Medicinrådet

Bilag til Medicinrådets anbefaling vedrørende brentuximab vedotin i kombination med cyclophosphamid, doxorubicin og prednisolon til behandling af systemisk anaplastisk storcellet T-cellelymfom

Vers. 1.0

Bilagsoversigt

1. Medicinrådets sundhedsøkonomiske afrapportering vedr. brentuximab vedotin, version 1.0
2. Forhandlingsnotat fra Amgros vedr. brentuximab vedotin
3. Høringssvar fra ansøger, inkl. eventuel efterfølgende dialog vedr. den sundhedsøkonomiske afrapportering og lægemidlets værdi
4. Medicinrådets vurdering vedr. brentuximab vedotin til behandling af systemisk anaplastisk storcellet t-cellelymfom, version 1.0
5. Ansøgers endelige ansøgning
6. Ansøgers tekniske dokument til den sundhedsøkonomiske ansøgning
7. Medicinrådets protokol for vurdering vedr. brentuximab vedotin til behandling af systemisk anaplastisk storcellet t-cellelymfom, version 1.0

Medicinrådet

Sundhedsøkonomisk afrapportering

Brentuximab vedotin i kombination med cyclophosphamid, doxorubicin og prednisolon

Systemisk anaplastisk storcellet T-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 brentuximab vedotin i kombination med cyclophosphamid, doxorubicin og prednisolon til systemisk anaplastisk storcellet T-cellelymfom (sALCL) 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	106963
Versionsnummer	1.0

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

Indholdsfortegnelse

1. Liste over forkortelser

AIP	Apotekernes indkøbspris
ASCT	Autolog stamcelletransplantation
CHOEP	Cyclophosphamid, doxorubicin, vincristin, etoposid og prednisolon
CHOP	Cyclophosphamid, doxorubicin, vincristin og prednisolon
CHP	Cyclophosphamid, doxorubicin og prednisolon
DHAP	Dexamethason, cytarabin og cisplatin
DKK	Danske kroner
DRG	Diagnose Relaterede Grupper
ESHAP	Etoposid, methylprednisolon, cytarabin og cisplatin
GDP	Gemcitabin, dexamethason, cisplatin
ICE	Ifosfamid, carboplatin, etoposid
KM	Kaplan-Meier
OS	Samlet overlevelse
PFS	Progressionsfri overlevelse
PTCL	Perifere T-cellelymfomer
sALCL	Systemisk anaplastisk storcellet T-cellelymfom
SAIP	Sygehusapotekernes indkøbspris

2. Opsummering

Baggrund
Brentuximab vedotin i kombination med cyclophosphamid, doxorubicin og prednisolon (CHP) er indiceret til behandling af voksne patienter med tidligere ubehandlet systemisk anaplastisk storcellet T-cellelymfom. Omkring 20 nye patienter kandiderer årligt til behandling af den ansøgte indikation i Danmark. Sekretariatets vurdering tager udgangspunkt i dokumentation indsendt af Takeda.

Analyse
Den sundhedsøkonomiske analyse estimerer de inkrementelle omkostninger pr. patient ved behandling med brentuximab vedotin + CHP over en tidshorisont på 30 år. Brentuximab vedotin + CHP sammenlignes med cyclophosphamid, doxorubicin, vincristin og prednisolon (CHOP) og cyclophosphamid, doxorubicin, vincristin, etoposid og prednisolon (CHOEP) til patienter med tidligere ubehandlet systemisk anaplastisk storcellet T-cellelymfom (sALCL). Rapporten indeholder to kliniske spørgsmål. I klinisk spørgsmål 1 sammenlignes brentuximab vedotin + CHP med CHOEP og CHOP til sALCL-patienter, der kandiderer til højdosis kemoterapi (HDT) og autolog stamcelletransplantation (ASCT). I klinisk spørgsmål 2 sammenlignes brentuximab vedotin + CHP med CHOP til sALCL-patienter, der ikke kandiderer til HDT og ASCT.

Inkrementelle omkostninger og budgetkonsekvenser
Klinisk spørgsmål 1
I det scenarie, sekretariatet mener er mest sandsynligt, er de inkrementelle omkostninger for brentuximab vedotin + CHP ca. [redacted] DKK sammenlignet med CHOEP og CHOP. Hvis analysen udføres med AIP, bliver de inkrementelle omkostninger til sammenligning ca. 312.000 DKK pr. patient.

Sekretariatet vurderer, at budgetkonsekvenserne for regionerne ved anbefaling af brentuximab vedotin + CHP som standardbehandling vil være ca. [redacted] DKK i år 5. Hvis analysen udføres med AIP, er budgetkonsekvenserne ca. 1,0 mio. DKK i år 5.

Klinisk spørgsmål 2
I det scenarie, sekretariatet mener, er mest sandsynligt, er de inkrementelle omkostninger for brentuximab vedotin + CHP ca. [redacted] DKK sammenlignet med CHOP. Hvis analysen udføres med AIP, bliver de inkrementelle omkostninger til sammenligning ca. 314.000 DKK pr. patient.

Sekretariatet vurderer, at budgetkonsekvenserne for regionerne ved anbefaling af brentuximab vedotin + CHP som standardbehandling vil være ca. [redacted] DKK i år 5. Hvis analysen udføres med AIP, er budgetkonsekvenserne ca. 1,6 mio. DKK i år 5.

Konklusion
De inkrementelle omkostninger er næsten udelukkende drevet af lægemiddelomkostningerne for brentuximab vedotin + CHP. Det har derfor stor betydning for analysens resultat, om patienterne modtager behandling med

brentuximab vedotin + CHP i 6 eller 8 cyklusser. Dette gælder både klinisk spørgsmål 1 og 2. Analyserne bygger på et usikkert datagrundlag, da der ikke er tilgængeligt data for CHOEP, som ikke indgik i det kliniske studie, og da det kliniske studie ikke helt afspejler dansk klinisk praksis. Dette skyldes, at patienterne, der i studiet modtog CHOP, muligvis har haft en bedre almentilstand, end de patienter man i dansk klinisk praksis vil behandle med CHOP.

3. Baggrund for den sundhedsøkonomiske analyse

Takeda (herefter omtalt som ansøger) er markedsføringstilladelsesindehaver af brentuximab vedotin og har den 24. november 2020 indsendt en ansøgning til Medicinrådet om anbefaling af brentuximab vedotin i kombination med CHP som standardbehandling på danske hospitaler af den nævnte indikation. Som et led i denne ansøgning vurderer Medicinrådets sekretariat, på vegne af Medicinrådet, den sundhedsøkonomiske analyse, ansøger har indsendt. Denne rapport er sekretariatets vurdering af den fremsendte sundhedsøkonomiske analyse (herefter omtalt som analysen).

3.1 Patientpopulation

SALCL et aggressivt lymfom, som hører til gruppen af perifere T-cellelymfomer (PTCL). SALCL har to overordnede undertyper, der defineres ved forekomsten af anaplastisk lymfomkinase (ALK) i de maligne celler. De to undertyper betegnes ALK-positiv og ALK-negativ. ALK-positiv sALCL udgør ca. 40 % og rammer hyppigst yngre (medianalder 34 år), mens ALK-negativ udgør ca. 60 % og oftest rammer ældre (medianalder 54-61 år).

Der diagnosticeres ca. 1.400 nye tilfælde af lymfekræft om året i Danmark, ca. 90 % af dem er non-Hodgkin lymfom, og ca. 10 % er Hodgkins lymfom. Fagudvalget skønner, at der diagnosticeres ca. 20 nye tilfælde af sALCL om året i Danmark [1].

3.1.1 Komparator

Medicinrådet har defineret CHOP og CHOEP som komparatorer til brentuximab + CHP for populationerne specificeret i Tabel 1.

Tabel 1: Definerede populationer og komparatorer.

