%)	31 (29.2%)
WITHDRAWAL BY SUBJECT	1 (2.4%)	2 (3.1%)	3 (2.8%)

Cutoff Date: 02JAN2020
SDTMv Zipfile Date 06MAR2020 Generated Based on CRF Extract on 05MAR2020.

Program:
root/clinical_studies/RO5541077/CDPT7898/GO29365/data_analysis/PRIMARY_CSR/prod/program/t_ds.sas
Output:
root/clinical_studies/RO5541077/CDPT7898/GO29365/data_analysis/PRIMARY_CSR/prod/output/t_ds_TRT_LBR
DLGH_SE.out
18MAR2020 2:34
Page 1 of 1

CSR s. 112 Follow up time for kohorte arm 1a, arm C og arm D = 42.2 – 42.9 måneder

In the randomized Phase II, median duration of follow-up was similar for patients with R/R DLBCL in the pola+BR and BR treatment arms (42.9 vs 42.2months, respectively) and similar for patients with R/R FL (42.2 vs. 41.4 months, respectively) (see Table 10).

Table 10 Duration of Follow-Up – Arms A-F (ITT Population)*

Study Phase	Phase Ib	Phase II (randomized)		Phase Ib	Phase II (expansion)
Treatment	**Pola+BR**	**BR**	**Pola+BR**	**Pola+BG**	**Pola+BG**
R/R DLBCL					
Cohort/Arm	**1a**	**D**	**C**	**1b**	**F**
Sample size	n=6	n=40	n=40	n=6	n=21
median, mo (95% CI)	56.1 (54.5, 60.1)	42.2 (26.3, 44.7)	42.9 (42.0, 43.8)	51.8 (NE)	46.3 (32.7, 46.4)
R/R FL					
Cohort/Arm	**1a**	**B**	**A**	**1b**	**E**
Sample size	n=6	n=41	n=39	n=6	n=20
median, mo (95% CI)	53.8 (50.7, 57.6)	41.4 (40.7, 42.8)	42.2 (41.2, 43.4)	49.3 (13.4, 51.4	44.5 (44.2, 45.4)

BG=bendamustine and obinutuzumab; BR=bendamustine and rituximab; DLBCL=diffuse large B-cell lymphoma; FL=follicular lymphoma; ITT=intent-to-treat; NE=not estimable.

* Survival follow-up calculated by reverse K-M method.

Source: t_durfu_OS_rBRDL_IT; t_durfu_OS_BGDL_IT; t_durfu_OS_BRFL_IT; t_durfu_OS_BGFL_IT; t_durfu_OS_PIFL_IT; t_durfu_OS_PIDL_IT.

CSR side 112-113: Follow up time for arm G (19.4 mdr) , arm H (8.8 mdr) og poolet arm G+H 9.7 mdr

Arms G and H:

The median duration of follow-up in Arm G and Arm H was19.4 months [16.1, 21.0] and 8.8 months [7.9, 9.1], respectively. The median duration of follow-up for the pooled Arms G and H was 9.7 months (see Table 11).

Table 11 Duration of Follow-Up – Arms G and H (ITT Population)

Duration of Follow-up for Overall Survival, Lyo Pola+BR Arm G and H, Intent-to-Treat Patients
Protocol: GO29365

	Lyo Pola+BR (Arm G) (N=42)	Lyo Pola+BR (Arm H) (N=64)	Lyo Pola+BR (Total) (N=106)
Patients with event (%)	15 (35.7%)	40 (62.5%)	55 (51.9%)
Earliest contributing event			
Alive	15	40	55
Patients without event (%)	27 (64.3%)	24 (37.5%)	51 (48.1%)
Time to event(month)			
Median	19.417	8.805	9.692
95% CI	(16.099, 20.994)	(7.918, 9.133)	(9.068, 10.579)
25% and 75%-ile	14.719, 20.994	7.491, 9.692	7.918, 16.099
Range	1.02* to 21.42	0.79* to 10.71	0.79* to 21.42

* Censored value, ^ Censored and event.
Duration of follow-up is calculated using the reverse KM method.
Cutoff Date: 02JAN2020
SDTMv Zipfile Date 06MAR2020 Generated Based on CRF Extract on 05MAR2020.

Information om censureringer fra CSR:

3.9.7 Missing Data

For response endpoints, patients with no response assessments (for any reason) were considered non-responders.

For the PFS analyses, patients who did not have documented disease progression or death had observations censored on the date of the last tumor assessment or, if no tumor assessments were performed after the baseline visit, at the time of randomization and enrollment +1 day.

For OS, patients for whom death had not been documented had observations censored on the last date at which they were known to be alive.

4.4 EXTENT OF FOLLOW-UP

Arms A – F:

The duration of follow-up in the study was estimated by the reverse Kaplan-Meier (K-M) method, whereby patients who died were censored at the death date and patients who did not die were treated as events at the last known alive date (duration of survival follow-up [Schemper and Smith, 1996]). Note: The extent of follow-up as determined by observation time (defined as the time from date of randomization/first study treatment until the last date the patient was known to be alive) would have underestimated potential follow-up in this study, particularly in patients with R/R DLBCL in the randomized BR arm due to their poorer survival compared to patients with R/R DLBCL in the pola+BR arm (see Section 5.1.2.2.4)

Cost and budget impact analysis of Polatuzumab + BR for the treatment of R/R DLBCL

V3.0

On 20 December 2019, Roche received the protocol for evaluating the clinical added value of Polivy® (polatuzumab vedotin) in combination with bendamustine and rituximab (BR) for adult patients with diffuse large B-cell lymphoma (DLBCL) whose cancer has returned or has stopped responding to other treatments and who cannot have a haematopoietic stem cell transplantation. The protocol included one clinical question and the economic impact is considered in these economic models.

This technical report describes the economic analysis which supports the application to the Danish Medicine Council. The economic analysis includes a cost per patient analysis and budget impact analysis. The purpose of this document is to explain the models, key assumptions and highlight the key results.

All confidential material in this document is highlighted in yellow.

Contact information	**Contact person**
Roche a/s Industriholmen 59 2650 Hvidovre Marketing authorization holder in Denmark Roche Registration GmbH Emil-Barrell-Strasse1 79639 Grenzach-Wyhlen Germany	Pavika Jain Value Demonstration Manager Mobil: 42 14 29 38 Mail: pavika.jain@roche.com

EXECUTIVE SUMMARY

Introduction

The objective of this technical report is to present both the economic model used for assessment of the cost per patient of Polatuzumab + Bendamustine + Rituximab (BR) vs BR for the treatment of relapsed/refractory (R/R) diffuse large B-cell lymphoma (DLBCL) and the budget impact model used to estimate the total budget of recommending Polatuzumab as possible standard treatment for the relevant population. These models have been developed to support the Danish Medicine Council (DMC) process and rely on the published clinical protocol. The economic analysis is based on the evidence from the Phase II study GO29365 and on published literature data.

Methods

A partitioned survival model was built to assess the cost per patient of Polatuzumab + BR Vs BR as a new treatment for patients with R/R DLBCL. The perspective of the analysis is a restricted societal perspective based on DMC's methods guidelines. Modelling of Progression Free Survival (PFS), Overall survival (OS), and Time to off treatment (TTOT) is based only on the Phase II GO29365 trial. This trial compares Polatuzumab + BR to BR. The costs are taken from published sources.

Results

Based on the base-case assumptions, the expected discounted incremental cost of treating R/R DLBCL patients with Polatuzumab and BR Vs BR was estimated to be [redacted] per patient. This is primarily driven by the increased drug costs associated with Polatuzumab + BR treatment.

The budget impact of recommending Polatuzumab + BR to R/R DLBCL patients is expected to be [redacted] in year 5.

Discussion

The economic models presented in this technical document allow for quantification of the cost per patient and budget impact of recommending Polatuzumab + BR for R/R DLBCL patients in Denmark. The drug acquisition costs are almost exclusively responsible for the estimated incremental costs.

TABLE OF CONTENTS

EXECUTIVE SUMMARY 3
1. Background 9
1.1 Patient Population 9
1.2 Standard Treatment 9
2. Purpose 10
3. Method 10
3.1 Intervention and Comparator 10
3.2 Model Description 11
3.2.1 Rationale for model structure 12
3.2.2 Model cycle duration 13
3.2.3 Clinical efficacy 13
3.3 Model parameterization 20
3.3.1 Progression free survival 20
3.3.2 Overall survival – standard parametric 25
3.3.3 Overall survival – Mixture cure rate models 26
3.3.4 Mixture-cure rate OS informed by PFS 27
3.3.5 Selection of the best-fitting curves for the informed-cure mixture approach 27
3.3.6 Treatment duration 29
3.3.1 Time horizon 29
3.3.2 Perspective 29
3.3.3 Discounting rate 29
3.4 Healthcare utilization and costs 30
3.4.1 Costs related to the intervention and comparator 30
3.4.2 Supportive care costs 33
3.4.3 Costs related to adverse events 35
3.4.4 Patient costs 39
3.4.5 Transportation costs 39
3.4.6 End-of-life costs 40
3.5 Model uncertainty 41
3.5.1 Scenario analysis 41
3.6 Base case settings 42
4. Results 43
4.1 Base-case 43
4.2 Scenario Analysis 44
5. Budget impact analysis 46

5.1 Methods 46
5.1.1 Incidence of DLBCL 46
5.1.2 Current treatment of DLBCL in Denmark 46
5.1.3 Market Shares 47
5.1.4 Costs 49
5.1.5 Scenario analyses 51
5.2 Results 52
5.2.1 Base case results 52
5.2.2 Scenarios 53
6. Discussion 54
References 55

LIST OF TABLES

Table 1 Summary of the study design with respect to efficacy evaluation 14

Table 2 Baseline characteristics 14

Table 3 Summary of key efficacy endpoints from GO29365 (ITT Population)

Table 4 Comparison between treatment exposure and treatment extrapolation

Table 5 AIC and BIC for PFS with ranks in bracketsTable 6 AIC and BIC for OS with ranks in brackets – standard parametric model – March 2019 cut.....

Table 7 Drug dose and administration schedule 31

Table 8 Drug costs (list prices - AIP) 31

Table 9 Drug administration costs 32

Table 10 Cost per administration.....33

Table 11 On treatment follow-up costs 34

Table 12 PFS follow-up costs (recurrent costs).....34

Table 13 Post-progression follow-up costs (one-off costs) 35

Table 14 Post-progression follow-up costs (recurrent costs) 35

Table 15 Estimated costs per model cycle stratified by disease state.....35

Table 16 Cost related to AE management 36

Table 17 Total cost related to AE management.....38

Table 18 Patients resource use per disease state.....39

Table 19 Patient costs per disease state.....39

Table 20 Transportation costs per disease state 39

Table 21 End of life care costs 40

Table 22 Scenarios included in Scenario analysis 41

Table 23 Base-case settings 42

Table 24 Incremental cost per patient.....43

Table 25 Results of Scenario analysis.....45

Table 26. Treatment Duration 47

Table 27. Market shares for 2L+ 47

Table 28 Market shares for 2L .....

Table 29 Market shares for 3L+ .....

Table 30 Drug dosing 50

Table 31 Drug costs.....50

Table 32 Scenarios for 2L+ .....

Table 33 Scenarios for 2L .....
Table 34 Scenarios for 3L+ .....
Table 35 Budget impact for 2L+ 52
Table 36 Budget impact for 2L 52
Table 37 Budget impact for 3L+ 52
Table 38 Scenario results 2L+.....53
Table 39 Scenario results 2L.....
Table 40 Scenario results 3L+.....

LIST OF FIGURES

Figure 1 Example of a partitioned survival model 11

Figure 2 Diagram of the model for a partitioned survival model 12

Figure 3 Design of GO29365 study 13

Figure 4 Kaplan-Meier curves showing investigator progression free survival (ITT population) 17

Figure 5 Kaplan-Meier curves showing overall survival (ITT population) 18

Figure 6 Kaplan-Meier curves showing Time to off treatment (TTOT)

Figure 7 Visual check of PH assumption, (a) KM PFS (INV), (b) log-cumulative hazard for PFS (INV), (c) PFS (IRC) KM data and (d) is the log-cumulative hazard for PFS by IRC. Visualizing these curves is not visible 21

Figure 8 Cumulative hazards compared to the for the exponential (left) and the Weibull (right).....

Figure 9 Cumulative hazards compared to the for the log-normal (left) and the generalized gamma (right) .....

Figure 10 Cumulative hazards compared to the log-logistic .....

Figure 11 Cumulative incidence of progressions (INV) from GO29365 a) Pola-BR and b) BR. Note the difference in x-axis (March 2019 cut) .....

Figure 12 Graph to check for proportional hazards, (a) is the OS KM data and (b) is the log-cumulative hazard.....

Figure 13 Example.....27

Figure 14 Progression free survival using a mixture cure model and log-normal distributions.....

Figure 15 Overall survival using a mixture cure model and log-normal distributions

Figure 16 Cost elements .....

1. Background

This application concerns Polivy® (polatuzumab vedotin) in combination with bendamustine and rituximab (BR) for the treatment of adult patients with relapsed/refractory diffuse large B-cell lymphoma (DLBCL) who are not candidates for haematopoietic stem cell transplant.

Based on the protocol from the DMC, the relevant clinical question for assessing the clinical value of Polivy® (Polatuzumab vedotin) is: *What value does polatuzumab vedotin offer, in combination with BR compared with bendamustine, GDP, GemOx or ICE in combination with rituximab for adult patients with R/R DLBCL who are not candidates for hematopoietic stem cell transplant (SCT)?*

1.1 Patient Population

Diffuse large B-cell lymphoma (DLBCL) is the most common histologic subtype of non-Hodgkin lymphoma (NHL), with an incidence of 433 new cases each year and represents approximately 40% of all NHL cases in Denmark[1]. The median age at time of diagnosis is 67 years in Denmark and approximately 60% of patients receiving 1L treatment may be cured. The current standard of care for these patients consists of rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone (R-CHOP)[2]. Nevertheless, despite the improvements in overall survival (OS) of patients with DLBCL, one-third of patients present with either a primary refractoriness to the 1L treatment or relapse after reaching a complete response (CR). Relapsed or refractory (R/R) DLBCL patients, who are ineligible for HSCT, have a poor prognosis with a median OS ranging from 3.4 to 9.0 months. Thus, a high unmet medical need continues to exist for patients with R/R DLBCL as there is limited efficacy and clinical evidence for the chemotherapy regimens currently used for treatment.

In the current Danish guidelines patients with R/R DLBCL are commonly referred to as second line (2L) and third line (3L), given the lines of previous treatment. The primary reason for this is that the literature generally does not distinguish between treatment options for patients with relapsed or refractory disease. In this final application the terms relapse/refractory will be used instead of 2L, 3L etc. since these terms are used in the European Commission Decision as well as in the DMC protocol.

Based on epidemiological data it is estimated that 76 new patients are eligible for polatuzumab treatment each year (48 patients in 2L and 29 patients in 3L+)[1–5].

1.2 Standard Treatment

Currently, there is no evidence to recommend a specific regimen for R/R DLBCL patients who are not eligible for SCT. The patients constitute a very heterogeneous group with varying prognosis. However, the prognosis is always poor. Based on data from 2013-2018, BR is the most widely used regimen for this patient subgroup in Denmark.

The DMC protocol defines two subpopulations[6]: 1) fit patients who are often offered a combination of chemotherapy agents e.g. rituximab, gemcitabine, dexamethasone and cisplatin (R-GDP), rituximab, gemcitabine and oxaplatin (R-GemOx) or rituximab, ifosfamide, carboplatin and etoposide (R-ICE) are referred to as the “combination chemotherapy subpopulation”, 2) relatively frail patients who are often offered single agent chemotherapy e.g. bendamustine in combination with rituximab (BR) are referred to as the “single agent chemotherapy subpopulation”.