Populationer	Komparatorer
Voksne med tidligere ubehandlet systemisk anaplastisk storcellet T-cellelymfom, som kandiderer til HDT og ASCT.	CHOEP og CHOP
Voksne med tidligere ubehandlet systemisk anaplastisk storcellet T-cellelymfom, som ikke kandiderer til HDT og ASCT.	CHOP

3.2 Problemstilling

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

Klinisk spørgsmål 1:
Hvilken værdi har brentuximab vedotin i kombination med cyclophosphamid, doxorubicin og prednisolon (CHP) sammenlignet med cyclophosphamid, doxorubicin, vincristin, etoposid og prednisolon (CHOEP) eller cyclophosphamid, doxorubicin, vincristin og prednisolon (CHOP) for tidligere ubehandlede patienter med systemisk anaplastisk storcellet T-cellelymfom, som kandiderer til HDT og ASCT?

Klinisk spørgsmål 2:
Hvilken værdi har brentuximab vedotin i kombination med cyclophosphamid, doxorubicin og prednisolon (CHP) sammenlignet med cyclophosphamid, doxorubicin, vincristin og prednisolon (CHOP) for tidligere ubehandlede patienter med systemisk anaplastisk storcellet T-cellelymfom, som ikke kandiderer til HDT og ASCT?

4. Vurdering af den sundhedsøkonomiske analyse

Ansøger har indsendt en sundhedsøkonomisk analyse, der estimerer de inkrementelle omkostninger pr. patient for brentuximab vedotin + CHP sammenlignet med CHOEP og CHOP. I det nedenstående vil den sundhedsøkonomiske model, som ligger til grund for estimeringen af de inkrementelle omkostninger pr. patient, blive præsenteret.

4.1 Antagelser og forudsætninger for model

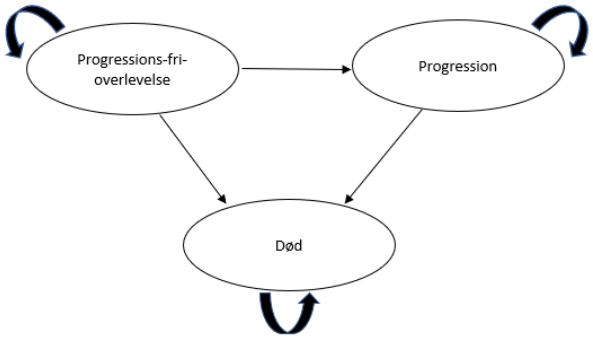
Den sundhedsøkonomiske model har til formål at estimere de inkrementelle omkostninger ved behandling af tidligere ubehandlet sALCL. Sammenligningen med brentuximab vedotin + CHP er lavet på baggrund af data fra et klinisk studie, ECHELON-2, som er et randomiseret, dobbeltblindet, dobbelt-dummy, placebo-kontrolleret studie [2]. I studiet sammenlignes brentuximab vedotin + CHP kun med CHOP, og grundet mangel på data for behandling med CHOEP antager ansøger, at CHOEP har samme effekt som CHOP. Det vil sige, at ansøger antager, at den progressionsfrie overlevelse (PFS), den samlede overlevelse (OS), behandlingslængden og bivirkningsprofilen er ens for behandling med CHOP og CHOEP.

Sekretariatets vurdering af antagelser og forudsætninger for modellen
Fagudvalget vurderer, at behandlingen i ECHELON-2-studiet til dels afviger fra dansk klinisk praksis, men at data fra studiet kan anvendes i sammenligningen mellem

brentuximab + CHP og CHOP. I Danmark tilbydes CHOP primært til patienter over 60 år og efterfølges for en mindre del også af konsoliderende HDT og ASCT (patienter mellem 60-70 år i god almen tilstand). Denne ældre undergruppe udgør kun en mindre del af sALCL-populationen i studiet (patienter over 60 år udgør ca. 36 % af patienterne med sALCL, og patienter over 65 år udgør under ¼ af patienterne med sALCL (23 %)). Det betyder, at studiepopulationen i ECHELON-2 samlet set må forventes at have en bedre prognose end de patienter, som i dansk klinisk praksis behandles med CHOP. Fagudvalget kan ikke vurdere, om dette har betydning for effektforholdet mellem brentuximab vedotin + CHP og CHOP, men det bidrager med usikkerhed i forhold til den eksterne validitet af studieresultaterne. Sekretariatet accepterer ansøgers antagelse om, at effektdata for CHOP kan bruges som proxy for behandling med CHOEP i den sundhedsøkonomiske analyse. Dette skyldes, at det er nødvendigt i den sundhedsøkonomiske analyse og valgte model at anvende antagelser for effekt og behandlingslængde for at kunne udføre beregninger og dermed estimere de totale omkostninger for behandling med CHOEP. Sekretariatet understreger dog, at denne antagelse skaber stor usikkerhed omkring estimeringen af omkostningerne for behandling med CHOEP.

4.1.1 Modelbeskrivelse

Ansøger har indleveret en *partitioned survival model*, der estimerer omkostninger baseret på den tid, patienten er i de tre stadier: PFS, progression (PD) og død. Figur 1 viser modellens struktur. En cyklus i modellen er 21 dage, og ansøger anvender *half-cycle correction*.



Figur 1: Beskrivelse af modelstrukturen i omkostningsanalysen.

Ansøger anvender Kaplan-Meier (KM)-data til at estimere tiden, patienterne befinder sig i stadierne. KM-data anvendes også til at ekstrapolere PFS og OS. Til ekstrapolering af både PFS og OS anvender ansøger generalised gamma som parametrisk funktion (røde kurver) for begge arme, se Figur 2, Figur 3, Figur 4 og Figur 5. Generalised gamma er valgt, da ansøger argumenterer for, at funktionen havde nogle af de bedste statistiske fit for PFS og OS og samtidig blev vurderet som mest klinisk plausible af kliniske eksperter, som ansøger har konsulteret.

Ansøger anvender den gennemsnitlige behandlingslængde fra ECHELON-2. Patienter, der blev behandlet med brentuximab + CHP, modtog i gennemsnit behandling i 5,99 cyklusser (ca. 18 uger), og patienter, der blev behandlet med CHOP, modtog i gennemsnit behandling i 5,84 cyklusser (ca. 17,5 uger). Grundet mangel på data antager ansøger, at den gennemsnitlige behandlingslængde ved behandling med CHOEP svarer til den gennemsnitlige behandlingslængde med CHOP, dermed 5,84 cyklusser.

Ansøger har opdelt de kliniske spørgsmål således, at brentuximab vedotin + CHP sammenlignes med CHOEP i klinisk spørgsmål 1 og med CHOP i klinisk spørgsmål 2. Klinisk spørgsmål 1 omhandler patienter, der er kandidater til HDT og ASCT. Formålet med behandling til disse patienter er at opnå tilstrækkelig respons, således at patienterne kan modtage HDT og ASCT. Ansøger antager, at 48 % af patienterne, der modtager brentuximab vedotin + CHP, vil opnå tilstrækkelig respons til at modtage HDT og ASCT. Dette bygger på data fra ECHELON-2-studiet. For patienter, der behandles med CHOEP, antager ansøger, at 43 % vil modtage HDT og ASCT. Ansøger har inkluderet et estimat på 14 % for andelen af patienter, der vil kandidere til HDT og ASCT efter behandling med CHOP. Dette er ekskluderet fra klinisk spørgsmål 1 men kan tillægges analysen. Estimaterne for CHOEP og CHOP bygger på vurderinger af kliniske eksperter, som ansøger har konsulteret.

Sekretariatets vurdering af modellen
Sekretariatet accepterer ansøgers valg af parametrisk funktion men vælger at præsentere følsomhedsanalyser, hvor Gompertz og en eksponentiel funktion anvendes til ekstrapolering af PFS og OS. Disse parametriske funktioner er valgt, da de repræsenterer de mest pessimistiske og optimistiske scenarier.