Based on the protocol from the DMC, the relevant standard treatments are:

Single drug chemotherapy:

- Bendamustine (70 mg/m^2 or 90mg/m^2 day 1-2) and rituximab (375 mg/m^2 day 1)

Combination chemotherapy:

- GDP and rituximab (375 mg/m^2 day 1)
- GemOx and rituximab (375 mg/m^2 day 1)
- ICE and rituximab (375 mg/m^2 day 1)

2. Purpose

The economic models were developed to estimate the incremental costs per patient of Polatuzumab + BR versus standard treatment for the treatment of R/R diffuse large B-cell lymphoma (DLBCL) as well as the budget impact of recommending Polatuzumab as possible standard treatment for the relevant population in Denmark.

3. Method

3.1 Intervention and Comparator

A systematic literature review (SLR) was performed to identify and summarise the current evidence around clinical treatments for patients with R/R DLBCL. The feasibility assessment on the clinical trials identified in systematic literature review showed that it was not possible to create an evidence network. It was therefore only possible to compare with other treatments through a match adjusted indirect comparison (MAIC) versus the two CAR-T treatments. Unfortunately, it was not possible to do a robust comparison against R-GemOx, GDP or ICE because no suitable KM has been published[7].

Based on the currently available evidence and the protocol from the DMC, the intervention and comparator in the economic analysis is therefore:

- Intervention*: Polatuzumab (1,8 mg/kg) + Bendamustine (90 mg/m^2) + Rituximab 375 mg/m^2. Polatuzumab is given on day 1, Bendamustine is given on day 1+2m and Rituximab is given on day 1 in cycles of 21 days.*
- Comparator: *Bendamustine (70 mg/m^2 or 90mg/m^2 day 1-2) and rituximab (375 mg/m^2 day 1) in cycles of 21 days.*

The lack of a combination chemotherapy arm in the model is a weakness. However, the model predictions are expected to be similar to a comparison with a combination chemotherapy regime for the following reasons:

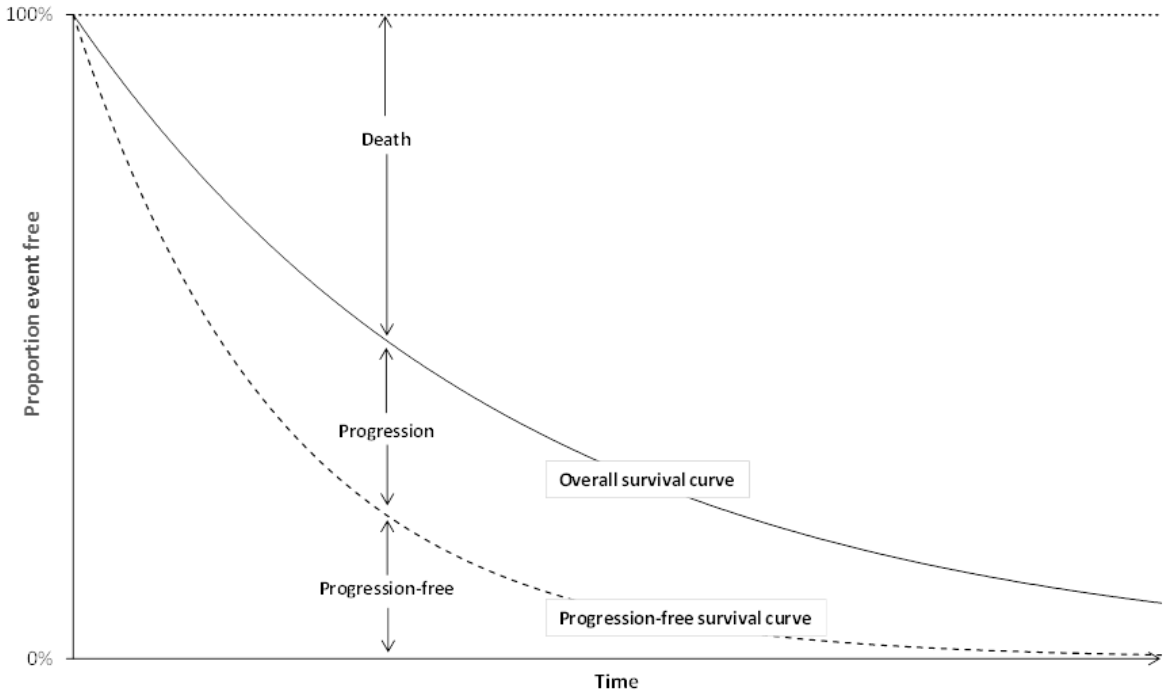
- The treatment duration is fixed for both single chemo and combination chemo (6 cycles)
- Both single- and combination regimens have a low cost and their costs are broadly similar
- The incremental costs compared to BR are expected to be similar to a combination regimen

3.2 Model Description

A partitioned survival model (Figure 1) was developed in Excel to assess the incremental cost per patient of Polatuzumab + BR vs. the relevant comparator for the treatment of TNBC, based upon the G029365 study[8]. This type of model allows for usage of the available clinical study data whilst also relying on the most commonly used health stages in previous oncology models, i.e. the mutually exclusive healing states of progression-free, post-progression and death.

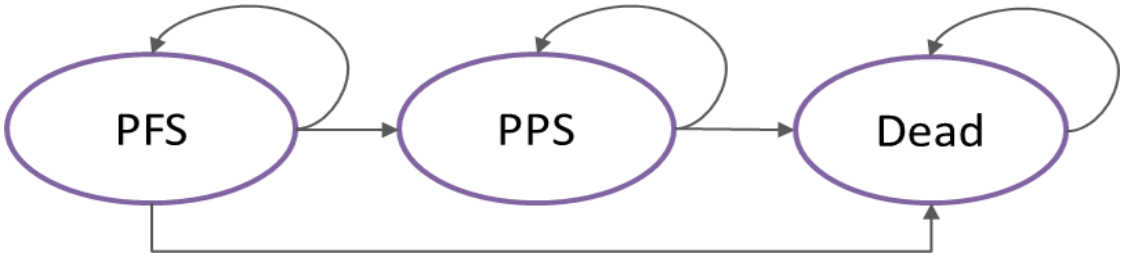
Partitioned survival models use time-to-event data to model the proportion of patients who are in the progression-free, post-progression and death state dependent on time since trial initiation. OS is partitioned into PFS and post-progression survival (PPS) based on the PFS curve (1). The proportion of patients in the post-progression health state at a given point in time is calculated as the difference of the proportion of patients who are alive and the proportions of patients who are progression free.

Figure 1 Example of a partitioned survival model



Patients enter the model in the progression-free state. In each cycle, patients can either remain in the progression-free health state, or transition to the post-progression or death health state (figure 2). Patients who have progressed can remain in the post-progression state or transition to the death state but never go back to the progression-free state. All patients eventually enter the death state.

Figure 2 Diagram of the model for a partitioned survival model



Progression free survival

Progression-free survival was the initial state in which all patients entered the model. The decrease in the proportion of patients who remained in the progression-free state over time was determined by the progression-free survival curves estimated based on the GO29365 trial data. The PFS curves indicate for each point in time the proportion of patients who have not progressed and not died yet.

Post-progression state

The post-progression state accommodated all patients who have experienced disease progression but have not died yet. The proportion of all patients in this state was calculated as the difference between the proportion of patients who were alive and the proportion of patients who were in the progression-free health state. The transitions into and out from the post-progression health state were thus not modelled explicitly but as a residual proportion of patients.

Death state

Death was modelled as an absorbing state meaning that all patients eventually enter this state and cannot leave it. The transitions of patients from the progression-free and post-progression health states into the death state were determined by the overall survival curves derived from the GO29365 trial. Overall survival curves indicate the proportion of patients who are alive at a given point in time or, equivalently, the proportion of patients who die during a model cycle dependent on the time since treatment initiation.

3.2.1 Rationale for model structure

There is a long history of using partitioned survival models for Health Technology Assessments. The main reason for this is that the direct usage of PFS and OS and the survival functions makes the models intuitive, easy to communicate whilst also allowing for good representation of the observed trial data. In addition, these models allow for modelling changes in the hazard rates dependent on time in a current state and do not rely on the rather restrictive assumption of time invariant hazard rates that is made in Markov models.

However, there are limitations to these models as they cannot model the underlying disease or account for recurrent events. The assumption that PFS and OS are independent is very strong and clearly violated in the case of three-state oncology models. PFS and OS are related because they both include death as an event, progression can never occur after death, and progression can be predictive of the time to death. Generally, the validity and robustness of partitioned survival models beyond the observed trial duration is dependent on the maturity of the used survival data. However, due to the maturity of the survival data in this case, we believe this to be less influential

In addition, these the model used for in this economic analysis model the curves independently, and this can result in crossover. We have adjusted the model so that crossover is not possible, and we have made sure survival in the model never can exceed normal background population survival in Denmark. Thus, we do not believe this is an issue with the analysis presented in this technical report.

3.2.2 Model cycle duration

The model cycle length is selected to be a weekly cycle. The rationale is that it is assumed that transitions from one health state to another occur at the beginning of each cycle. In reality, however, patient transition is a continuous process, which may occur any time during the cycle. By applying a relatively short cycle length of weekly cycle, the difference between the actual transition time and the model predicted time is reduced. This allows for more accurate estimation of the length of time patients remain in the health states. This allows also flexibility and accuracy in costing and dosing calculations, since the administration cycles of the different treatments assessed in the model vary between them.

Half-cycle correction is applied to the model in order to account for mid-cycle transitions. This assumes that state transitions occur, on average, half-way through the cycle. Due to the short cycle length of weekly cycle, the half-cycle correction does not have a large impact on the results, but it is included in the model for completeness.

3.2.3 Clinical efficacy

Trial design

GO29365 study is an ongoing phase Ib/II, open-label, multi-center, randomized study in total it contains 8 arms (A-H), this report will solely focus on arm C and D. The purpose of these arms is to investigate the efficacy and safety of Polatuzumab + BR against BR in patients with R/R DLBCL. The design of the study is shown in figure 3 and described in table 1.

Figure 3 Design of GO29365 study

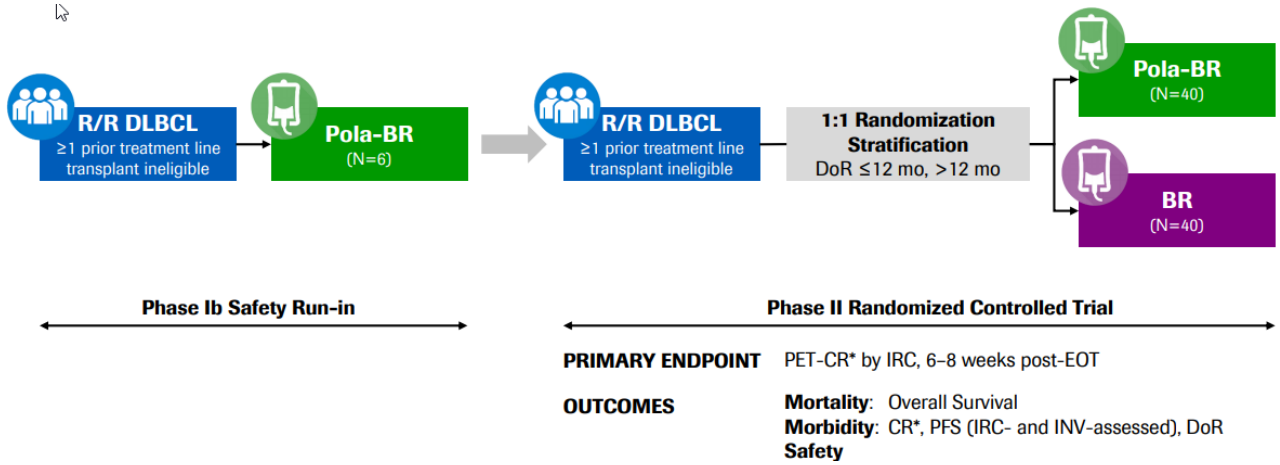


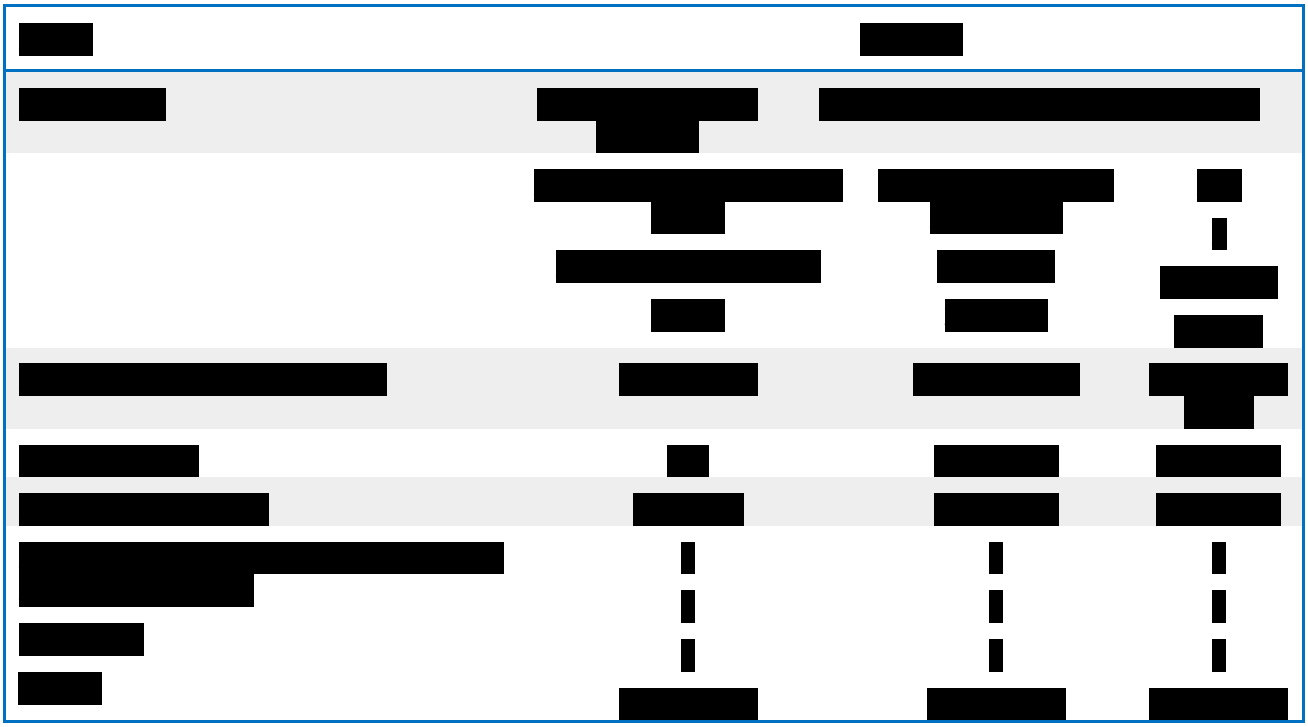
Table 1 Summary of the study design with respect to efficacy evaluation

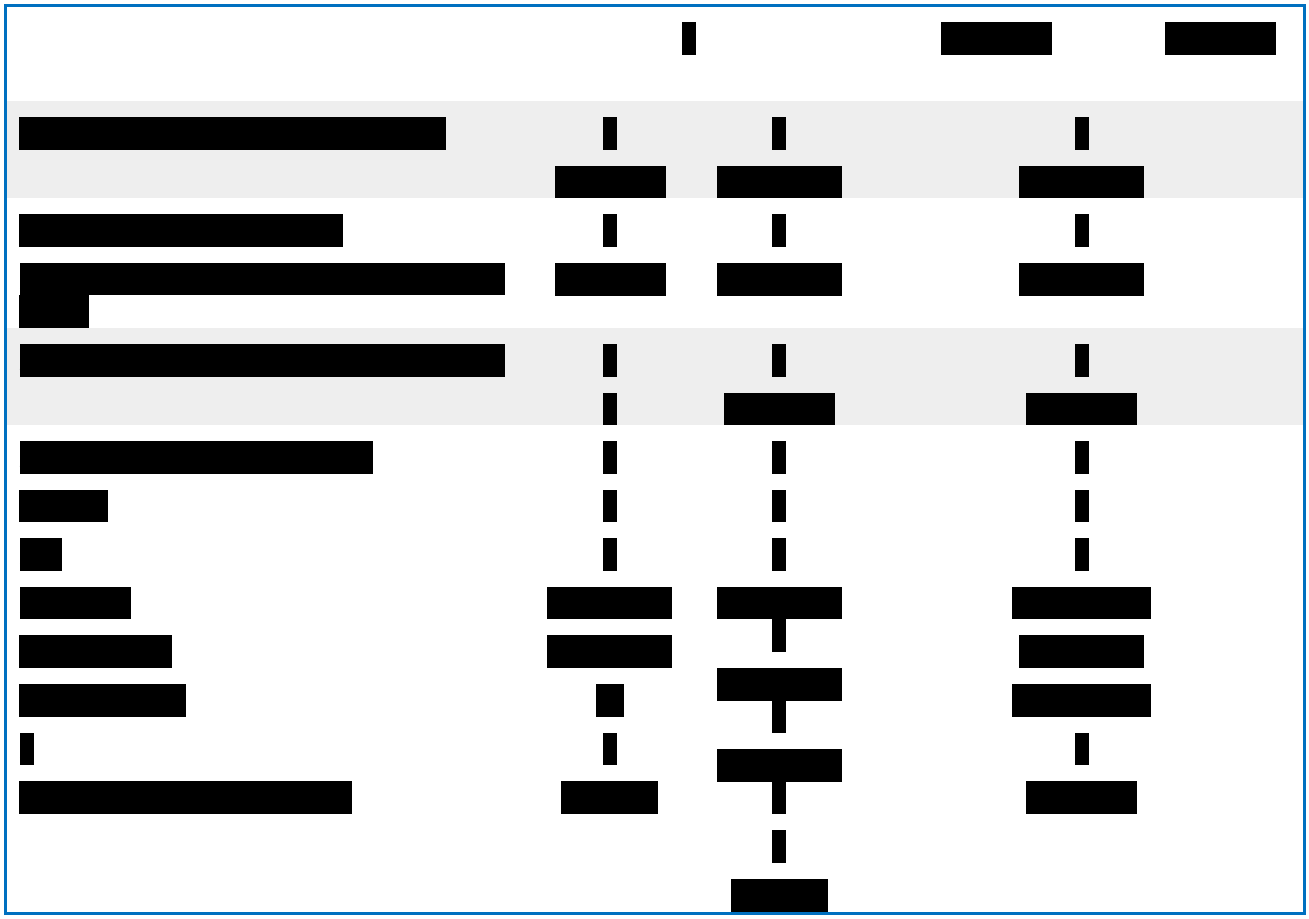
Study no. Phase II	Clinical cut-off dates: April 2018, October 2018
Study design, control type	*Prospective, two-arm randomized, multicenter, multinational, double-blind, placebo-controlled*
Population	Patients with relapse and refractory DLBCL, who are ineligible to SCT
Number of patients	Efficacy Population (ITT): • Total: patients: 80 patients • Polatuzumab + BR: patients: 40 patients • BR: patients: 40 patients
Dose and Regimen (all given IV)	• Polatuzumab vedotin 1.8 mg/kg up to 6 cycles • Rituximab 375 mg/m2 up to 6 cycles • Bendamustine 90mg/m2 up to 6 cycles
Endpoints	
Primary	Complete response (CR) based upon the modified Lugano, PET-CR* by IRC, 6–8 weeks post-end of treatment
Others	Overall Survival (OS), PFS (IRC- and INV-assessed), Duration of Response (DoR) and Event Free Survival (EFS)
Stratification factors	Duration of response to previous therapy < 12 months vs > 12 months

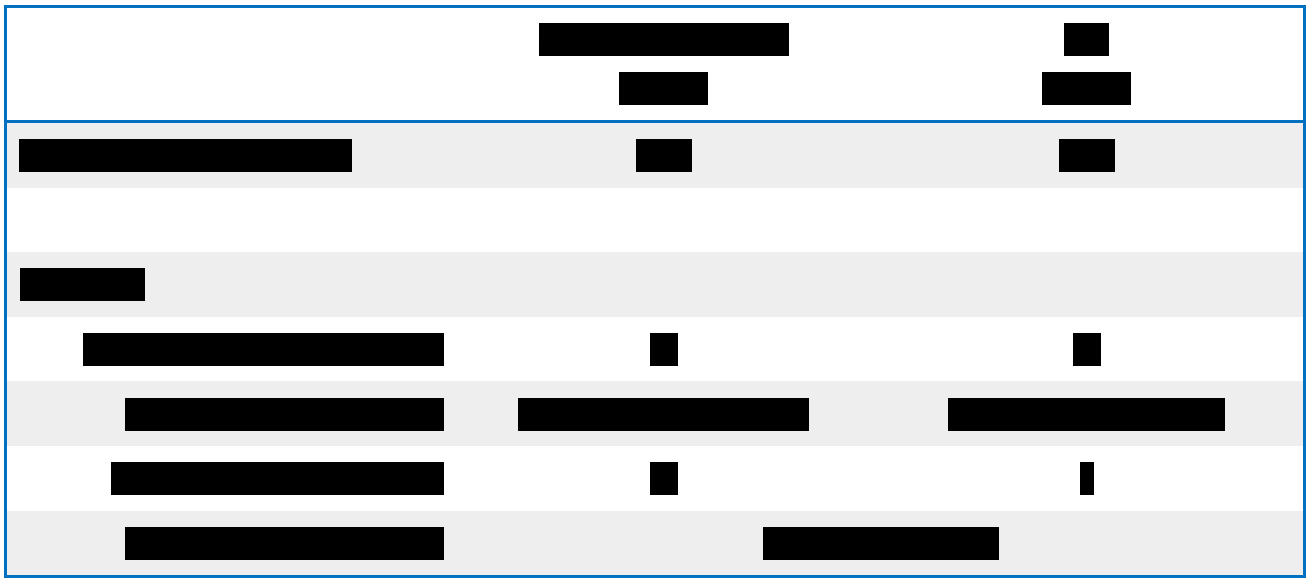
Study population

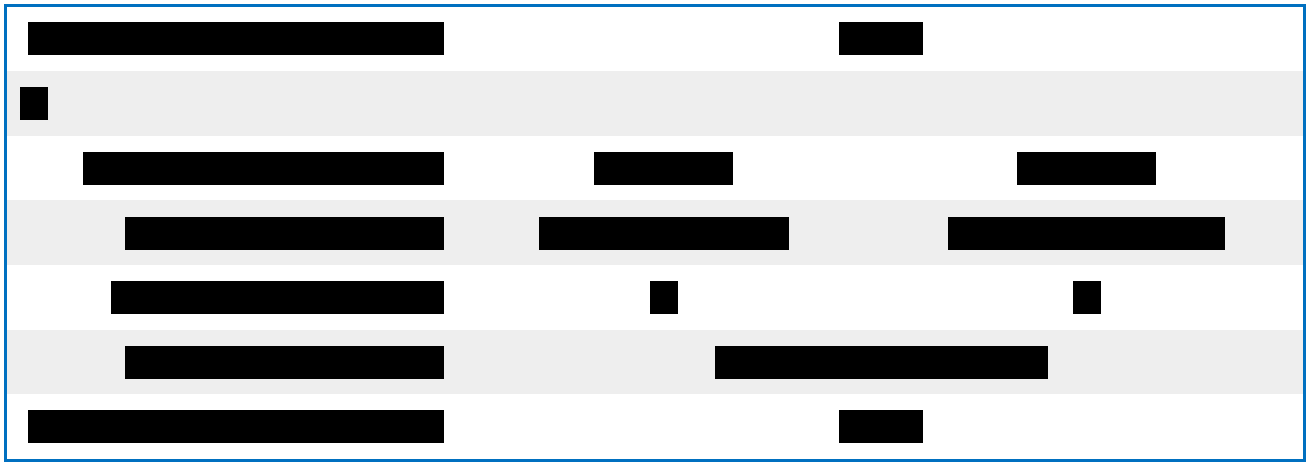
Table 2 shows the baseline characteristics for the Phase 1b and the phase 2 part of the GO29365 study.

Table 2 Baseline characteristics





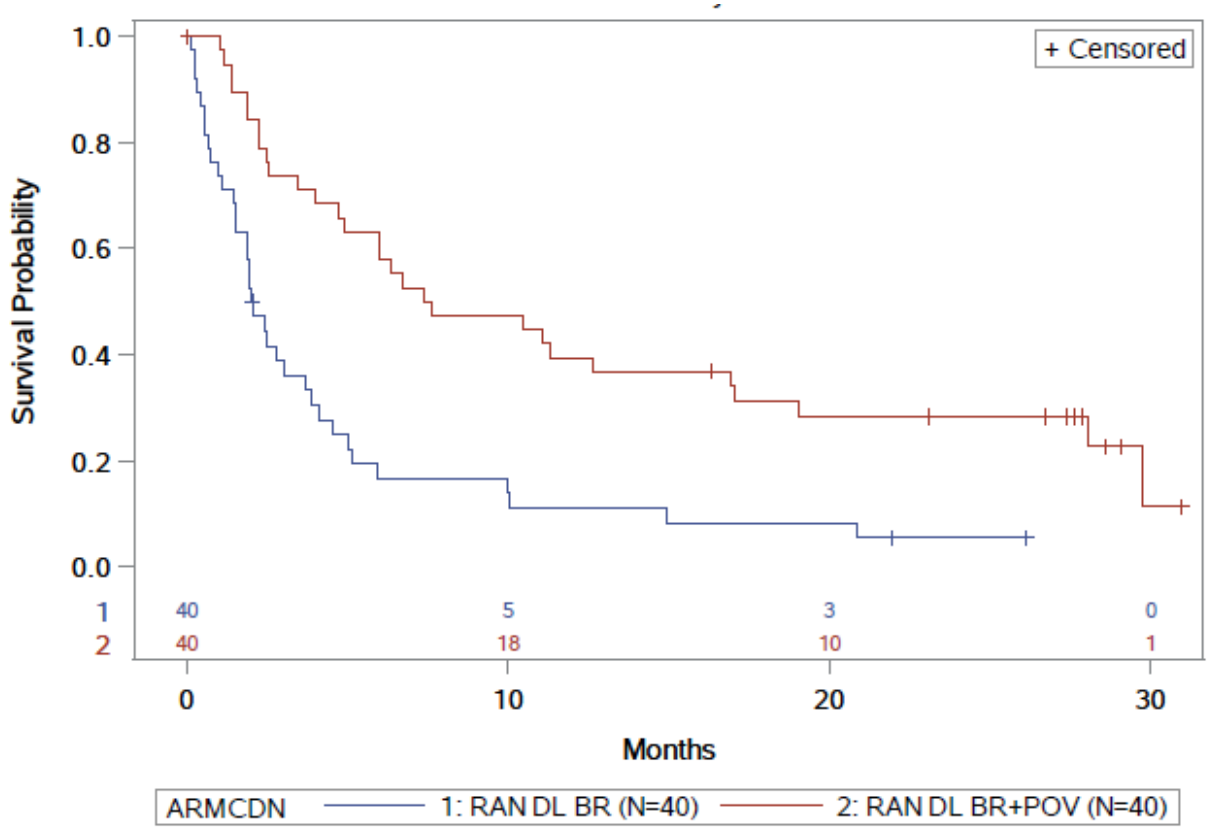




Progression free survival

The progression free survival based upon the investigator assessment is presented in figure 4, the red line shows the Pola-BR and the blue line shows the BR alone.

Figure 4 Kaplan-Meier curves showing investigator progression free survival (ITT population)

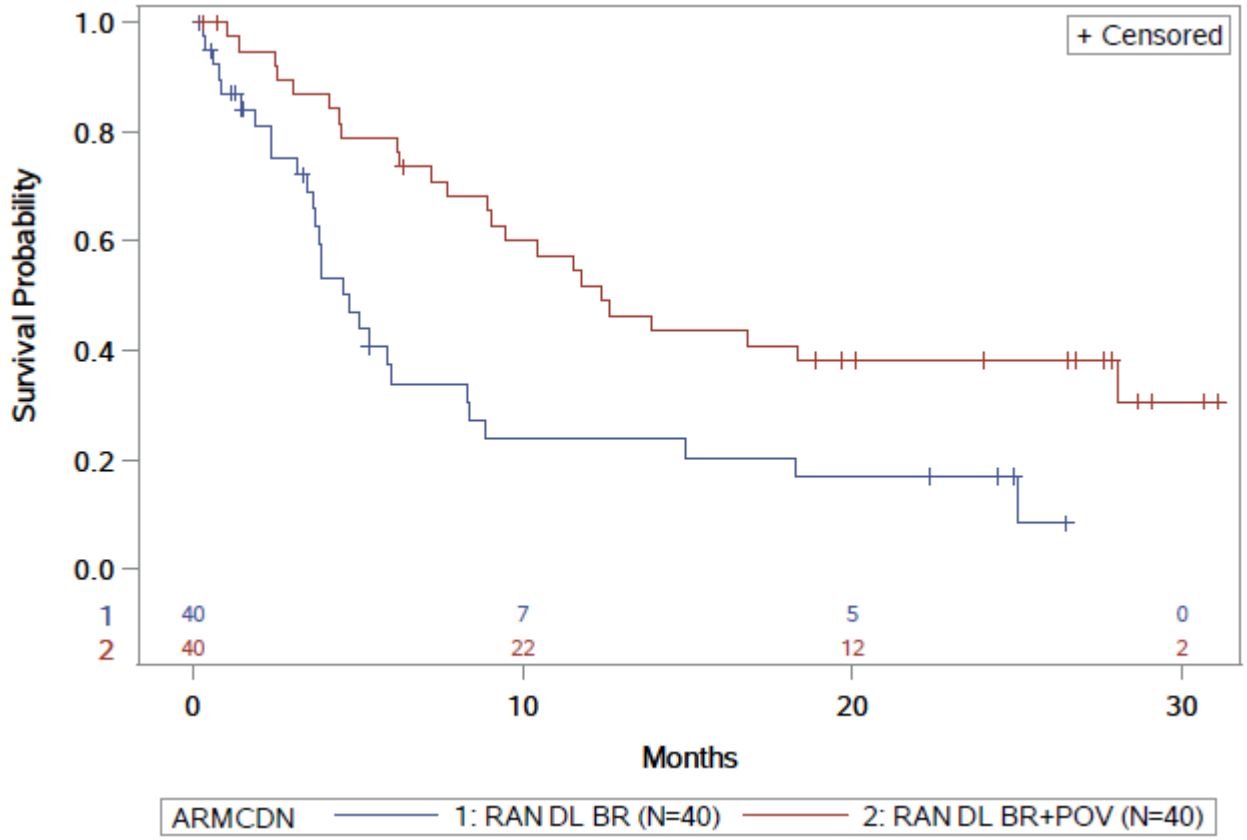


Data-cut, October 2018. BR – Bendmustine + Rituximab, BR+ POV - Bendmustine + Rituximab + Polatuzumab vedotin

Overall survival

The overall survival based upon the investigator assessment is presented in figure 5.