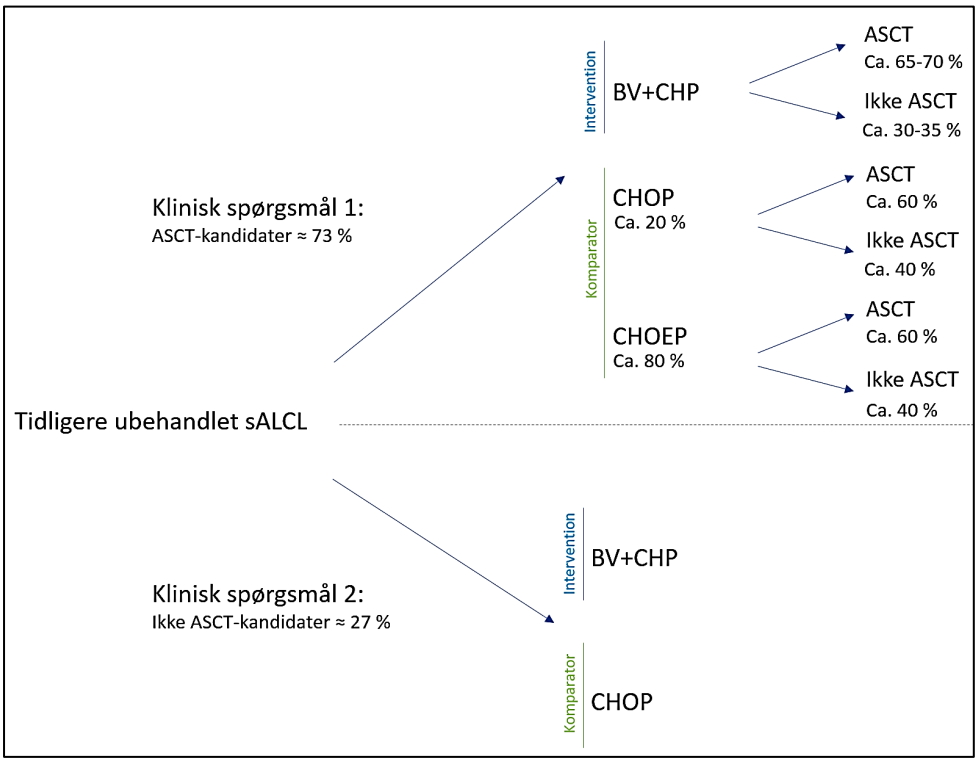
Ifølge fagudvalget vil man i dansk klinisk praksis oftest behandle patienter, der kandiderer til HDT og ASCT, med CHOEP, men en lille gruppe patienter mellem 60-70 år i god almentilstand vil modtage CHOP med henblik på at opnå tilstrækkelig respons til efterfølgende HDT og ASCT. Fagudvalget vurderer, at ca. 80 % af patienterne, der kandiderer til HDT og ASCT, vil modtage CHOEP, og ca. 20 % vil modtage CHOP.

Sekretariatet ændrer derfor andelene for klinisk+ spørgsmål 1 således, at 20 % modtager CHOP, og 80 % modtager CHOEP.

Fagudvalget vurderer yderligere for klinisk spørgsmål 1, at mellem 65-70 % af patienterne, der modtager brentuximab vedotin + CHP, vil opnå tilstrækkelig respons til at modtage HDT og ASCT. For patienter, der behandles med CHOP med henblik på at modtage HDT og ASCT, vurderer fagudvalget, at 60 % af patienterne vil modtage HDT og ASCT. Hvorvidt flere patienter vil opnå tilstrækkelig respons til at modtage HDT og ASCT efter behandling med CHOEP end med CHOP, er usikkert. Fagudvalget vurderer, at patienterne, der kandiderer til behandling med CHOEP, formentlig vil opnå bedre respons, og dermed vil flere patienter potentielt modtage HDT og ASCT. Da dette er yderst usikkert, vælger sekretariatet dog at anvende samme andel af patienter, der modtager HDT og ASCT efter CHOP, altså 60 % for CHOEP.

Sekretariatet præsenterer følsomhedsanalyser, hvor det antages, at andelen, der modtager HDT og ASCT efter behandling med CHOEP, sættes til samme andel, som modtager HDT og ASCT efter behandling med brentuximab vedotin + CHP. Yderligere præsenteres følsomhedsanalyser, hvor andelen af patienter, der modtager HDT og ASCT efter brentuximab vedotin + CHP, sættes til 50 % og 80 %.

Figur 6 opsummerer fagudvalgets vurdering af opdeling af patienter, der indgår i klinisk spørgsmål 1 og 2, andelen af CHOP og CHOEP i klinisk spørgsmål 2 og andelene af patienter, der forventes af modtage HDT og ASCT afhængig af valg af behandling.



Figur 2: Overblik over klinisk spørgsmål 1 og klinisk spørgsmål 2.

Sekretariatet ændrer sin hovedanalyse således, at brentuximab vedotin + CHP sammenlignes med 80 % CHOEP og 20 % CHOP i klinisk spørgsmål 1. Yderligere ændrer sekretariatet andelene af patienter, der modtager HDT og ASCT efter fagudvalgets vurdering. Sekretariatet præsenterer følsomhedsanalyser, hvor andelene af patienter, der modtager HDT og ASCT efter behandling med brentuximab vedotin + CHP varieres, og en følsomhedsanalyse, hvor andelen der modtager HDT og ASCT efter CHOEP sættes til at være den samme som andelen, der modtager HDT og ASCT efter brentuximab vedotin + CHP. Yderligere præsenteres følsomhedsanalyser, hvor den parametriske funktion, der anvendes til ekstrapolering af PFS og OS, ændres.

4.1.2 Analyseperspektiv

Ansøgers omkostningsanalyse har et begrænset samfundsperspektiv. Analysen har en tidshorisont på 30 år, og omkostninger, der ligger efter det første år, er diskonteret med en rate på 4 %.

Sekretariatets vurdering af analyseperspektivet
Sekretariatet accepterer ansøgers valg vedr. analyseperspektiv.

4.2 Omkostninger

I det følgende præsenteres ansøgers antagelser for omkostningerne i den sundhedsøkonomiske analyse af brentuximab vedotin + CHP sammenlignet med CHOEP og CHOP. De inkluderede omkostninger i ansøgers analyse er lægemiddelomkostninger, hospitalsomkostninger, bivirkningsomkostninger, patientomkostninger og omkostninger til efterfølgende behandling.

4.2.1 Lægemiddelomkostninger

Brentuximab vedotin + CHP kan gives i 6-8 cyklusser [1]. Ansøger antager, at brentuximab vedotin + CHP i gennemsnit gives i 5,99 cyklusser, og CHOP og CHOEP gives i 5,84 cyklusser på baggrund af ECHELON-2-studiet. Til beregning af lægemiddelomkostninger benytter ansøger kropsfladearealet (BSA) på 1,87 m^2 og gennemsnitsvægten 75,5 kg fra ECHELON-2-studiet. Følgende doseringer er antaget:

<u>Brentuximab vedotin + CHP:</u>

- Brentuximab vedotin: 1,8 mg/kg hver 3. uge
- Cyclophosphamid: 750 mg/m^2 hver 3. uge
- Doxorubicin: 50 mg/m^2 hver 3. uge
- Prednisolon: 100 mg dag 1-5 i 3-ugers cyklusser

<u>CHOEP:</u>

- Cyclophosphamid: 750 mg/m^2 hver 3. uge

- Doxorubicin: 50 mg/m^2 hver 3. uge
- Vincristin: 1,4 mg/m^2 hver 3. uge
- Etoposid: 100 mg/m^2 dag 1-3 hver 3. uge
- Prednisolon: 100 mg dag 1-5 i 3-ugers cyklusser

CHOP:

- Cyclophosphamid: 750 mg/m^2 hver 3. uge
- Doxorubicin: 50 mg/m^2 hver 3. uge
- Vincristin: 1,4 mg/m^2 hver 3. uge
- Prednisolon: 100 mg dag 1-5 i 3-ugers cyklusser

Ansøger antager, at alle patienter modtager G-CSF som profylaktisk behandling sammen med brentuximab vedotin + CHP, CHOP og CHOEP. Følgende dosering er antaget:

G-CSF:

- Filgrastim: 300 mg hver 3. uge
- Levofloxacin: 500 mg hver 3. uge
- Aciclovir: 400 mg hver 3. uge

Klinisk spørgsmål 1 omhandler patienter, der er kandidater til HDT og ASCT, og ansøger har derfor inkluderet omkostninger til HDT. HDT er inkluderet i analysen i form af BEAM, og omkostningerne er kun inkluderet for den andel af patienter, der antages at modtage ASCT. Ansøger antager nedenstående dosering:

BEAM:

- Carmustin: 300 mg/m^2, én gang på dag 1
- Etoposid: 100 mg/m^2, to gange dagligt på dag 2 til 5
- Cytarabin: 200 mg/m^2, to gange dagligt på dag 2 til 5
- Melphalan: 140 mg/m^2, én gang på dag 6

Ansøgers estimering af lægemiddelomkostninger bygger på AIP, hvilket sekretariatet udskifter med SAIP. Se lægemiddelpriserne i Tabel 2.

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

Lægemiddel	Styrke	Pakningsstørrelse	Pris [DKK]	Kilde
Brentuximab vedotin	50 mg	1 stk.	[redacted]	Amgros
Cyclophosphamid	50 mg	100 stk.	[redacted]	Amgros

Lægemiddel	Styrke	Pakningsstørrelse	Pris [DKK]	Kilde
Doxorubicin	2 mg/ml	100 ml	[redacted]	Amgros
Prednisolon	5 mg	100 stk.	[redacted]	Amgros
Vincristin	1 mg/ml	2 ml	[redacted]	Amgros
Etoposid	20 mg/ml	25 ml	[redacted]	Amgros
Filgrastim	0,3 mg/ml	5 x 1 ml	[redacted]	Amgros
Levofloxacin	5 mg/ml	30 x 0,3 ml	[redacted]	Amgros
Aciclovir	200 mg	100 stk.	[redacted]	Amgros
Carmustin	100 mg	1 stk.	[redacted]	Amgros
Cytarabin	100 mg/ml	20 ml	[redacted]	Amgros
Melphalan	2 mg	25 stk.	[redacted]	Amgros

*[redacted] DKK er den forhandlede pris for brentuximab vedotin. Prisen er betinget af, at brentuximab vedotin + CHP bliver anbefalet som standardbehandling som alternativ til både CHOP og CHOEP. Såfremt brentuximab vedotin + CHP ikke anbefales til begge populationer, vil prisen på [redacted] DKK være gældende. Som det vil fremgå af afsnit 6.1, vurderer fagudvalget, at brentuximab vedotin + CHP kun vil blive givet til patienter, der ellers ville have modtaget CHOP. Sekretariatet beregner derfor hovedanalysen ud fra den ikke-betingede SAIP, men præsenterer en følsomhedsanalyse, hvis den betingede SAIP anvendes.

Sekretariatets vurdering af lægemiddelomkostninger

Jævnfør protokollen vil CHOEP blive doseret med to-ugers intervaller i seks cyklusser [1] og ikke hver tredje uge i seks cyklusser, som ansøger antager. Dette har dog ikke betydning for analysens resultat, da antallet af administrationer er begrænset til seks i alt. Doseringen af etoposid i CHOEP-regimet afhænger af administrationsformen. Ved intravenøs infusion er dosis pr. administration 100 mg/m^2 og ved peroral administration er dosis 200 mg/m^2. Ansøger antager, at patienter, der modtager CHOEP, vil modtage 100 mg/m^2 etoposid pr. administration. Fagudvalget vurderer, at der er en ligelig fordeling mellem intravenøs administration og peroral administration for etoposid. Sekretariatet ændrer derfor dosen for etoposid til at være 50 % 100 mg/m^2 og 50 % 200 mg/m^2.

Sekretariatet accepterer ansøgers antagelser vedr. lægemiddelomkostninger men ændrer sekretariatets hovedanalyse således, at 50 % af patienterne, der behandles med CHOEP, får 100 mg/m^2 etoposid pr. administration, og 50 % får 200 mg/m^2 per administration.

4.2.2 Hospitalsomkostninger

Ansøger antager, at brentuximab vedotin + CHP, CHOP og CHOEP administreres intravenøst på hospitalet. Ansøger benytter 2020 DRG-takster til estimering af hospitalsomkostningerne. Til estimering af omkostningerne ved hver

lægemiddeladministration anvender ansøger DRG-taksten på 17.622 DKK (DRG-kode: 27MP21).

Ansøger har inkluderet monitoreringsomkostninger til CT-scanninger, PET-scanninger, konsultationer med en læge og kliniske tests. Antallet af scanninger, konsultationer og tests bygger på gennemsnittet fra ECHELON-2 og kan ses i Tabel 3. Ansøger antager, at monitoreringen er ens for alle tre behandlingsregimer.

Tabel 3: Omkostninger til monitorering under behehandling.

	Frekvens under behandling	Enhedsomkostning [DKK]	DRG 2020
CT-scanning	2	2.032	30PR06
PET-scanning	2	2.470	36PR07
Lægekonsultation	11	1.512	23MA04
Blodtælling, test af urin og elektrolytter	6	28.271	17MA03
Knoglemarvsbiopsi	3	14.935	17PR01
Test af leverfunktion	6	28.271	17MA03

Ansøger har inkluderet omkostninger til opfølgning af patienter, der ikke har progredieret efter ophørt behandling med brentuximab vedotin + CHP, CHOP eller CHOEP. Ansøger antager, at patienterne vil modtage en CT-scanning hver 1,5 måned i det første år og en CT-scanning hvert kvartal i år 2-5 som opfølgning for de patienter, der ikke er progredieret. Til estimering af omkostningerne for ASCT anvender ansøger DRG-taksten på 171.378 DKK (DRG 2020: 26MP24).

Som tillæg til behandling med brentuximab vedotin + CHP, CHOP og CHOEP antager ansøger, at nogle patienter vil modtage strålebehandling. Ansøger antager, at ca. 9 % af patienterne, der behandles med brentuximab vedotin + CHP, vil modtage strålebehandling, og ca. 3 % af patienterne, der behandles med CHOP eller CHOEP, vil modtage strålebehandling. Til estimering af omkostningerne forbundet med strålebehandling anvender ansøger DRG-taksten på 4.426 DKK (DRG 2020: 27MP07).

Sekretariatets vurdering af hospitalsomkostninger

Ansøger antager, at etoposid administreres intravenøst på hospitalet. Fagudvalget vurderer dog, at 50 % af patienterne modtager etoposid peroralt på dag 2 og 3 i hver cyklus, som beskrevet i afsnit 4.2.1. Sekretariatet ekskluderer derfor de ekstra omkostninger forbundet med intravenøs administration af etoposid på dag 2 og 3 for 50 % af patienterne.

Sekretariatet vurderer, at de anvendte takster til lægekonsultation, intravenøs infusion og parakliniske tests (herunder blodtælling og test af urin, elektrolytter og leverfunktion) er overestimeret, og sekretariatet vælger derfor at ændre enhedsomkostningerne, se Tabel 4.

Tabel 4: Sekretariatets estimater for enhedsomkostninger til monitorering.

	Enhedsomkostning [DKK]	Kilde
Lægekonsultation	1.316	Medicinrådets værdisætning af enhedsomkostninger
Intravenøs infusion	3.235	DRG 2020: 17MA98
Blodtælling	30	Rigshospitalets Labportal
Test af urin og elektrolytter	26	Rigshospitalets Labportal
Test af leverfunktion	202	Rigshospitalets Labportal

Fagudvalget vurderer, at man i dansk klinisk praksis ikke vil behandle patienterne med strålebehandling, og sekretariatet ekskluderer derfor omkostningen.