Figure 5 Kaplan-Meier curves showing overall survival (ITT population)



Data-cut, October 2018. BR – Bendmustine + Rituximab, BR+ POV - Bendmustine + Rituximab + Polatuzumab vedotin

Time to off treatment (TTOT)

All

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

	[redacted]	[redacted]
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Safety outcomes

A complete list of Adverse Events (AE) can be seen in the "AE Cost" worksheet of the model.

3.3 Model parameterization

Parametric survival analysis

Extrapolation beyond the GO29365 clinical follow-up period was per-formed by fitting the following standard parametric distributions to the observed data.

- Exponential
- Weibull
- Log-normal
- Generalized Gamma
- Log-logistic
- Gompertz

Goodness of fit

Parametric distributions were assessed for their goodness of fit to the data using the Akaike Information Criterion (AIC) and graphical assessment of each parametric function. Low values for AIC indicate a better mathematical assessment of the fit of the parametric function to the actual data. However, the quality and plausibility of the extrapolation beyond the observed data cannot be assessed mathematically and is not reflected in the AIC.

Statistical model

Pola + BR in the treatment of (R/R) DLBCL has demonstrated a proportion of long-term survivors. Such proportion can be visually assessed by looking at the Kaplan-Meier curves for Overall Survival plateau after a relatively long follow up time. (Figure 5).

Mixture cure rate models are valuable when it is believed that the cancer population consist of two distinct parts, one being long-term survivors and another group consisting of patients dying faster. The standard parametric survival distributions struggle in a situation with a mixed population, because the majority of the events observed will mainly be from the patients who are at higher risk. In addition to the standard parametric survival models, a mixture cure rate model approach was also investigated to determine the most appropriate statistical model for the population.

3.3.1 Progression free survival

Proportional hazards tests – parametric function

The first assumption to check when choosing an extrapolation model is whether proportional hazards are present or not. The proportional hazard (PH) assumption states that the hazard in one group (arm A) is a constant proportion of the hazard in the other group (arm B), this proportion is the hazard ratio. The hazard may vary with time, but ratio of the hazard rates remains constant.

Figure 6 Visual check of PH assumption, (a) KM PFS (INV), (b) log-cumulative hazard for PFS (INV), (c) PFS (IRC) KM data and (d) is the log-cumulative hazard for PFS by IRC. Visualizing these curves is not visible

If proportional hazards are present, then the extrapolation can be fitted simultaneously for all treatment arms with treatment as a covariate in the model (Exponential, Weibull and Gompertz are the parametric distributions that can hold the proportional hazard assumption). If the hazards are not proportional, then the treatment arms should be fitted independently.

In the latter case the same type of extrapolation should be used, only with different sets of parameters, i.e. one treatment arm should not be modelled via a Weibull distribution and the other arm with a log-logistic distribution (unless there is a very good justification to do so). Using different types of functions is more likely to lead to effects, for example curves which are crossing in the extrapolation part of the functions, which necessitate additional explanations.

Internal validity and goodness of fit - parametric

Table 5 provides the AIC and Bayesian Information Criterion (BIC) goodness of fit results for the functions used to model PFS.

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Key: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion.

In order to describe which distribution that would be appropriate figure 8-10 compares the cumulative hazards to the model estimates. Dotted lines indicate the standard parametric model and the dashed lines indicate the mixture cure rate model.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Rationale for a mixture cure rate model for PFS

Progression free survival is a combination of progression and deaths, in the case of R/R DLBCL and there is a notion that the rate of progressions decreases by time. This is exactly the trend which has been observed in GO29365, from the KMs presented in figure 7 (PFS-INV and PFS-IRC) a plateau can be seen. Progression free survival is a composite of progressions and death; the number of progressions may be reduced but the deaths will continue to occur.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Consequently, in the base case a mixture cure rate model was chosen. See choice of distribution in section 3.3.4.

3.3.2 Overall survival – standard parametric

Proportional hazards tests – parametric function

Figure 12 displays the KM (a) and cumulative log-hazards (b) for the OS data from GO29365. Figure 12b has been generated by taking the logarithm of the negative logarithm of survival from the KM (a) and logarithm of the time. The proportional hazards assumption holds if the two lines are parallel to each other in (b).

[redacted]

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Key: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion.

3.3.3 Overall survival – Mixture cure rate models

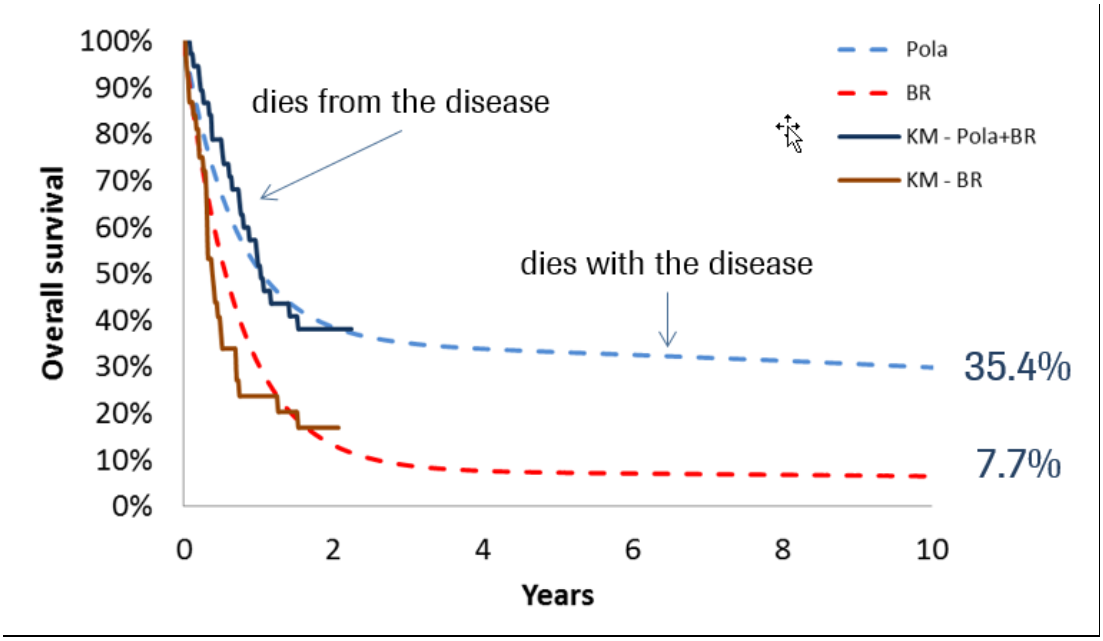
Pola + BR in the treatment of (R/R) DLBCL has demonstrated a proportion of long-term survivors. Such proportion can be visually assessed by looking at the Kaplan-Meier curves for Overall Survival plateau after a relatively long follow up time. (Figure 5).

Mixture cure rate models are valuable when it is believed that the cancer population consist of two distinct parts, one being long-term survivors and another group consisting of patients dying faster. The standard parametric survival distributions struggle in a situation with a mixed population, because the majority of the events observed will mainly be from the patients who are at higher risk.

In order to address the long-term survivor fraction, extensions of several parametric models were explored by including a cure rate fraction. In such models, a fraction of the patients ($\pi > 0$) are expected to become long-term survivors. This group of long-term survivors' experience stable disease and are therefore no longer at risk of dying from the cancer, but rather from other causes. [redacted]

[redacted]

Figure 7 Example



3.3.4 Mixture-cure rate OS informed by PFS

In prior economical evaluations it was stated that only patients that have not yet progressed can be considered long-term survivors. We therefore included an additional step in the methodology described above by constraining the overall survival to the progression free survival times.

3.3.5 Selection of the best-fitting curves for the informed-cure mixture approach

Based on AIC the statistics suggest the following best fits (see “cure rate data” sheet):

- PFSINV - control arm: log-normal
- PFSINV – intervention arm: Generalized gamma
- OS – control arm: log-logistic

- OS – intervention arm: log-normal
-

In any case, AIC values are a measure of the goodness-of-fit for the observed period and do not necessarily reflect the long-term behavior. Thus, the log-normal distribution was chosen for all end points as this generally had the best fit to the data and predicted plausible results for both the mixture cure rate- and standard parametric approach. Nonetheless, since the choice of distribution only affects the survival outcomes (time spent in the PFS and OS state), and not the treatment duration (see section 3.2.3), the choice of distribution had very small impact on the overall result. The impact of choosing alternative distributions were investigated in the scenario analyses.

3.3.6 Treatment duration

In GO29365 all treatments were given with a fixed treatment and all patients have either completed the full treatment cycle or discontinued treatment at the last data-cut. Hence only the Kaplan-Meier estimate (see figure 6) was used to estimate the treatment duration in the cost-effectiveness model, and there was no need for any extrapolation.

3.3.1 Time horizon

It is recommended that the selected time horizon should be long enough to reflect all important differences in costs between the technologies being compared[10].

For the base-case analysis, a time horizon of 45 years has been selected. This recommended time horizon is 45 years since more than 99% of the cohort is dead by that time and, as predicted by the model using base case OS parametric distribution. In addition, the average age after 45 years would be 115 years, and it would therefore be unrealistic to expect survivors beyond that time horizon.

3.3.2 Perspective

The perspective of the economic model analysis is a restricted societal perspective, which includes cost related to drug acquisition, drug administration, monitoring, adverse events, routine care, patient time, and transportation. Indirect costs are not included in accordance with DMC's guidelines[10].

3.3.3 Discounting rate

In the base-case, the annual discount rate for future costs were 4% for model year ≤35, and 3% for model year >35 in alignment with DMC's guidelines.

3.4 Healthcare utilization and costs

3.4.1 Costs related to the intervention and comparator

Drug dosing and acquisition costs

Polatuzumab follows a mg/kg, whereas all the other drugs follow a mg/m2 dosing regimen (table 8). In this respect, the actual administered dose will depend on the body weight and body surface area (BSA) of the patients.

The expected drug costs per patient were calculated using time to off treatment KM curves (TTOT) and accounting for the full weight and the distribution of BSA.

[redacted]

[redacted]There is also an option in the model to adjust the proportion of vial sharing used directly. In the base-case, no vial sharing is assumed.

Table 3 Drug dose and administration schedule

Regimen	Treatment	Dosing	Maintenance dose (mg)	Cycle length (in days)
Pola + BR	Polatuzumab	mg/kg	1,8	21
Pola + BR	Rituximab	mg/m2	375	21
Pola + BR	Bendamustine	mg/m2	180	21
BR	Rituximab	mg/m2	375	21
BR	Bendamustine	mg/m2	180	21

List prices of drugs for the intervention and comparator have been sourced from the Lægemiddelstyrelsen[11] (accessed 23rd of January 2020). Drug costs and resulting cycle costs can be seen in table 8.

Table 4 Drug costs (list prices - AIP)

Treatment	Vial/total pack size (mg)		Vial/pack price (DKK)		Cost per cycle (DKK)	Source
	small	large	small	large		
Polatuzumab		140		[redacted]	83.553,33	Roche
Polatuzumab	30		[redacted]			Roche
Bendamustine	25	100	171,64	691,53	2.373,48	Medicinpriser.dk*
Rituximab	100	500	1.337,90	6.687,00	9.897,93	Medicinpriser.dk*
Carboplatin	150	450	84,00	203,00	573,49	Medicinpriser.dk*
Etoposide	100	500	90,00	278,72	207,60	Medicinpriser.dk*

*Accessed 23 January 2020

Drug administration costs

In addition to the drug acquisition costs, the cost of administration was also considered within the model. DRG 2020 rates[12] were used for the administration costs. Interactive DRG 2020 was used using the diagnosis

"Diffust storcellet B-celle lymfom". Procedure codes were available for Bendamustine only ((BWHA177) Behandling med bendamustin). No combination procedure codes were available for combination therapies with Bendamustine. For Rituximab only one procedure code was available. However, this was for R-CHOP, which is a completely different regime than the regimes in this application. Therefore, the procedure code (BWHA177) Behandling med bendamustin was used for both Pola + BR and R-Benda. To validate this approach, it was investigated whether this approach resulted in a different tariff than the general tariff for administration of i.v. infusion ((BWAA62) Medicingivning ved intravenøs infusion). The tariff was the same for both approaches (DKK 3235), and the approach therefore seemed reasonable.

A micro costing approach could also be used to estimate the administration costs. However, the micro costing approach was expected to estimate lower administration cost than the tariff costing approach. Consequently, this the tariff approach was chosen as this was considered the most conservative approach in favour of the comparator-arm. Regardless of the approach, the administration costs have minor impact in the end result, and therefore this element was not investigated further.

All administration costs were validated by two Danish clinical experts within DLBCL.

The administration costs per treatment are presented in table 10.

To accommodate potential start-up costs, the model allows to have one administration cost for the first cycle and a different cost for the subsequent cycles. However, in the base-case the costs for all cycles are assumed the same.

Table 5 Drug administration costs

Administration	Administration cost (DKK)	Reference
IV	3235,00	DRG 2020: 17MA98 MDC17 1-dagsgruppe, pat. mindst 7 år - (DC833) Diffust storcellet B-celle lymfom - (BWHA177) Behandling med bendamustin

Table 6 Cost per administration

Cycle	Treatment	Cost per treatment cycle (DKK)
[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]

3.4.2 Supportive care costs

The details of the health state costs are described in table 11-15. Costs were separated based upon patients' disease status (progression-free on treatment/progression free off treatment/post-progression). A micro-costing approach was applied for specialist and nurse resource use based on the average duration of each visit, while official available tariffs were applied for the remaining procedures. The resource use for the two health states have been estimated in collaboration with Danish clinical expert within DLBCL. A micro-costing approach was chosen for supportive care to avoid double counting of resources, since a tariff-based approach was used for the administration costs, where additional costs are often included in the tariff. A tariff-based approach would require a bundling of several of the elements, which would necessitate further assumptions.

Table 7 On treatment follow-up costs

Activity	Proportion of patients	Frequency / year	Unit cost (DKK)	Reference
Nurse visit	100%	[redacted]	552,61	Cost of nurse including overhead costs calculated according to The Danish Medicines Council Estimating unit costs using average salary from July 2019, assuming a duration of 1 hour per visit.
PET-CT	100%	[redacted]	2.470	DRG 2020: (DC833) Diffust storcellet B-celle lymfom - (WDTCPXYXX) CT-scanning, PET/CT, uspecificeret isotop
Heamoglobin + Thrombocytes	100%	[redacted]	31,00	Rigshospitalets Labportal
LDH	100%	[redacted]	24,00	Rigshospitalets Labportal
Liver function	100%	[redacted]	72,00	Rigshospitalets Labportal
Renal function	100%	[redacted]	79,00	Rigshospitalets Labportal
Immunoglobulin G	100%	[redacted]	24,00	Rigshospitalets Labportal
Creatinine	100%	[redacted]	24,00	Rigshospitalets Labportal
Leucocytes	100%	[redacted]	15,00	Rigshospitalets Labportal
CRP	100%	[redacted]	24,00	Rigshospitalets Labportal
Sodium	100%	[redacted]	14,00	Rigshospitalets Labportal
Potassium	100%	[redacted]	14,00	Rigshospitalets Labportal
Albumin	100%	[redacted]	53,00	Rigshospitalets Labportal

Table 8 PFS follow-up costs (recurrent costs)

Activity	Proportion of patients	Frequency / year	Unit cost (DKK)	Reference
Specialist visit	100%	[redacted]	552,61	Cost of chief physician including overhead costs calculated according to The Danish Medicines Council Estimating unit costs using average salary from July 2019, assuming a duration of 20 minutes per visit.
CT scan	100%	[redacted]	2.470	DRG 2020: (DC833) Diffust storcellet B-celle lymfom - (WDTCPXYXX) CT-scanning, PET/CT, uspecificeret isotop
Heamoglobin + Thrombocytes	100%	[redacted]	31,00	Rigshospitalets Labportal
LDH	100%	[redacted]	24,00	Rigshospitalets Labportal
Liver function	100%	[redacted]	72,00	Rigshospitalets Labportal
Renal function	100%	[redacted]	79,00	Rigshospitalets Labportal
Immunoglobulin G	100%	[redacted]	24,00	Rigshospitalets Labportal
Creatinine	100%	[redacted]	24,00	Rigshospitalets Labportal
Leucocytes	100%	[redacted]	15,00	Rigshospitalets Labportal
CRP	100%	[redacted]	24,00	Rigshospitalets Labportal
Sodium	100%	[redacted]	14,00	Rigshospitalets Labportal
Potassium	100%	[redacted]	14,00	Rigshospitalets Labportal

Albumin	100%	[redacted]	53,00	Rigshospitalets Labportal

Table 9 Post-progression follow-up costs (one-off costs)

Activity	Proportion of patients	Unit cost (DKK)	Reference for proportion	Reference for cost
Chemotherapy (3 cycles)	[redacted]		GO29365 NALT data, pooled	Assume ICE cost for chemo administration
R+Chemotherapy (3 cycles)	[redacted]		GO29365 NALT data, pooled	Assume R-ICE cost for R- chemo administration
AntiCD20 (mono 3 cycles)	[redacted]	43.292,51	GO29365 NALT data, pooled	Assume R-cost
Radiotherapy	[redacted]	2.877	Danish clinical experts	DRG 2020: (DC833) Diffust storcellet B-celle lymfom - (BWGC1) Konventionel ekstern strålebehandling
Total one-off cost		**4.069,53**		

Table 10 Post-progression follow-up costs (recurrent costs)

Activity	Proportion of patients	Frequency / year	Unit cost (DKK)	Reference
Specialist visit	100%	[redacted]	552,61	Cost of chief physician including overhead costs calculated according to The Danish Medicines Council Estimating unit costs using average salary from July 2019, assuming a duration of 20 minutes per visit.
Palliative care team	100%	[redacted]	3.235,00	DRG 2020: (DC833) Diffust storcellet B-celle lymfom - (BXBA) Specialiseret palliativ indsats

Table 11 Estimated costs per model cycle stratified by disease state

Disease state	Cost per cycle (DKK)
Progression-free (on treatment)	201,23
Progression-free (off treatment)	156,80
Progressed disease	529,45

3.4.3 Costs related to adverse events

For the analysis only AEs, that were deemed treatment related with a severity grade of 3 and higher were considered. All included AEs lead to a hospital visit or prolonged and ongoing hospitalisation.

The costs of adverse events during the time on treatment were calculated separately for both treatment arms based on the average number of treatment-related adverse events per patient week in the GO29365 trial and

the unit costs of these adverse events. The costs of adverse events were assigned as a one-off cost in the first cycle of the model. Estimated costs per AE are illustrated in table 16, and total estimated AE costs per treatment arm are illustrated in table 17.

Table 12 Cost related to AE management

AEs	Grade	% AE Polatuzumab + BR	% AEs BR	Unit cost (DKK)	Reference
Acute Kidney Injury	3	[redacted]	[redacted]	22.546	Average of DRG 2020, 11MA98 MDC11 1-dagsgruppe, pat. mindst 7 år and 11MA01 Akutte medicinske nyresygdomme uden dialyse og uden plasmaferese - DN179 "Akut nyreinsufficiens UNS"
Atrial Fibrillation	3	[redacted]	[redacted]	8.544	Average of DRG 2020, 05MA98 MDC05 1-dagsgruppe, pat. mindst 7 år 05MA07 Hjertearytmi og synkope: (DI489) "Atrieflagren eller atrieflimren UNS"
Atrial Flutter	3	[redacted]	[redacted]	8.544	Average of DRG 2020, 05MA98 MDC05 1-dagsgruppe, pat. mindst 7 år 05MA07 Hjertearytmi og synkope: (DI489) "Atrieflagren eller atrieflimren UNS"
Cytomegalovirus Infection	3	[redacted]	[redacted]	9.603	Average of DRG 2020, 18MA98 MDC18 1-dagsgruppe, pat. mindst 7 år and 18MA06 Virussygdomme, pat. mindst 18 år, u. kompl. Faktorer - (DB259) "Cytomegaloviral sygdom UNS"
Decreased Appetite	3	[redacted]	[redacted]	8.431	Average of DRG 2020, 10MA98 MDC10 1-dagsgruppe, pat. mindst 7 år and 10MA04 Ernærings- og diverse metaboliske sygdomme - (DR630) "Appetitløshed"
Diarrhoea	3	[redacted]	[redacted]	5.297	DRG 2020, 06MA11 Malabsorption og betændelse i spiserør, mave og tarm, pat. mindst 18 år,

					u. kompl. bidiag. - (DK529B1) Kemoterapi-induceret diaré
Enterocolitis Viral	3	[redacted]	[redacted]	5.297	DRG 2020, 06MA11 Malabsorption og betændelse i spiserør, mave og tarm, pat. mindst 18 år, u. kompl. Bidiag - (DK529D) "Ikke-infektiøs enterocolitis UNS"
Febrile Neutropenia	3	[redacted]	[redacted]	20.376	Average of DRG 2020, 16MA98 MDC16 1-dagsgruppe, pat. mindst 7 år and 16MA03 Granulo- og trombocytopeni - (DT888N) Neutropen feber ved cytostatisk behandling
Febrile Neutropenia	4	[redacted]	[redacted]	37.603	DRG 2020, 16MA03 Granulo- og trombocytopeni - (DT888N) Neutropen feber ved cytostatisk behandling
Herpes Virus Infection	4	[redacted]	[redacted]	43.180	DRG 2020, 18MA01 Sepsis - (DB007) Herpes generalisata
Leukoencephalopathy	5	[redacted]	[redacted]	28.714	DRG 0123, DG361: "Akut eller subakut hæmoragisk leukoencephalitis"
Leukopenia	4	[redacted]	[redacted]	22.589	DRG 2020, 16MA10 Øvrige sygdomme i blod og bloddannende organer - (DD728H) Leukopeni
Lower Respiratory Tract Infection	3	[redacted]	[redacted]	27.072	Average of DRG 2020, 04MA98 MDC04 1-dagsgruppe, pat. mindst 7 år and 4MA05 Infektioner og betændelse i luftveje, pat. mindst 65 år - Lungeinfektion med Mycobacterium avium
Meningoencephalitis Herpetic	5	[redacted]	[redacted]	58.620	DRG 2020, 1MA03 Infektion i nervesystemet ekskl. virus meningit - (DB004A) Meningoencephalitis forårsaget af Herpes simplex-virus
Myelodysplastic Syndrome	4	[redacted]	[redacted]	44.533	DRG 2020, 17MA01 Malign hæmatologisk sygdom uden specifik behandling, pat. mindst 18 år - (DD469) Myelodysplastisk syndrom UNS
Neutropenia	4	[redacted]	[redacted]	37.603	DRG 2020, 16MA03 Granulo- og trombocytopeni - (DD709) Neutropeni UNS
Neutropenic Sepsis	4	[redacted]	[redacted]	37.603	DRG 2020, 16MA03 Granulo- og trombocytopeni - (DD709) Neutropeni UNS

Oedema Peripheral	3	[redacted]	[redacted]	4.082	DRG 2020, 23MA03 Symptomer og fund, u. kompl. bidiag. - (DR609) Ødem UNS
Pneumonia	3	[redacted]	[redacted]	19.425	Average of DRG 2020, 04MA98 MDC04 1-dagsgruppe, pat. mindst 7 år and 04MA13 Lungebetændelse og pleurit, pat. mindst 60 år - (DJ189) Pneumoni UNS
Pneumonia	5	[redacted]	[redacted]	37.050	DRG 2020, 04MA13 Lungebetændelse og pleurit, pat. mindst 60 år - (DJ189) Pneumoni UNS
Pulmonary Oedema	5	[redacted]	[redacted]	34.746	DRG 2020, 04MA10 Lungeødem og respirationssvigt - (DJ819) Lungeødem UNS
Pyrexia	3	[redacted]	[redacted]	19.268	DRG 2020, 8MA04 Feber af ukendt årsag, pat. mindst 18 år, uden biopsi og/eller scopi - (DR509) Feber UNS
Septic Shock	5	[redacted]	[redacted]	43.180	DRG 2020, 18MA01 Sepsis - (DR572) Septisk shock
Supraventricular Tachycardia	3	[redacted]	[redacted]	8.544	Average of DRG 2020, 05MA98 MDC05 1-dagsgruppe, pat. mindst 7 år and 05MA07 Hjertearytmi og synkope - Supraventrikulær takykardi
Thrombocytopenia	4	[redacted]	[redacted]	37.603	DRG 2020, 16MA03 Granulo- og trombocytopeni - (DD695) Sekundær trombocytopeni
Vomiting	3	[redacted]	[redacted]	5.297	DRG 2020, 06MA11 Malabsorption og betændelse i spiserør, mave og tarm, pat. mindst 18 år, u. kompl. bidiag. - (DR119C) Opkastning

Table 13 Total cost related to AE management

Regime	Total costs (DKK)
Pola + BR	7.983,82
BR	10.487,99

3.4.4 Patient costs

Patient costs are included in the model in line with DMC's method guidelines. The unit cost per hours is assumed to be DKK 179,00 which is in line with "Medicinrådets – værdisætning af enhedsomkostninger v. 1.3".. The number of patient hours for the drug administration is based on the SmPCs[14], and the number of patient hours for the monitoring is based on available public sources for the duration of the resource element. Patient costs are illustrated in table 18 and 19.

Table 14 Patients resource use per disease state

Activity	Proportion of patients	Frequency / model cycle	Patient time per visit (hours)	Reference
Patient administration costs	100%	[redacted]	[redacted]	1,5 hours assumed per administration
Patient PFS follow-up costs	100%	[redacted]	[redacted]	1,5 hours assumed per visit for consultation, tests, etc
Patient OS follow-up costs	100%	[redacted]	[redacted]	1,5 hours assumed per visit for consultation, tests, etc

Table 15 Patient costs per disease state

Disease state	Cost per cycle (DKK)
Progression-free (on treatment)	179,00
Progression-free (off treatment)	20,58
Progressed disease	20,58

3.4.5 Transportation costs

Transportation costs are included in the model. An average rate of DKK 3,56 per km is assumed with an average distance of 28 km per hospital visit in line with DMC's methods guidelines. In the model the number of visits are calculated based on to the number of visits assumed for administration and routine care. Transportation costs are illustrated in table 20.

Table 16 Transportation costs per disease state

Disease state	Cost per cycle (DKK)
Progression-free (on treatment)	[redacted]
Progression-free (off treatment)	[redacted]

Progressed disease	[redacted]

3.4.6 End-of-life costs

To reflect the fact that individuals incur additional resources shortly before death, a one-off end-of-life cost was applied to patients at the point of dying to reflect the cost of terminal care. This cost will surely be present, but will be hard to accurately calculate and there are no relevant tariffs in Denmark that can be used to assess this cost accurately. However, an article by Round et al. has calculated the mean cost of end-of-life care[15]. The calculation is based on English tariffs for four cancer types. The cost includes hospital care, hospice care and social municipal care. Due to the similarities between the health care systems in UK and Denmark, the estimates are expected to be somewhat representative of the costs in Denmark. The estimate has been used and was accepted by NICE in the assessment of avelumab for metastatic Merkel-cell carcinoma. The estimate has also been accepted by Amgros in previous assessments. The cost has been converted to DKK, inflated to 2019 numbers and adjusted for price level indices between UK and DK. The end-of-life cost applied in the model are illustrated in table 21.

Table 17 End of life care costs

Reported cost (DKK)	Cost inflated to 2019	Reference
55.744,69	68.601,90	Round et al., 2015. Mean cost of health care over all cancer types (table 5)

3.5 Model uncertainty

3.5.1 Scenario analysis

Scenario analyses assess the model results at multiple values of single input variables. The scenarios included in the scenario analysis can be seen in table 22.

Table 18 Scenarios included in Scenario analysis

Scenario	Explanation of the scenario	Min value	Maximum value
Excess mortality	Add a multiplier to the life-table to adjust	[redacted]	[redacted]
Survival function (s)	Parametric survival		
	Mixture cure rate model		
	Mixture cure rate model (informed by PFS)		
Time horizon		[redacted]	[redacted]
Discount rate		[redacted]	[redacted]
Vial sharing		[redacted]	[redacted]

3.6 Base case settings

The base-case settings used in the model can be seen in table 23.

Table 19 Base-case settings

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

4. Results

4.1 Base-case

[redacted]

Incremental cost per patient

[redacted]

[redacted]387.388[redacted]

Table 20 Incremental cost per patient

	Poly + BR (DKK)	BR (DKK)	Incremental costs (DKK)
Drug costs	[redacted]	39.803	[redacted]
Administration costs	28.700	20.986	7.714
AE costs	7.984	10.488	-2.504
Supportive care	23.973	22.088	1.885
Patient costs	4.247	1.881	2.366
Transportation costs	11.439	5.066	6.373
End of life costs	60.342	67.091	-6.749
Total costs	570.412	167.404	403.008

The incremental costs are almost exclusively driven by the increased drug costs, which represent approximately 99% of the increased cost per patient. Cost elements can be seen in figure 16.