Sekretariatet ekskluderer administrationsomkostninger forbundet med etoposid på dag 2 og 3 for 50 % af patienterne og ændrer enhedsomkostningerne for lægekonsultation, intravenøs infusion og parakliniske tests. Yderligere ekskluderes omkostninger til strålebehandling.

4.2.3 Bivirkningsomkostninger

Ansøger anvender 2020 DRG-takster til at estimere bivirkningsomkostningerne. Ansøger estimerer bivirkningsomkostningerne på baggrund af frekvenserne for alle bivirkninger af grad 3 eller 4 registreret i ECHELON-2-studiet. Der er ikke inkluderet bivirkningsomkostninger relateret til behandling med etoposid, da ansøger argumenterer for, at der ikke er anvendeligt data, der kan informere omkring bivirkningerne ved behandling med etoposid i CHOEP-regimet til sammenligningen i klinisk spørgsmål 1. Bivirkningsprofilen for CHOEP antages derfor at være den samme som bivirkningsprofilen for CHOP. Tabel 5 viser de estimerede bivirkningsfrekvenser for brentuximab vedotin + CHP, CHOP og CHOEP.

Tabel 5: Bivirkningsfrekvenser for brentuximab vedotin + CHP, CHOP og CHOEP.

	Brentuximab vedotin + CHP [%]	CHOP og CHOEP [%]	Enhedsomkostning [DKK]	DRG 2020
Anæmi	0,20	0,19	4.732	16PR02

Febril neutropeni	0,20	0,16	58.620	01MA03
Leukopeni	0,09	0,21	6.114	16PR01
Pneumoni	0,04	0,03	37.050	04MA13
Trombocytopeni	0,07	0,06	37.603	16MA03

Sekretariatets vurdering af bivirkningsomkostninger
Sekretariatet accepterer ansøgers tilgang vedr. bivirkningsomkostninger.

4.2.4 Patientomkostninger

Patientomkostninger er estimeret på baggrund af lægemiddeladministration på hospitalet og inkluderer den effektive tid på hospitalet, ventetid og transport. Ansøger anvender enhedsomkostningen på 179 DKK per time for patienttid og 100 DKK for transportomkostninger per hospitalsbesøg, jævnfør Medicinrådets værdisætning af enhedsomkostninger. Da ansøger antager, at etoposid skal administreres ved intravenøs infusion på hospitalet på dag 1, 2 og 3, er der tillagt ekstra patientomkostninger til to yderligere hospitalsbesøg for de patienter, der behandles med CHOEP. Ansøger antager således, at behandling med brentuximab vedotin + CHP eller CHOP tager 3,5 time per cyklus og 10,5 time per cyklus ved behandling med CHOEP.

Sekretariatets vurdering af patientomkostninger
Som beskrevet i afsnit 4.2.1 vurderer fagudvalget, at 50 % af patienterne får etoposid intravenøst på dag 2 og 3, og 50 % får etoposid peroralt. Sekretariatet ekskluderer derfor 50 % af hospitalsbesøgene på dag 2 og 3 i estimeringen af patientomkostningerne for CHOEP. Dermed reduceres antallet af timer til lægemiddeladministration per cyklus til 7 timer ved behandling med CHOEP.

Sekretariatets accepterer ansøgers tilgang vedr. patientomkostninger, men ekskluderer de ekstra omkostninger til administration af etoposid for 50 % af patienterne.

4.2.5 Efterfølgende behandling

Ansøger har inkluderet omkostninger til efterfølgende behandling af patienter, som er progredieret. Dette indebærer brentuximab vedotin som monoterapi, kemoterapi og stamcelletransplantation. Tabel 6 viser ansøgers estimat for andelen af patienter, der vil modtage henholdsvis brentuximab vedotin som monoterapi, kemoterapi og stamcelletransplantation efter progression.

Tabel 6: Ansøgers estimater for fordeling af efterfølgende behandling.

	Brentuximab vedotin + CHP	CHOP og CHOEP
Brentuximab vedotin monoterapi	10 %	23 %

	Brentuximab vedotin + CHP	CHOP og CHOEP
Kemoterapi	22 %	36 %
Stamcelletransplantation	7 %	10 %

Der antages samme dosering af brentuximab vedotin som monoterapi, som når det gives i kombination med CHP. Ansøger har inkluderet følgende kemoterapier med tilhørende andele: ICE: 28 %, DHAP: 15 %, GDP: 33 %, ESHAP: 24 %. Andelene er estimeret på baggrund af data fra ECHELON-2. Følgende doseringer er antaget:

ICE:

- Ifosfamid: 5.000 mg/m^2, én dag pr. cyklus i tre cyklusser a 14 dage
- Carboplatin: 800 mg/kg, én dag pr. cyklus i tre cyklusser a 14 dage
- Etoposid: 100 mg/m^2, tre dage pr. cyklus i tre cyklusser a 14 dage

DHAP:

- Dexamethason: 40 mg/kg, fire dage pr. cyklus i tre cyklusser a 21 dage
- Cytarabin: 2.000 mg/m^2, to dage pr. cyklus i tre cyklusser a 21 dage
- Cisplatin: 100 mg/m^2, én dag pr. cyklus i tre cyklusser a 21 dage

GDP:

- Gemcitabin: 1.250 mg/m^2, to dage pr. cyklus i fire cyklusser a 21 dage
- Dexamethason: 40 mg/kg, fire dage pr. cyklus i fire cyklusser a 21 dage
- Cisplatin: 25 mg/m^2, tre dage pr. cyklus i fire cyklusser a 21 dage

ESHAP:

- Etoposid: 40 mg/m^2, fire dage pr. cyklus i syv cyklusser a 21 dage
- Methylprednisolon: 500 mg/kg, fem dage pr. cyklus i syv cyklusser a 21 dage
- Cytarabin: 2.000 mg/m^2, én dag pr. cyklus i syv cyklusser a 21 dage
- Cisplatin: 25 mg/m^2, fire dage pr. cyklus i syv cyklusser a 21 dage

Ansøgers estimering af lægemiddelomkostninger bygger på AIP, hvilket sekretariatet udskifter med SAIP. Se lægemiddelpriserne i Tabel 7.

Tabel 7: Lægemiddelpriser for kemoterapi i efterfølgende behandling, SAIP [december 2020].

Lægemiddel	Styrke	Pakningsstørrelse	Pris [DKK]	Kilde
Ifosfamid	1.000 mg	1.000 mg	[redacted]	Amgros

Lægemiddel	Styrke	Pakningsstørrelse	Pris [DKK]	Kilde
Carboplatin	10 mg/ml	45 ml	[redacted]	Amgros
Dexamethason	4 mg	100 stk.	[redacted]	Amgros
Cisplatin	1 mg/ml	100 ml	[redacted]	Amgros
Gemcitabin	40 mg/ml	50 ml	[redacted]	Amgros
Methylprednisolon	500 mg	1 stk.	[redacted]	Amgros

Ansøger antager, at nogle patienter vil modtage stamcelletransplantationer efter progression. Patienterne antages at modtage enten autologe eller allogene stamcelletransplantationer. Omkring 63 % af stamcelletransplantationerne efter progression antages at være autologe, og 27 % antages at være allogene. Som beskrevet i afsnit 4.2.2 anvender ansøger DRG-taksten på 171.378 DKK (DRG 2020: 26MP24) for en autolog stamcelletransplantation. For en allogen stamcelletransplantation anvendes DRG-taksten 688.233 DKK (DRG 2020: 26MP22).