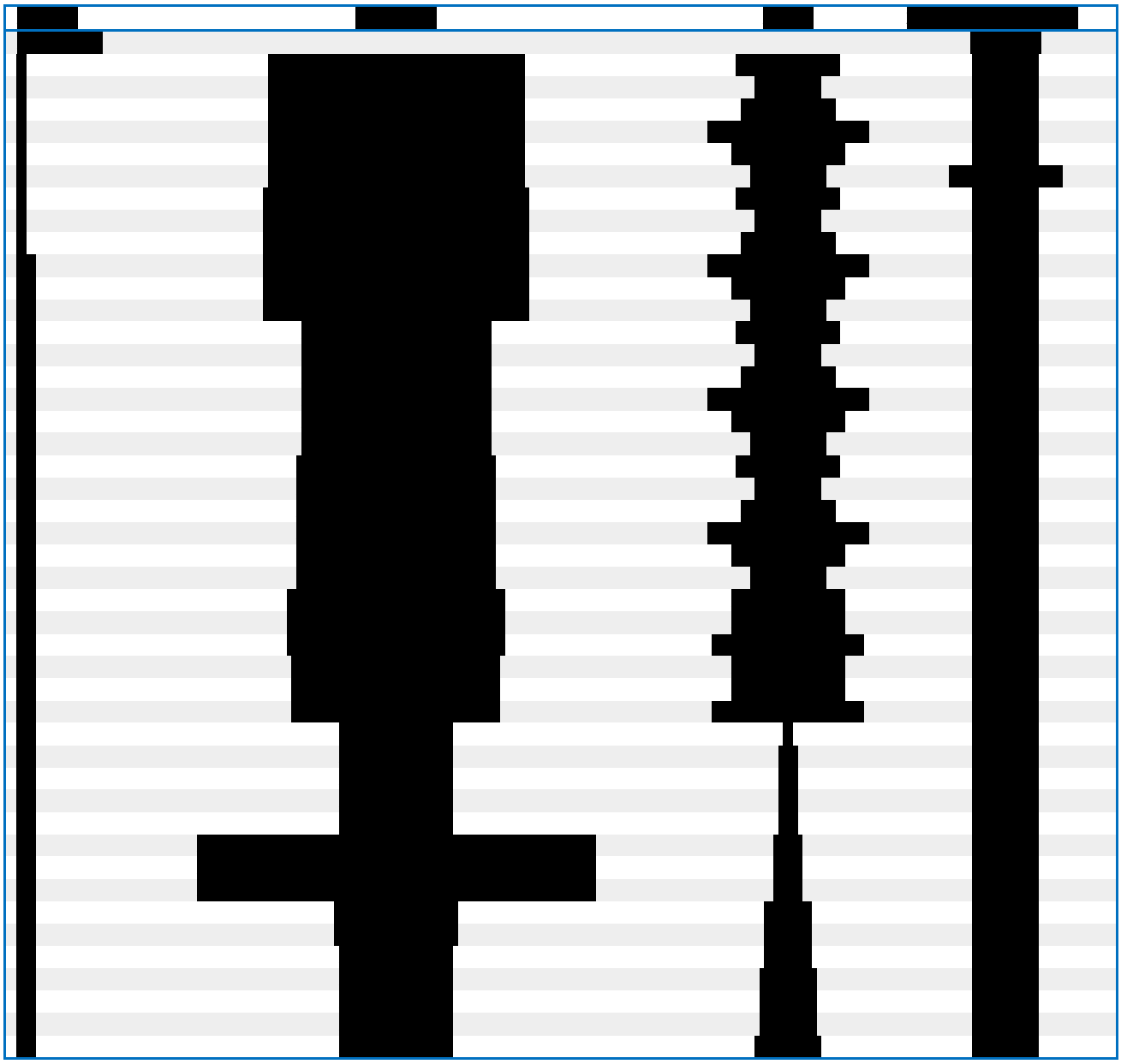
[redacted]

[redacted]

4.2 Scenario Analysis

Scenario analyses were undertaken to assess impact of varying structural and methodological assumptions implemented in the model. The results of the scenario analysis can be seen in Table 22. As illustrated, the different scenarios have minor impact on the overall results for the incremental costs. The elements that that the greatest impact on the incremental costs the most are the vial sharing, discount rate, the log-logistic function for PFS of Pola + BR, and the choice of statistical model for PFS. If vial sharing is assumed the incremental costs would decrease. The discount rate is set out by the DMC and therefore is not expected to differ. The log-logistic function for PFS had a poor statistical fit and was therefore not deemed an appropriate function for PFS. The choice of statistical model had a big impact when the statistical model was only changed for PFS and not for OS. However, different statistical models for PFS and OS should not be assumed, and when a proportional hazard model is assumed for both OS and PFS the incremental costs inly increases by approximately [redacted] compared to the base-case.

Table [redacted]



5. Budget impact analysis

5.1 Methods

The budget impact model was developed to estimate the expected budget impact of recommending Pola + BR as possible standard treatment in Denmark. The budget impact was estimated per year for the first 5 years after introduction of Pola + BR in Denmark.

The cost per patient model was partially nested within the budget impact model, and therefore any changes in settings in the cost per patient model would affect the results of the budget impact model. This also means that the budget impact result is only presented for the chosen population in the cost per patient model.

The budget impact model was developed for the three relevant patient cohorts, which is 2L+ (the ITT population from GO29365), the 2L subgroup, and the 3L+ subgroup. The analysis was developed by comparing the costs for the Danish regions per year over five years in the scenario where Pola + BR is recommended as possible standard treatment, and the scenario where Pola + BR is not recommended as possible standard treatment. The total budget impact per year is the difference between the two scenarios.

5.1.1 Incidence of DLBCL

Epidemiological forecast

The “BIM input” worksheet shows the typical patient flow for DLBCL patients. The epidemiological estimation leads to 76 patients in 2L+. This differs from the estimate (100 patients) from the expert committee included in the protocol. However, the model also allows the user to select the population from DMC Protocol.

5.1.2 Current treatment of DLBCL in Denmark

A budget impact model must be based on the current treatment landscape. Therefore, we included the interventions that are currently primarily used in Denmark. As the cost of the chemo regimens are low and broadly similar, we used R-ICE as a proxy for the combination chemotherapy regimens, as this is the most widely used regimen in Denmark. CAR T treatments are used for some patients in 3L+ in Denmark. In order to avoid unnecessary complexity, we used Tisagenlecleucel (Kymriah®) as a proxy for the CAR T treatments used in Denmark.

Treatment Duration

Treatment duration is computed by taking the area-under curve of the KM curve for time-to-off-treatment for Polatuzumab + BR and BR. For R-ICE, we assumed the treatment duration was similar to BR. Tisagenlecleucel is primarily a one-treatment regimen, therefore treatment duration was not relevant to consider in the model. Estimated treatment durations are illustrated in table 26.

Table 21. Treatment Duration

Treatment regimen	Maximum duration	Estimated TTOT
Polatuzumab + BR	[redacted]	[redacted]
BR	6 cycles	2,0 (months)
R – ICE	6 cycles	2,0 (months)
Tisagenlecleucel	1 cycle	1,0 (treatment)

5.1.3 Market Shares

Future market shares depend on multiple factors such as developments in the treatment landscape, and available physical and economic resources. Regardless, the estimates will be associated with uncertainty, and therefore different scenarios were tested in the model.

The expected market shares were estimated for each population based on the current use[1] and expected projections.

The market shares used in the budget impact analysis can be seen in table 27-29.

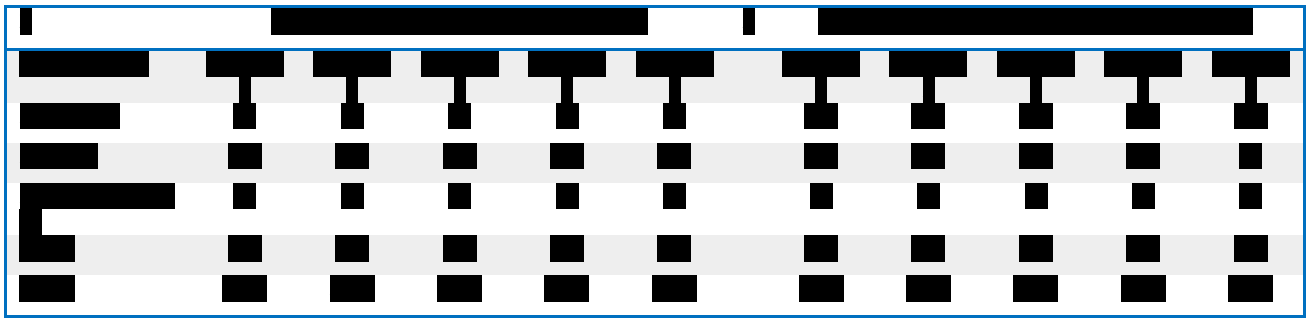
The market shares for the overall 2L+ population is calculated as a weighted average of the market shares of the 2L and 3L+ populations.

Table 22. Market shares for 2L+

	No recommendation for Pola + BR					Recommendation for Polatuzumab + BR				
Treatment	Year 1	Year 2	Year 3	Year 4	Year 5	Year 1	Year 2	Year 3	Year 4	Year 5
[redacted]										
[redacted]										
[redacted]										
[redacted]										
[redacted]										

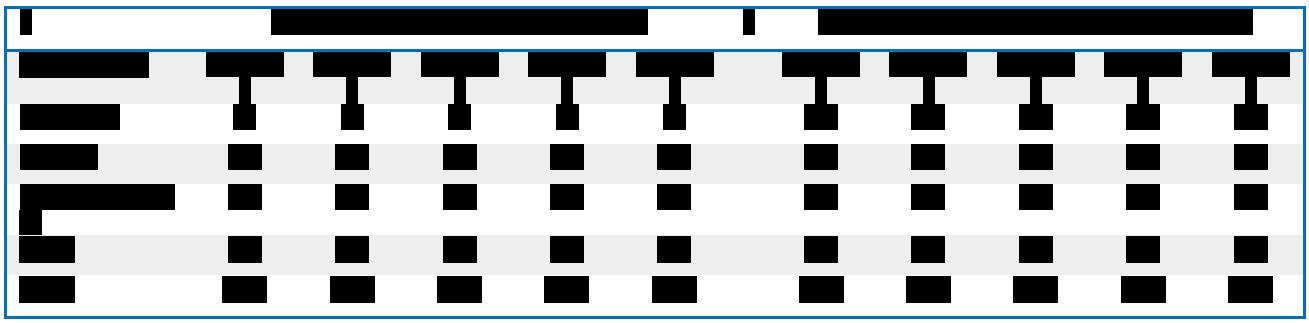
The expected market shares for the 2L population is based in the following:

[redacted]



[redacted]

[redacted]



5.1.4 Costs

Drug dosing and acquisition costs

Included costs in the budget impact model were drug acquisition costs, administration costs, supportive care costs, adverse event costs, and end-of-life care costs. Patient-, and transportation costs were not included as these are not part of the regional budgets. Discounting was not used in the budget impact model in line with DMC's methods guidelines. The undiscounted cost output of the cost per patient model were used directly to inform the cost per year per patient in the budget impact model for Pola + BR and BR.

For R-ICE and Tisagenlecleucel the expected costs per patient were calculated using the expected treatment duration (table 26). Only drug costs were included for R-ICE and Tisagenlecleucel as a conservative approach to avoid unnecessary complications. However, costs associated with hospitalizations and adverse events are estimated to be very high for CAR-T treatments. For Kymriah, Amgros estimated the total costs per patient for these elements to be approximately DKK 500.000. The approach taken in the budget impact model is therefore a conservative approach.

Dosing of R-ICE and Tisagenlecleucel are illustrated in table 30.

Table 23 Drug dosing

Treatment regimen	Drug		Dose
R-ICE	Rituximab	375 mg/m2	Day 1, of a 3-week cycle
	Ifosfamide	3000 mg/m2	Day 2 and 3, of a 3-week cycle
	Carboplatin	635 mg/m2	Day 2, of a 3-week cycle
	Etoposide	100 mg/m2	Day 1, of a 3-week cycle
Tisagenlecleucel	Tisagenlecleucel	1 dose	1 dose

Drug costs were based on medicinpriser.dk and resulting cycle costs can be seen in table 31.

Table 24 Drug costs

Treatment regimen		Cost per cycle (DKK)
R-ICE	Rituximab	9.897,93
	Ifosfamide	1.870,59
	Carboplatin	573,49
	Etoposide	207,60
Tisagenlecleucel		2.244.226,76

5.1.5 Scenario analyses

Alternative scenarios were tested to assess the result of different assumptions for the market shares. The scenarios tested for the budget impact model are illustrated in table 32-34.

[redacted]

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

[redacted]

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

[redacted]

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

5.2 Results

5.2.1 Base case results

Based on the base case assumptions, the estimated budget impact of recommending Pola + BR as a possible standard treatment in Denmark for the 2L+ population was DKK 9 mil. DKK in year 1, and DKK 15 mil. in year 5 (table 35).

Table 25 Budget impact for 2L+

	Year 1	Year 2	Year 3	Year 4	Year 5
[redacted]					
[redacted]					
[redacted]					

For the 2L population the budget impact was estimated to be DKK 6 mil. in year 1, and DKK 10 mil. in year 5 (table 36).

Table 26 Budget impact for 2L

	Year 1	Year 2	Year 3	Year 4	Year 5
[redacted]					
[redacted]					
[redacted]					

For the 3L+ population the budget impact was estimated to be DKK 3 mil. in year 1, and DKK 4 mil. DKK in year 5 (table 37).

Table 27 Budget impact for 3L+

	Year 1	Year 2	Year 3	Year 4	Year 5
[redacted]					
[redacted]					
[redacted]					

5.2.2 Scenarios

The results of the scenario analyses are illustrated in table 38-40.

Table [redacted]

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

[redacted]

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

[redacted]

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

6. Discussion

In general, the results were not very sensitive to changes in the different assumptions. This is explained by the fact that the full treatment duration was observed for both treatment arms in the clinical trial, and extrapolations were not necessary. Choice of statistic and/or parametric models for PFS and OS had very little impact on the results.

A limitation to the analysis is the lack of comparison with a combination chemotherapy as indirect statistical analyses were not possible. However, the model predictions are expected to be similar to a comparison with a combination chemotherapy regime since the treatment duration and costs of the single- and combination chemotherapy are broadly similar.

The estimated incremental cost of Pola + BR compared to standard treatment is well within what is generally considered a reasonable cost associated with the estimated benefit for oncology treatment in Denmark.

References

1. Dansk Lymfom Gruppe. LYFO Database 2017. Available at: http://www.lymphoma.dk/.
2. Lymfomgruppe, D. *Diffust storcellet B-celle lymfom - klinisk retningslinje*.
3. Arboe, B. *et al.* Treatment intensity and survival in patients with relapsed or refractory diffuse large B-cell lymphoma in Denmark: A real-life populationbased study. *Clin. Epidemiol.* **11**, 207–216 (2019).
4. Gisselbrecht, C. *et al.* Salvage regimens with autologous transplantation for relapsed large B-cell lymphoma in the rituximab era. *J. Clin. Oncol.* **28**, 4184–4190 (2010).
5. Van Den Neste, E. *et al.* Outcome of patients with relapsed diffuse large B-cell lymphoma who fail second-line salvage regimens in the International CORAL study. *Bone Marrow Transplant.* **51**, 51–57 (2016).
6. Medicinrådet. Medicinrådets protokol for vurdering af polatuzumab vedotin i kombination med bendamustin og rituximab til behandling af diffust storcellet Bcellelymfom. (2019). Available at: https://medicinraadet.dk/media/12742/protokol-10-polatuzumab-vedotin-diffust-storcellet-b-celle-lymfom_godkendt-af-formandskabet.pdf. (Accessed: 4th February 2020)
7. Mounier, N. *et al.* Rituximab plus gemcitabine and oxaliplatin in patients with refractory/relapsed diffuse large B-cell lymphoma who are not candidates for high-dose therapy. A phase II lymphoma study Association trial. *Haematologica* **98**, 1726–1731 (2013).
8. A Study of Polatuzumab Vedotin (DCDS4501A) in Combination With Rituximab or Obinutuzumab Plus Bendamustine in Participants With Relapsed or Refractory Follicular or Diffuse Large B-Cell Lymphoma - Full Text View - ClinicalTrials.gov. Available at: https://clinicaltrials.gov/ct2/show/NCT02257567. (Accessed: 4th February 2020)
9. Overview | Tisagenlecleucel for treating relapsed or refractory diffuse large B-cell lymphoma after 2 or more systemic therapies | Guidance | NICE.
10. Medicinrådet. *Metodevejledning for omkostningsanalyser af nye laegemidler og indikationer i hospitalssektoren*.
11. Lægemiddelstyrelsen. Medicinpriser.dk. Available at: https://medicinpriser.dk/default.aspx. (Accessed: 30th September 2019)
12. Sundhedsdatastyrelsen. Afregning og finansiering (DRG). Available at: https://sundhedsdatastyrelsen.dk/drg. (Accessed: 18th October 2019)
13. Nettoprisindeks - Danmarks Statistik. Available at: https://www.dst.dk/da/Statistik/emner/priser-og-forbrug/forbrugerpriser/nettoprisindeks. (Accessed: 5th February 2020)
14. *ANNEX I SUMMARY OF PRODUCT CHARACTERISTICS*.
15. Round, J., Jones, L. & Morris, S. Estimating the cost of caring for people with cancer at the end of life: A modelling study. *Palliat. Med.* **29**, 899–907 (2015).

Medicinrådet

BESTIL PDF/UA

Medicinrådets protokol for vurdering af polatuzumab vedotin i kombination med bendamustin og rituximab til behandling af diffust storcellet B-cellelymfom

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 indikationsudvidelser 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 protokollen

Protokollen er grundlaget for Medicinrådets vurdering af et nyt lægemiddel. Den indeholder et eller flere kliniske spørgsmål, som den ansøgende virksomhed skal besvare i den endelige ansøgning, og som Medicinrådet skal basere sin vurdering på.

Lægemidlet vurderes efter Håndbog for Medicinrådets proces og metode vedr. nye lægemidler og indikationsudvidelser – version 2. Se Medicinrådets metodehåndbog for yderligere information.

Dokumentoplysninger	
Godkendelsesdato	13. december 2019
Ikrafttrædelsesdato	13. december 2019
Dokumentnummer	66856
Versionsnummer	1.0

Fremkommer der nye og væsentlige oplysninger i sagen af betydning for protokollens indhold, kan Medicinrådet tage protokollen op til fornyet behandling. Det samme gælder, hvis der er begået væsentlige fejl i forbindelse med sagsbehandlingen vedrørende protokollen. Hvis Medicinrådet foretager ændringer i protokollen, vil ansøgende virksomhed få besked.

Medicinrådet, Dampfærgevej 27-29, 3. th., 2100 København Ø
www.medicinraadet.dk
Sprog: dansk
Format: pdf
Udgivet af Medicinrådet, 13. december 2019

Indhold

1 Lægemiddelinformationer 3
2 Forkortelser 4
3 Formål 5
4 Baggrund 5
4.1 Nuværende behandling 6
4.2 Polatuzumab vedotin 6
5 Kliniske spørgsmål 6
5.1 Klinisk spørgsmål 1 6
5.2 Valg af effektmål 7
6 Litteratursøgning 10
7 Databehandling og analyse 12
8 Andre overvejelser 13
9 Referencer 14
10 Sammensætning af fagudvalg og kontaktinformation til Medicinrådet 15
11 Versionslog 16

1 Lægemiddelinformationer

Lægemidlets oplysninger	
Handelsnavn	Polivy®
Generisk navn	Polatuzumab vedotin
Firma	Roche
ATC-kode	N/A
Virkningsmekanisme	Et antistoflægemiddelkonjugat rettet mod B-celler der udtrykker antigenet CD79b på celleoverfladen. Efter optag i cellen bindes tubulin, der medfører stop af celledeling med celledød til følge.
Administration/dosis	Koncentrat til infusionsvæske: gives ved intravenøs infusion. Den anbefalede dosis er 1,8 mg/kg, der gives hver 21. dag i kombination med bendamustin og rituximab i seks cyklusser.
Forventet EMA-indikation	Indiceret som kombinationsterapi med bendamustin og rituximab til behandling af voksne med recidiverende/refraktært diffust storcellet B-cellelymfom (DLBCL), som ikke er kandidater til hæmatopoietisk stamcelletransplantation.

2 Forkortelser

CI:	Konfidensinterval
CNS:	Centralnervesystemet
DLBCL:	Diffust storcellet B-cellelymfom
EMA:	*European Medicines Agency*
GRADE:	System til vurdering af evidens (*Grading of Recommendations Assessment, Development and Evaluation*)
HR:	*Hazard ratio*
MMAE:	Monometyl auristatin E
NHL:	Non-Hodgkin-lymfom
OR:	*Odds ratio*
RR:	Relativ risiko
R-GDP:	Rituximab, gemcitabin, dexamethason og cisplatin
R-GemOx:	Rituximab, gemcitabin og oxaliplatin
R-ICE:	Rituximab, ifosfamid, carboplatin og etoposid

3 Formål

Protokollen har til formål at definere de kliniske spørgsmål, der ønskes belyst i vurderingen af polatuzumab vedotin i kombination med bendamustin og rituximab som mulig standardbehandling af patienter med recidiverende/refraktært diffust storcellet B-cellelymfom (DLBCL), som ikke er kandidater til hæmatopoietisk stamcelletransplantation. I protokollen angives en definition af population(er), komparator(er) 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 polatuzumab vedotin, modtaget den 26. juni 2019.

Protokollen danner grundlag for den endelige ansøgning for vurdering af polatuzumab vedotin i kombination med bendamustin og rituximab sammenlignet med dansk standardbehandling. Alle effektmål, der er opgivet i denne protokol, skal besvares med en sammenlignende analyse mellem polatuzumab vedotin i kombination med bendamustin og rituximab og de angivne komparatorer 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.

4 Baggrund

DLBCL er en aggressiv undertype af non-Hodgkin-lymfom (NHL), der kan opstå *de novo* eller udvikles fra andre undertyper af NHL. Der diagnosticeres ca. 450 tilfælde årligt i Danmark, og incidensen er stigende [1]. Risikoen for at udvikle DLBCL øges med alderen, og medianalderen ved diagnosetidspunktet er 67 år [1]. DLBCL-patienter udgør en meget heterogen gruppe, hvor behandlingsvalg efter første linje i høj grad afhænger af parametre som alder, WHO-performance score (indeks for funktionsniveau), komorbiditet, tidligere behandlinger og patientpræferencer. En stor andel over 65 år vil være i stand til at tåle standardbehandling i form af kombinationskemoterapi. Efter standardbehandling kan patienter under 65-70 år tilbydes konsoliderende højdosis kemoterapi i kombination med stamcelletransplantation [1]. Alder over 75 år og en performance status større end 2 er forbundet med en højere rate af komplikationer og et dårligere udfald [1,2].

DLBCL viser sig typisk som en eller flere forstørrede lymfeknuder, ofte på hals, i mediastinum og/eller i abdomen [1]. Hos 40 % af patienterne kan sygdommen lokaliseres til andet væv. Prognosen er stadieafhængig og forværres med antallet af ekstranodale manifestationer [1].

Omkring 35 % af alle DLBCL-patienter opleve recidiv eller være refraktære overfor behandling efter første linje (typisk R-CHOP: rituximab, cyclophosphamid, doxorubicin, vincristin, og prednison) [1,2]. Fagudvalget skønner, at DLBCL-patienter, som konkret vil være tilgængelige for behandling i anden eller tredje linje, udgør omkring 150 patienter årligt i Danmark. Af disse vil 100 ikke være egnet til stamcelletransplantation grundet alder, tidligere autolog stamcelletransplantation, komorbiditet eller toleranceproblemer i forbindelse med højdosis kemoterapi inden stamcelletransplantation og er således mulige kandidater til behandling med antistofkonjugatet polatuzumab vedotin.

Den samlede population af patienter med recidiverende/refraktært DLBCL har en dårlig prognose [1,3,4]. I en litteraturgennemgang estimeres den mediane overlevelse (overall survival; OS) hos patienter med recidiverende/refraktært DLBCL egnet til stamcelletransplantation til 9,9-44,0 måneder sammenlignet med 3,4-9,0 måneder hos patienter uegnet til stamcelletransplantation [5]. Fagudvalget vurderer, at patienter, der er refraktære overfor behandling, har en dårligere prognose end patienter, der oplever recidiv. Behandlingsmulighederne er som udgangspunkt ens for patienter med recidiv eller refraktær sygdom, der ikke er kandidater til stamcelletransplantation [1].

4.1 Nuværende behandling

I henhold til de nuværende kliniske retningslinjer anbefales højdosis kemoterapi med stamcelletransplantation til patienter under 65-70 år med recidiverende/refraktært DLCBL [1]. Der findes ikke evidens for at anbefale et bestemt regime til den undergruppe af patienter, som ikke er kandidater til stamcelletransplantation [1]. Disse patienter udgør en meget heterogen gruppe med varierende prognose, om end prognosen altid er dårlig. Behandlingsvalget baseres på individuelle vurderinger af patientens almentilstand, hvor bl.a. alder, komorbiditet, tidligere behandlinger, performance status og patientpræferencer spiller en rolle. Ifølge den foreløbige ansøgning fra ansøger var bendamustin evt. i kombination med rituximab i perioden 2013-2018 den hyppigst anvendte behandling til patienter, der ikke er kandidater til stamcelletransplantation. Det fremgår dog ikke af opgørelsen, i hvilken behandlingslinje bendamustin har været anvendt, eller hvor hyppigt rituximab blev valgt i kombination.

Patienter, der har en god almen tilstand, kan ofte tilbydes en kombinationskemoterapi (f.eks. R-GDP; rituximab, gemcitabin, dexamethason og cisplatin, R-GemOx; rituximab, gemcitabin og oxaliplatin eller R-ICE; rituximab, ifosfamid, carboplatin og etoposid), mens patienter, der har en dårligere almen tilstand, ofte tilbydes enkeltstof(kemo)terapi (f.eks. bendamustin, prednisolon alene eller blot "best supportive care") i kombination med rituximab, der generelt er veltolereret.

Behandling af patienter med recidiverende/refraktært DLBCL, som ikke tåler stamcelletransplantation, har pallierende sigte. Formålet er at forlænge livet og forbedre livskvaliteten på trods af en alvorlig og livstruende sygdom.

4.2 Polatuzumab vedotin

Polatuzumab vedotin er et antistoflægemiddelkonjugat rettet mod CD79b på celleoverfladen af B-celler. Efter optag i cellen kløves polatuzumab vedotin i enklere dele, hvoraf konjugatet (en kemoterapeutisk fraktion; MMAE) binder til tubulin. Binding af B-cellernes tubulin medfører stop af celledeling og deraf celledød.

Polatuzumab vedotin produceres som koncentrat til infusionsvæske, der gives intravenøst. Den anbefalede dosis er 1,8 mg/kg og gives hver 21. dag i kombination med bendamustin og rituximab i seks cyklusser. Polatuzumab vedotin, bendamustin og rituximab kan administreres på dag et i hver cyklus. Ved koadministrering med polatuzumab vedotin er den anbefalede dosis af bendamustin 90 mg/m^2 på dag et og dag to i hver cyklus, og den anbefalede dosis af rituximab er 375 mg/m^2 på dag et i hver cyklus.

5 Kliniske spørgsmål

5.1 Klinisk spørgsmål 1

Hvad er værdien af polatuzumab vedotin i kombination med bendamustin og rituximab sammenlignet med bendamustin, GDP, GemOx eller ICE i kombination med rituximab til voksne patienter med recidiverende/refraktært diffust storcellet B-cellelymfom, der ikke er kandidater til hæmatopoietisk stamcelletransplantation?

Population
Voksne patienter med recidiverende/refraktært diffust storcellet B-cellelymfom, der ikke er kandidater til hæmatopoietisk stamcelletransplantation.

Intervention
Polatuzumab vedotin plus bendamustin og rituximab (dosering jf. afsnit 4.2).

Komparatorer

Enkeltstofkemoterapi:

Bendamustin (70 mg/m^2 eller 90 mg/m^2 dag 1-2) og rituximab (375 mg/m^2 dag 1)

Kombinationskemoterapi:

GDP og rituximab (375 mg/m^2 dag 1)

GemOx og rituximab (375 mg/m^2 dag 1)

ICE og rituximab (375 mg/m^2 dag 1)

Komparatorer er valgt jævnfør afsnit 4.1 i nærværende protokol, der beskriver, hvordan den heterogene sammensætning af populationen giver anledning til forskellige behandlingsvalg (enkeltstofkemoterapi eller kombinationskemoterapi) afhængigt af, om patienterne har en god eller dårlig almentilstand. Der ønskes sammenligning med hhv. enkeltstofkemoterapi (bendamustin og rituximab) og kombinationskemoterapi (GDP, GemOx eller ICE i kombination med rituximab). De tre kombinationskemoterapier betragtes som ligeværdige valg i dansk klinisk praksis og ansøger opfordres til at vælge den komparator blandt kombinationskemoterapierne, som giver det bedste sammenligningsgrundlag.

Effektmål
En samlet beskrivelse af valgte effektmål og baggrunden herfor er givet i afsnit 5.2.

5.2 Valg af effektmål

Tabel 1 summerer de valgte effektmål, deres vigtighed, den retningsgivende mindste klinisk relevante forskel, en evt. justeret mindste klinisk relevant forskel og effektmålsgruppe. I forbindelse med justeringen af Medicinrådets metodehåndbog, som trådte i kraft pr. 1. januar 2019, vil absolutte effektforskelle fremover blive kategoriseret ud fra konfidensintervaller (tabel 3, side 29 i metodehåndbogen). Det er derfor nødvendigt at foretage en justering af den mindste klinisk relevante forskel. Den *retningsgivende* mindste klinisk relevante forskel er fremkommet på samme måde som under den gamle metode og afspejler den mindste forskel, som, fagudvalget vurderer, er klinisk relevant. Når lægemidlets værdi for det enkelte effektmål skal kategoriseres, vil grænsen for konfidensintervallet blive sammenholdt med den *justerede* mindste klinisk relevante forskel. Den justerede værdi vil være det halve af den retningsgivende værdi i de tilfælde, hvor et konfidensinterval forventes at være tilgængeligt. Rationalet for denne tilgang er at sikre, at alle værdier i konfidensintervallet ligger tættere på den *retningsgivende MKRF* end på 'ingen forskel' (absolut effektforskel på 0). Eller sagt på en anden måde – alle de sandsynlige værdier for effekten er tættere på en klinisk relevant effekt end på 'ingen effekt'.

For alle effektmål ønskes både absolutte og relative værdier, jf. ansøgningsskemaet. Der ønskes både punktestimater og konfidensintervaller (for de absolutte værdier ønskes dog ikke konfidensintervaller, hvor metoderne til beregning af disse ikke er veldefinerede). For de absolutte værdier, hvor der kan beregnes konfidensintervaller efter veldefinerede metoder, vurderes den kliniske relevans (værdi), jf. tabel 3 i Medicinrådets håndbog for vurdering af nye lægemidler. For de relative værdier vurderes den kliniske relevans (værdi), jf. væsentlighedskriterierne beskrevet i Medicinrådets håndbog. De relative effektestimater skal angives i relativ risiko (RR) eller hazard ratio (HR). Hvis studierne resulterer i en odds ratio (OR), skal denne transformeres til relativ risiko, jf. appendiks 2 i Medicinrådets håndbog. Det skal begrundes i ansøgningen, hvis der afviges fra de ønskede effektmål.

Tabel 1. Oversigt over valgte effektmål for klinisk spørgsmål 1 og klinisk spørgsmål 2. For hvert effektmål er angivet deres vigtighed. For kritiske og vigtige effektmål er desuden angivet den mindste klinisk relevante forskel (retningsgivende og evt. justeret) samt indplacering i de tre effektmålsgrupper (”dødelighed”, ”livskvalitet, alvorlige symptomer og bivirkninger” og ”ikkealvorlige symptomer og bivirkninger”).