Sekretariatets vurdering af efterfølgende behandling
Fagudvalget vurderer, at man ikke vil behandle med brentuximab vedotin som monoterapi efter progression, hvis patienten allerede har modtaget behandling med brentuximab vedotin. For patienter, der har modtaget CHOP eller CHOEP, vurderes ansøgers estimat for den andel, som skal behandles med brentuximab vedotin monoterapi på 23 %, rimelig. Sekretariatet ekskluderer derfor omkostninger til efterfølgende behandling med brentuximab vedotin for patienter, der har modtaget behandling med brentuximab vedotin tidligere.

Det er usikkert, hvilke kemoterapiregimer der behandles med efter progression, men fagudvalget vurderer, at man i de fleste tilfælde vil behandle med ICE eller DHAP og ikke vil behandle med ESHAP. Det vurderes, at fordelingen vil være således: ICE: ca. 77 %, DHAP: ca. 15 % og GDP: ca. 8 %. Fagudvalget vurderer, at man vil behandle den samme andel patienter, der har progredieret, med kemoterapi, uanset om de har modtaget behandling med brentuximab vedotin + CHP, CHOP eller CHOEP. Det vurderes, at < 20 % af patienterne modtager kemoterapi efter progression, og sekretariatet sætter andelen til 15 %. Det vil sige, at 15 % af patienterne, der har modtaget behandling med brentuximab vedotin + CHP, antages at modtage kemoterapi efter progression. Ligeledes antages det, at 15 % af patienterne, der har modtaget CHOP eller CHOEP vil modtage kemoterapi efter progression.

Fagudvalget vurderer yderligere, at patienter ikke vil modtage en stamcelletransplantation efter progression, da de patienter, der kandiderer til stamcelletransplantation, vil modtage det inden progression. Sekretariatet ekskluderer derfor omkostninger til stamcelletransplantationer efter progression.

Sekretariatets antagelser vedrørende efterfølgende behandling kan ses i Tabel 8.

Tabel 8: Sekretariatets estimater for fordeling af efterfølgende behandling.

	Brentuximab vedotin + CHP	CHOP og CHOEP
Brentuximab vedotin monoterapi	0 %	23 %
Kemoterapi	15 %	15 %
Stamcelletransplantation	0 %	0 %

Sekretariatet ændrer hovedanalysen således, at patienter, der har modtaget brentuximab vedotin + CHP, ikke vil modtage brentuximab vedotin i de efterfølgende behandlingslinjer. Sekretariatet ændrer fordelingen af kemoterapi som efterfølgende behandling, og sekretariatet ekskluderer omkostninger til stamcelletransplantationer som efterfølgende behandling.

4.3 Følsomhedsanalyser

Formålet med følsomhedsanalyserne er at undersøge usikkerhederne i analysen. Ansøger har lavet følgende følsomhedsanalyser:

- Ekskludering af brentuximab vedotin som monoterapi til efterfølgende behandling.
- CHOEP har samme bivirkningsprofil som brentuximab vedotin + CHP.

Sekretariatets vurdering af følsomhedsanalyser
Sekretariatet vælger at præsentere en følsomhedsanalyse for klinisk spørgsmål 1, hvor andelen af patienter, der opnår tilstrækkelig respons til at modtage HDT og ASCT efter behandling med brentuximab vedotin + CHP, varieres. I en følsomhedsanalyse sættes andelen af patienter, der modtager HDT og ASCT efter behandling med brentuximab vedotin, til 80 %, og i en anden følsomhedsanalyse sættes andelen til at være 50 %. Derudover præsenterer sekretariatet en følsomhedsanalyse, hvor andelen af patienter, der modtager HDT og ASCT efter behandling med CHOEP, sættes til at være tilsvarende andelen, der modtager HDT og ASCT efter behandling med brentuximab vedotin + CHP.

Ansøger har forhandlet en pris på brentuximab vedotin med Amgros. Den forhandlede pris er betinget af, at brentuximab vedotin + CHP anbefales som standardbehandling som alternativ til både CHOP og CHOEP. Sekretariatet præsenterer følsomhedsanalyser, hvor den betingede forhandlede pris anvendes for begge kliniske spørgsmål.

Der er usikkerhed forbundet med estimeringen af omkostninger til efterfølgende behandling, og ansøger har lavet en følsomhedsanalyse, hvor efterfølgende behandling med brentuximab vedotin som monoterapi er ekskluderet. På baggrund af fagudvalgets vurdering omkring usikkerhed af de efterfølgende behandlinger, vælger sekretariatet at præsentere en følsomhedsanalyse, hvor omkostninger til al efterfølgende behandling ekskluderes. Følsomhedsanalysen udføres for begge kliniske spørgsmål.

Sekretariatet vurderer, at det ikke vil have stor betydning for analysens resultat, hvis bivirkningsprofilen for CHOEP sættes til at være den samme som bivirkningsprofilen for brentuximab vedotin + CHP, og præsenterer derfor ikke ansøgers følsomhedsanalyse. Ifølge protokollen kan brentuximab vedotin + CHP gives i 6-8 cyklusser [1]. Sekretariatets hovedanalyser for klinisk spørgsmål 1 og 2 bygger på den gennemsnitlige behandlingslængde i ECHELON-2-studiet på ca. 6 cyklusser. Sekretariatet præsenterer en følsomhedsanalyse, hvor det antages, at patienterne modtager behandling med brentuximab vedotin + CHP i 8 cyklusser. Følsomhedsanalysen udføres for begge kliniske spørgsmål.

Sekretariatet præsenterer følsomhedsanalyser, hvor de parametriske funktioner til ekstrapolering af PFS og OS varieres. Både Gompertz og en eksponentiel funktion anvendes i følsomhedsanalyser for begge kliniske spørgsmål.

Sekretariatet vælger at præsentere følsomhedsanalyser, hvor andelene, der modtager HDT og ASCT efter behandling med brentuximab vedotin + CHP, varieres. Der præsenteres også en følsomhedsanalyse, hvor andelen af patienter, der modtager HDT og ASCT efter behandling med CHOEP, sættes til at være tilsvarende andelen, der modtager HDT og ASCT efter behandling med brentuximab vedotin + CHP. Der præsenteres følsomhedsanalyser for begge kliniske spørgsmål, hvor den betingede forhandlede pris for brentuximab vedotin anvendes. Yderligere præsenterer sekretariatet følsomhedsanalyser, hvor efterfølgende behandling ekskluderes, hvor behandlingslængden for brentuximab vedotin + CHP sættes til 8 cyklusser, og hvor de parametriske funktioner til ekstrapolering af PFS og OS varieres.

4.4 Opsummering af basisantagelser

I Tabel 9 opsummeres basisantagelserne for ansøgers hovedanalyse sammenlignet med de ændringer, som sekretariatet har lavet i egen hovedanalyse.

Tabel 9: Basisantagelser for ansøgers og sekretariatets hovedanalyse.

Basisantagelser	Ansøger	Sekretariatet
Tidshorisont	30 år	30 år
Diskonteringsrate	4 %	4 %
Inkluderede omkostninger	Lægemiddelomkostninger Hospitalsomkostninger Bivirkningsomkostninger Patient- og transportomkostninger Omkostninger til efterfølgende behandling	Lægemiddelomkostninger Hospitalsomkostninger Bivirkningsomkostninger Patient- og transportomkostninger Omkostninger til efterfølgende behandling
Komparator(er) i klinisk spørgsmål 1	CHOEP	CHOEP (80 %), CHOP (20 %)
Komparator i klinisk spørgsmål 2	CHOP	CHOP
CHOEP datagrundlag	PFS, OS, behandlingslængde og bivirkningsprofil for CHOP bruges som proxy for CHOEP	PFS, OS, behandlingslængde og bivirkningsprofil for CHOP bruges som proxy for CHOEP
Dosering af brentuximab vedotin	1,8 mg/kg	1,8 mg/kg
Behandlingslængder (cyklusser) Brentuximab vedotin + CHP	5,99 cyklusser	5,99 cyklusser
CHOP og CHOEP	5,84 cyklusser	5,84 cyklusser
Parametriske funktioner til ekstrapolering af PFS og OS Brentuximab vedotin + CHP	Generalised gamma	Generalised gamma
CHOP	Generalised gamma	Generalised gamma

5. Resultater

5.1 Resultatet af sekretariatets hovedanalyse

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

Klinisk spørgsmål 1:

- Der antages en fordeling for komparatoren på 80 % CHOEP og 20 % CHOP.
- Andelene, der modtager HDT og ASCT efter behandling med brentuximab vedotin + CHP, CHOP og CHOEP, er justeret jævnfør fagudvalgets vurdering.
- Ekstra administrationsomkostninger og patientomkostninger til administration af etoposid på dag 2 og 3 ekskluderes for 50 % af patienterne.
- Der ekskluderes omkostninger til stamcelletransplantationer som efterfølgende behandling efter patienterne er progredieret (ikke som konsoliderende behandling efter brentuximab + CHP, CHOP eller CHOEP).

Både klinisk spørgsmål 1 og 2:

- Enhedsomkostninger for lægemiddeladministration og monitorering er ændret.
- Omkostninger til strålebehandling er ekskluderet.
- Efterfølgende behandling med brentuximab vedotin som monoterapi er ekskluderet for patienter, der har modtaget brentuximab vedotin + CHP.
- Andelene af patienter, der modtager kemoterapi som efterfølgende behandling, er sat til 15 % uanset tidligere behandlingsregime.

Den inkrementelle omkostning pr. patient bliver ca. [redacted] DKK i sekretariatets hovedanalyse for klinisk spørgsmål 1. Udføres analysen med AIP bliver den inkrementelle omkostning pr. patient ca. 312.000 DKK. Resultaterne fra sekretariatets hovedanalyse for klinisk spørgsmål 1 præsenteres i Tabel 10.

Tabel 10: Resultatet af sekretariatets hovedanalyse, klinisk spørgsmål 1, DKK, diskonterede tal.

	Brentuximab vedotin + CHP	CHOEP og CHOP	Inkrementelle omkostninger
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Hospitalsomkostninger	268.266	261.233	7.033
Bivirkningsomkostninger	17.857	14.457	3.400
Patientomkostninger	4.212	6.561	-2.349

	Brentuximab vedotin + CHP	CHOEP og CHOP	Inkrementelle omkostninger
Efterfølgende behandling	[redacted]	[redacted]	[redacted]
Totale omkostninger	[redacted]	[redacted]	[redacted]

Den inkrementelle omkostning pr. patient bliver ca. [redacted] DKK i sekretariatets hovedanalyse for klinisk spørgsmål 2. Udføres analysen med AIP bliver den inkrementelle omkostning pr. patient ca. 314.000 DKK. Resultaterne fra sekretariatets hovedanalyse for klinisk spørgsmål 2 præsenteres i Tabel 11.

Tabel 11: Resultatet af sekretariatets hovedanalyse, klinisk spørgsmål 2, DKK, diskonterede tal.

	Brentuximab vedotin + CHP	CHOP	Inkrementelle omkostninger
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Hospitalsomkostninger	117.328	111.538	5.790
Bivirkningsomkostninger	17.857	14.457	3.400
Patientomkostninger	4.212	3.952	259
Efterfølgende behandling	[redacted]	[redacted]	[redacted]
Totale omkostninger	[redacted]	[redacted]	[redacted]

5.1.1 Resultatet af sekretariatets følsomhedsanalyser

Ved samme antagelser som i sekretariatets hovedanalyser for meromkostninger for klinisk spørgsmål 1 og 2, udfører sekretariatet følsomhedsanalyser, se Tabel 12.

Tabel 12: Resultatet af sekretariatets følsomhedsanalyse sammenlignet med hovedanalysen, DKK

Scenarie	Inkrementelle omkostninger
Klinisk spørgsmål 1	
Resultatet af hovedanalysen, klinisk spørgsmål 1	[redacted]
Andelen af patienter, der modtager HDT og ASCT efter behandling med brentuximab vedotin + CHP 80 %: 50 %:	[redacted] [redacted]
Andel af patienter, der modtager HDT og ASCT efter behandling med CHOEP, sættes til at være lig andelen, der modtager HDT og ASCT efter behandling med brentuximab + CHP	[redacted]

Scenarie	Inkrementelle omkostninger
Parametriske funktioner for PFS og OS ændres til: Gompertz Eksponentiel funktion	[redacted]
Ekskludering af omkostninger til efterfølgende behandling	[redacted]
Behandling med brentuximab vedotin + CHP sættes til 8 cyklusser	[redacted]
Den betingede pris på brentuximab vedotin anvendes	[redacted]
Klinisk spørgsmål 2	
Resultatet af hovedanalysen, klinisk spørgsmål 2	[redacted]
Parametriske funktioner for PFS og OS ændres til: Gompertz Eksponentiel funktion	[redacted]
Ekskludering af omkostninger til efterfølgende behandling	[redacted]
Behandling med brentuximab vedotin + CHP sættes til 8 cyklusser	[redacted]
Den betingede pris på brentuximab vedotin anvendes	[redacted]

6. Budgetkonsekvenser

Budgetkonsekvenserne pr. år er baseret på antagelsen om, at brentuximab vedotin + CHP vil blive anbefalet som standardbehandling. Man ser derfor på to scenarier:

- Brentuximab vedotin + CHP bliver anbefalet som standardbehandling af Medicinrådet til indikationen, som denne analyse omhandler.
- Brentuximab vedotin + CHP bliver ikke anbefalet som standardbehandling.

Budgetkonsekvenserne bliver differencen mellem budgetkonsekvenserne i de to scenarier.

6.1 Ansøgers estimat af patientantal og markedsandel

Ansøger antager, at 21 patienter årligt kandiderer til behandling med brentuximab vedotin + CHP for klinisk spørgsmål 1. For komparator i klinisk spørgsmål 1 antages det, at 60 % af patienterne vil modtage CHOEP, og 40 % vil modtage CHOP. I klinisk spørgsmål 2 antager ansøger, at 8 patienter kandiderer til behandling med brentuximab vedotin + CHP. Her er kun CHOP komparator. Hvis brentuximab vedotin + CHP anbefales som standardbehandling, antager ansøger et markedsoptag på 20 % i år 1 stigende til 100 % i år 4 for begge kliniske spørgsmål. Tabel 13 viser estimatet af antal patienter årligt i budgetkonsekvenserne for klinisk spørgsmål 1, og Tabel 14 viser estimatet af antal patienter årligt i budgetkonsekvenserne for klinisk spørgsmål 2.

Tabel 13: Ansøgers estimat af antal nye patienter pr. år, klinisk spørgsmål 1.

	År 1	År 2	År 3	År 4	År 5
Anbefales					
Brentuximab vedotin + CHP	4	11	17	21	21
CHOP	5	2	0	0	0
CHOEP	12	8	4	0	0
Anbefales ikke					
Brentuximab vedotin + CHP	0	0	0	0	0
CHOP	8	8	8	8	8
CHOEP	13	13	13	13	13

Tabel 14: Ansøgers estimat af antal nye patienter pr. år, klinisk spørgsmål 2.

	År 1	År 2	År 3	År 4	År 5
Anbefales					
Brentuximab vedotin + CHP	2	4	7	8	8
CHOP	7	4	2	0	0
Anbefales ikke					
Brentuximab vedotin + CHP	0	0	0	0	0
CHOP	8	8	8	8	8

Sekretariatets vurdering af patientantal og markedsandel
Fagudvalget vurderer, at omkring 20 patienter kandiderer til behandlingen med brentuximab vedotin + CHP årligt. Heraf vil ca. 15 patienter indgå i klinisk spørgsmål 1 (hvoraf ca. 12 patienter i dag behandles med CHOEP, og 3 patienter behandles med CHOP) og 5 patienter i klinisk spørgsmål 2 (hvor i dag 100 % af patienterne behandles med CHOP).