Effektmål*	Vigtighed	Effektmålsgruppe	Måleenhed	Retningsgivende mindste klinisk relevante forskel	Justeret mindste klinisk relevante forskel
Samlet overlevelse (OS)	Kritisk	Dødelighed/overlevelse	Medianoverlevelse i måneder	6 måneder	-
			Andel af patienter, der opnår 2-års overlevelse	10 %-point	5 %-point
Helbredsrelateret livskvalitet	Vigtig	Livskvalitet, alvorlige symptomer og bivirkninger	Gennemsnitlig ændring fra baseline på SF-36 til efter endt behandling	5 point	2,5 point
			Gennemsnitlig ændring fra baseline på SF-36 til efter endt opfølgning	5 point	2,5 point
			Gennemsnitlig ændring fra baseline på FACT-Lym til efter endt behandling	4 point	2 point
			Gennemsnitlig ændring fra baseline på FACT-Lym til efter endt opfølgning	4 point	2 point
Progressionsfri overlevelse (PFS)	Vigtig	Livskvalitet, alvorlige symptomer og bivirkninger	Medianoverlevelse i måneder	6 måneder	-
			Andel af patienter, der opnår 2-års progressionsfri overlevelse	10 %-point	5 %-point
Uønskede hændelser	Vigtig	Alvorlige symptomer og bivirkninger	Andel frafald pga. uønskede hændelser (behandlingsophør)	10 %-point	5 %-point
			Andel patienter med uønskede hændelser grad 3 og grad 4	10 %-point	5 %-point

* For alle effektmål ønskes data med længst mulig opfølgningstid, med mindre andet er angivet.

Kritiske effektmål

Samlet overlevelse (overall survival; OS): Er guldstandard for at demonstrere klinisk effekt i cancerstudier, herunder lymfekræft. Det er et patientrelevant effektmål, der belyser patienternes levetid. Overlevelse defineres som tiden fra randomisering eller opstart af behandling til død uanset årsag. Patienter med recidiverende/refraktært DLBCL, der er uegnet til stamcelletransplantation, har en median OS på 3,4-9,0 måneder. Fagudvalget finder det relevant at fastlægge den mindste klinisk relevante forskel til OS på 6 måneder. Denne forskel er valgt ud fra et rationale om, at patienten med en OS på yderligere 6 måneder sammenlignet med standardbehandling har mærkbart gavn af den nye behandling. Fagudvalget estimerer, at omkring 10 % af den definerede population 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

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 [6]. Livskvalitet skal opgøres på den globale score af SF-36, hvor forskellen mellem grupperne i ændring fra baseline skal angives. En forskel på 3-5 point på SF-36-skalaen (dvs. 0,3-0,5 SD) har vist sig klinisk relevant [7]. Fagudvalget har på denne baggrund vurderet at en forskel på 5 point udgør den mindste klinisk relevante forskel. Fagudvalget ønsker livskvalitet opgjort ved henholdsvis endt behandling og endt opfølgning. Førstnævnte vil primært være udtryk for uønskede hændelsers indflydelse på patienternes livskvalitet, mens opgørelsen efter endt opfølgning overvejende vil være udtryk for en potentiel bedre sygdomskontrol, som først må forventes at komme til udtryk efter en længere opfølgningsperiode.

Såfremt der ikke findes data for livskvalitet målt på SF-36, ønskes livskvalitet opgjort med det sygdomsspecifikke spørgeskema Functional assessment 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 i sin korte form [8], hvor den mindste klinisk relevante score for denne patientgruppe er angivet til at være 3-5 point ud af en total score, der går fra 0-60 point [8]. På den baggrund har fagudvalget valgt 4 point som den mindste klinisk relevante forskel.

Progressionsfri overlevelse (progression free survival; PFS): Defineret som tiden fra initiering af behandling til progression eller død uafhængigt af årsag. PFS anvendes i vurderingen af polatuzumab vedotin som et udtryk for graden og længden af sygdomskontrol, som opnås under og efter behandling. Længden af den progressionsfri periode for patienter, der behandles med nuværende behandlingsmuligheder, er meget varierende, dog oftest kun af måneders varighed. Baseret på fagudvalgets erfaringer med de nuværende behandlingsmuligheder vurderer fagudvalget, at det nye lægemiddel skal tilbyde en forbedring i median PFS på minimum 6 måneder. Andelen af patienter, der opnår 2-års PFS, anses som klinisk relevant, hvis der opnås en forskel på 10 procentpoint. Da OS ikke præciserer andel af patienter i live med eller uden sygdom, opfattes OS og PFS som komplementære effektmål.

Uønskede hændelser (adverse events, AE): Er et effektmål der har til formål at vurdere sikkerheden af polatuzumab vedotin og inkluderer bivirkninger. Fagudvalget ønsker uønskede hændelser opgjort eller beskrevet i tre former:

i) Som andel frafald pga. uønskede hændelser: Fagudvalget vurderer, at omfanget af de uønskede hændelser skal stå mål med potentialet for de gavnlige effekter af polatuzumab vedotin. Et øget frafald pga. uønskede hændelser indikerer omfattende belastning af patienten til et niveau, hvor

behandlingens potentielt gavnlige effekter overskygges. En forskel mellem grupperne på 10 procentpoint anses som klinisk relevant, hvilket skal ses i lyset af, at behandlingen potentielt er livsforlængende.

ii) Som andel patienter med alvorlige uønskede hændelser (SAE) grad 3 og grad 4: Andel af patienter, der oplever ≥ 1 alvorlig uønsket hændelser grad 3 eller 4. Disse har stor betydning for den enkelte patients livskvalitet og gennemførlighed af behandlingen. En forskel mellem grupperne på 10 procentpoint anses som klinisk relevant, hvilket skal ses i lyset af, at behandlingen potentielt er livsforlængende.

iii) Fagudvalget ønsker også, at der i forbindelse med vurderingen foretages en kvalitativ/kvantitativ gennemgang af følgende betydende uønskede hændelser under og efter behandling: Neuropati; infektioner, herunder særskilt pneumonier; infusionsrelaterede hændelser; immunologiske hændelser. Beskrivelserne skal baseres på længst mulig opfølgningstid.

6 Litteratursøgning

Vurderingen af klinisk værdi baseres som udgangspunkt på data fra peer-reviewed publicerede fuldtekstartikler og data fra EMAs EPAR – public assessment report(s). Data skal derudover stemme overens med protokollens beskrivelser.

Sekretariatet har på baggrund af den foreløbige ansøgning undersøgt, om der findes et eller flere peer-reviewede publicerede fuldtekstartikler, hvor polatuzumab vedotin, bendamustin og rituximab er sammenlignet direkte med de valgte komparatorer.

Klinisk spørgsmål 1

Sekretariatet fandt følgende studie, som er relevant til sammenligning af polatuzumab vedotin, bendamustin og rituximab med bendamustin og rituximab:

- GO29365-studiet kan anvendes til direkte sammenligning af de definerede effektmål.

Sekretariatet har ikke fundet artikler, som kan anvendes til direkte sammenligning af polatuzumab vedotin, bendamustin og rituximab og GDP eller GemOx eller ICE i kombination med rituximab.

Virksomheden skal derfor søge efter studier, der kan anvendes til en indirekte sammenligning af polatuzumab vedotin, bendamustin og rituximab med GDP eller GemOx eller ICE i kombination med rituximab. Fagudvalget ønsker en sammenligning med én af de tre komparatorer og opfordrer ansøger til at vælge den komparator, som giver det bedste sammenligningsgrundlag. Det betyder, at der både skal søges efter primærstudier af effekten af kombinationsbehandlingen polatuzumab vedotin, bendamustin og rituximab og efter primærstudier af effekten af GDP eller GemOx eller ICE i kombination med rituximab. Til det formål har sekretariatet udarbejdet søgestrenge, som skal anvendes i MEDLINE (via PubMed) og CENTRAL (via Cochrane Library).

MEDLINE (via PubMed)

#1	"Lymphoma, Large B-Cell, Diffuse"[mh]	Population
#2	(diffuse[tiab] AND (large cell[tiab] OR large-cell[tiab] OR b-cell[tiab] OR b cell[tiab] OR histiocytic[tiab]) AND lymphoma*[tiab]) OR DLBCL[tiab]	
#3	#1 OR #2	
#4	"gemcitabine-oxaliplatin regimen" [nm] OR ("gemcitabine" [nm] AND "Oxaliplatin"[mh])	Komparator
#5	gemox[tiab] OR gem-ox[tiab] OR R-gemox[tiab] OR (gemcitabin*[tiab] AND (oxaliplatin*[tiab] OR Eloxatin*[tiab] OR ACT078[tiab] OR ACT-078[tiab]))	
#6	"GDP protocol" [nm] OR ("gemcitabine" [nm] AND "Dexamethasone"[mh] AND "Cisplatin"[mh])	
#7	GDP[tiab] OR RGDP[tiab] OR R-GDP[tiab] OR (gemcitabin*[tiab] AND dexamethason*[tiab] AND (cisplatin*[tiab] OR cis-platin*[tiab]))	
#8	"ICE protocol 1"[nm] OR "ICE protocol 2"[nm] or "ICE protocol 3"[nm] or "ICE protocol 4"[nm] or "ICE protocol 5"[nm] or "ICE protocol 6"[nm] OR ("Ifosfamide"[mh] AND "Carboplatin"[mh] AND "Etoposide"[mh])	
#9	((iphosphamid*[tiab] OR isophosphamid*[tiab] OR isofosfamid*[tiab]) AND Carboplat*[tiab] AND (eposi*[tiab] OR etopos*[tiab] OR VP-16*[tiab] OR VP16[tiab])) OR R-ICE[tiab] OR RICE[tiab]	
#10	"polatuzumab vedotin" [nm]	Intervention
#11	polatuzumab[tiab] OR Polivy[tiab]	
#12	#4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11	Kombination af intervention og komparator
#13	#3 AND #12	Kombination af population, intervention og komparator
#14	"case reports"[pt] OR "comment"[pt] OR "editorial"[pt] OR "guideline"[pt] OR "systematic review"[pt] OR "review"[pt]	Eksklusion af ikkerelevante publikationstyper
#15	#13 NOT #14	Endelig søgning

CENTRAL (via Cochrane Library)

#1	[mh "Lymphoma, Large B-Cell, Diffuse"]	Population
#2	((diffuse AND (large cell OR large-cell OR b-cell OR b cell OR histiocytic) AND lymphoma*) OR DLBCL):ti,ab,kw	
#3	#1 OR #2	
#4	(gemox OR gem-ox OR R-gemox OR (gemcitabin* AND ([mh "Oxaliplatin"] OR oxaliplatin* OR Eloxatin* OR ACT078 OR ACT-078))):ti,ab,kw	Komparator
#5	(GDP OR RGDP OR R-GDP OR (gemcitabin* AND (dexamethason* OR [mh "Dexamethasone"]) AND ([mh "Cisplatin"] cisplatin* OR cis-platin*))):ti,ab,kw	
#6	[mh "Ifosfamide"] AND [mh "Carboplatin"] AND [mh "Etoposide"]	
#7	(((iphosphamid* OR isophosphamid* OR isofosfamid*) AND Carboplat* AND (eposi* OR etopos* OR VP-16* OR VP16)) OR R-ICE OR RICE):ti,ab,kw	

#8	(polatuzumab OR Polivy):ti,ab,kw	Intervention
#9	#4 OR #5 OR #6 OR #7 OR #8	Kombination af intervention og komparator
#10	#3 AND #9	Kombination af population, intervention og komparator
#11	("conference abstract" OR review):pt	Eksklusion af ikkerelevante publikationstyper
#12	NCT*:au	
#13	("clinicaltrials.gov" OR trialsearch):so	
#14	#11 or #12 or #13	
#15	#10 NOT #14	Endelig søgning

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

7 Databehandling og 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 de forhåndsdefinerede PICO-beskrivelser, 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 relativ risiko (RR) = 0,5 og antaget andel med hændelse i komparatorgruppen er 30 %, da er den absolutte risikoreduktion (ARR) = 30 – 30 x 0,5 = 15 %-point).

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.

8 Andre overvejelser

Fagudvalget bemærker, at DLBCL udgør en meget heterogen gruppe, som indeholder mange biologiske subtyper med potentiel forskellig klinik og følsomhed for behandling. På den baggrund ønsker fagudvalget en oversigt over, hvilke DLBCL-undertyper som er inkluderet i polatuzumab vedotinstudiet. Oversigten bør inkludere histologisk klassifikation efter WHO's seneste kriterier.

9 Referencer

1. Dansk Lymfomgruppe. Kliniske retningslinjer for diffust storcellet b-celle-lymfom [internet]. 2019. Tilgængelig fra: http://www.dmcg.dk/siteassets/forside/kliniske-retningslinjer/godkendte-kr/dlg_diffust-storcellet-b-celle-lymfom_v1.0_090419.pdf
2. Friedberg JW. Relapsed/refractory diffuse large B-cell lymphoma. I: ASH Education Program Book 20111. 2011. s. 498–505.
3. Green TM, Young KH, Visco C, Xu-Monette ZY, Orazi A, Go RS, et al. Immunohistochemical double-hit score is a strong predictor of outcome in patients with diffuse large B-cell lymphoma treated with rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone. J Clin Oncol. 2012;30(28):3460–7.
4. Copie-Bergman C, Cuillière-Dartigues P, Baia M, Briere J, Delarue R, Canioni D, et al. MYC-IG rearrangements are negative predictors of survival in DLBCL patients treated with immunochemotherapy: A GELA/LYSA study. Blood. 2015;126(22):2466–74.
5. Lenz G, Rutherford SC, Davies A, Zinzani PL, Salles G et al. The Burden of Relapsed/Refractory (R/R) Diffuse Large B-Cell Lymphoma (DLBCL): A Systematic Literature Review (SLR). Blood, 132(Suppl 1), 2241.
6. Ware JE, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care [internet]. 1992;30(6):473–83. Tilgængelig fra: http://www.ncbi.nlm.nih.gov/pubmed/1593914
7. Samsa G, Edelman D, Rothman ML, Williams GR, Lipscomb J, Matchar D. Determining clinically important differences in health status measures: A general approach with illustration to the Health Utilities Index Mark II. PharmacoEconomics. 1999.
8. Hlubocky F, Webster K, Cashy J, Beaumont J, Cella D. The development and validation of a measure of health-related quality of life for Non-Hodgkin's lymphoma: the functional assessment of caner therapy-lymphoma (FACT-Lym). Lymphoma. 2013

10 Sammensætning af fagudvalg og kontaktinformation til Medicinrådet

Medicinrådets fagudvalg vedrørende lymfekræft (lymfomer)

Formand	**Indstillet af**
Lars Møller Pedersen Forskningsansvarlig overlæge	Lægevidenskabelige Selskaber og Region Hovedstaden
Medlemmer	**Udpeget af**
Jakob Madsen Overlæge	Region Nordjylland
Paw Jensen Ledende overlæge	Region Nordjylland
Peter Kamper Overlæge, ph.d.	Region Midtjylland
Jacob Haaber Christensen Overlæge, ph.d.	Region Syddanmark
Dorte Maegaard Tholstrup Afdelingslæge	Region Sjælland
Michael Pedersen Overlæge	Region Hovedstaden
Michael Boe Møller Overlæge	Dansk Patologiselskab
Kathrine Bruun Svan Farmaceut	Dansk Selskab for Sygehusapoteksledelse
Kenneth Skov Afdelingslæge	Dansk Selskab for Klinisk Farmakologi
Jørn Søllingvrå 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: Snezana Djurisic (projekt- og metodeansvarlig) Jesper Skov Neergaard (projektdeltager) Anette Pultera Nielsen (fagudvalgskoordinator) Jan Odgaard-Jensen (biostatistiker) Bettina Fabricius Christensen (informationsspecialist) Annemette Anker Nielsen (teamleder)

11 Versionslog

Version	Dato	Ændring
1.0	13. december 2019	Godkendt af Medicinrådet.