Værdien af brentuximab vedotin + CHP sammenlignet med CHOEP kan ikke kategoriseres, og fagudvalget mener derfor, at det er usikkert, om man i dansk klinisk praksis vil behandle nogle patienter med brentuximab vedotin + CHP i stedet for CHOEP. Fagudvalget vurderer, at brentuximab vedotin + CHP formentlig kun vil blive anvendt til patienter, der ellers ville modtage behandling med CHOP.

Fagudvalget vurderer, at såfremt brentuximab vedotin + CHP anbefales som standardbehandling, vil behandlingen have et markedsoptag på 90 % i år 1 stigende til 100 % fra år 2. For klinisk spørgsmål 1 gælder dette kun for andelen af patienter, der ellers ville blive behandlet med CHOP (ca. 3 patienter). For klinisk spørgsmål 2 gælder det hele populationen (ca. 5 patienter). Tabel 15 og Tabel 16 viser sekretariatets estimat af nye patienter pr. år per klinisk spørgsmål på baggrund af fagudvalgets vurderinger.

Tabel 15: Sekretariatets estimat af antal nye patienter pr. år, klinisk spørgsmål 1.

	År 1	År 2	År 3	År 4	År 5
Anbefales					
Brentuximab vedotin + CHP	2	3	3	3	3
CHOEP	12	12	12	12	12
CHOP	1	0	0	0	0

	År 1	År 2	År 3	År 4	År 5
Anbefales ikke					
Brentuximab vedotin + CHP	0	0	0	0	0
CHOEP	12	12	12	12	12
CHOP	3	3	3	3	3

Tabel 16: Sekretariatets estimat af antal nye patienter pr. år, klinisk spørgsmål 2.

	År 1	År 2	År 3	År 4	År 5
Anbefales					
Brentuximab vedotin + CHP	4	5	5	5	5
CHOP	1	0	0	0	0
Anbefales ikke					
Brentuximab vedotin + CHP	0	0	0	0	0
CHOP	5	5	5	5	5

Sekretariatet udfører budgetkonsekvensanalyser med fagudvalgets vurdering af markedsoptaget ved en anbefaling og uden en anbefaling og med 15 patienter i klinisk spørgsmål 1 og 5 patienter i klinisk spørgsmål 2.

6.2 Sekretariatets budgetkonsekvensanalyse

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

- Antal patienter i klinisk spørgsmål 1: 15 patienter.
- Antal patienter i klinisk spørgsmål 2: 5 patienter.
- Ved anbefaling af brentuximab vedotin + CHP antages et markedsoptag på 90 % i år 1 og 100 % fra år 2 for patienter, der ellers ville blive behandlet med CHOP i begge kliniske spørgsmål.

Klinisk spørgsmål 1:
Sekretariatet estimerer, at anvendelse af brentuximab vedotin + CHP vil resultere i budgetkonsekvenser på ca. [redacted] DKK i år 5. Resultatet er præsenteret i Tabel 17.

Hvis analysen udføres med AIP, bliver budgetkonsekvenserne ca. 1,0 mio. DKK i år 5.

Tabel 17: Sekretariatets analyse af totale budgetkonsekvenser, klinisk spørgsmål 1, 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]

Klinisk spørgsmål 2:
Sekretariatet estimerer, at anvendelse af brentuximab vedotin + CHP vil resultere i budgetkonsekvenser på ca. [redacted] DKK i år 5. Resultatet er præsenteret i Tabel 18.

Hvis analysen udføres med AIP, bliver budgetkonsekvenserne ca. 1,6 mio. DKK i år 5.

Tabel 18: Sekretariatets analyse af totale budgetkonsekvenser, klinisk spørgsmål 2, 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]

6.2.1 Resultat af følsomhedsanalyser for budgetkonsekvensanalysen

Ansøger har forhandlet en betinget pris på brentuximab vedotin, som kun er gældende, såfremt at brentuximab vedotin + CHP anbefales til begge populationer, der indgår i klinisk spørgsmål 1 og 2. Sekretariatet præsenterer derfor følsomhedsanalyser for budgetkonsekvenserne, hvor det antages, at brentuximab vedotin + CHP anbefales til samtlige patienter, der ellers ville have modtaget CHOP eller CHOEP. Fagudvalget har allerede i hovedanalysen vurderet, at brentuximab vedotin + CHP vil blive anvendt til patienter, der ellers ville modtage CHOP. For klinisk spørgsmål 1 vurderer fagudvalget, at der indgår omkring 15 patienter i populationen, hvoraf 12 patienter antages at modtage CHOEP. Ved anbefaling af brentuximab vedotin + CHP anslår fagudvalget, at 50 % af patienter, der i dag vil modtage CHOEP, vil modtage brentuximab vedotin + CHP.

Ved samme antagelser som i Medicinrådets hovedanalyse for budgetkonsekvenser, men med antagelse om, at brentuximab vedotin + CHP anbefales til samtlige patienter, vil omkostningerne i år 5 være ca. [redacted] DKK for klinisk spørgsmål 1, se Tabel 19.

Tabel 19. Medicinrådets analyse af totale budgetkonsekvenser med brug af den betingede forhandlede pris for klinisk spørgsmål 1, 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]

Ved samme antagelser som i Medicinrådets hovedanalyse for budgetkonsekvenser, men med antagelsen om, at brentuximab vedotin + CHP anbefales til samtlige patienter, vil omkostningerne i år 5 være ca. [redacted] DKK for klinisk spørgsmål 2, se Tabel 20.

Tabel 20. Medicinrådets analyse af totale budgetkonsekvenser med brug af en betingede forhandlede pris for klinisk spørgsmål 2, 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 brentuximab vedotin er forbundet med betydelige meromkostninger sammenlignet med behandling med CHOP og CHOEP. De inkrementelle omkostninger er næsten udelukkende drevet af lægemiddelomkostningerne for brentuximab vedotin.

7.1 Usikkerheder

I sammenligningen med CHOEP i klinisk spørgsmål 1 antages det, at PFS, OS, behandlingslængde og bivirkningsprofil for CHOP kan anvendes som proxy for behandling med CHOEP, da der ikke er data for CHOEP. Dette bidrager til stor usikkerhed i analysens resultat for klinisk spørgsmål 1. Derudover vurderer fagudvalget, at klinisk praksis i ECHELON-2 ikke helt afspejler dansk klinisk praksis, da man typisk vil tilbyde CHOP til patienter over 60 år, og kun en mindre del (patienter i god almentilstand) vil modtage konsoliderende HDT og ASCT. Kun 36 % af patienterne i ECHELON-2 var over 60 år, og det kan derfor forventes, at CHOP-patienterne i ECHELON-2 havde en bedre prognose end de patienter, som i dansk klinisk praksis behandles med CHOP. Fagudvalget kan ikke vurdere, om dette har betydning for effektforholdet mellem brentuximab vedotin + CHP og CHOP, men det bidrager med usikkerhed i forhold til den eksterne validitet af studieresultaterne. Sekretariatet vurderer derfor, at datagrundlaget for både klinisk spørgsmål 1 og 2 er usikkert, og resultaterne skal derfor tolkes med forsigtighed.

Det har nogen betydning for analysens resultat for klinisk spørgsmål 1, om andelen af patienter, der modtager HDT og ASCT efter behandling med brentuximab vedotin + CHP, sættes til 80 % eller 50 %. Det har lille betydning for analysens resultat, om andelen af patienter, der modtager HDT og ASCT efter behandling med CHOEP, sættes til at være lig andelen, der modtager HDT og ASCT efter behandling med brentuximab vedotin + CHP. Valg af parametrisk funktion til ekstrapolering af PFS og OS har lille betydning for analysens resultat for både klinisk spørgsmål 1 og 2.

Hvorvidt efterfølgende behandling ekskluderes, har nogen betydning for både klinisk spørgsmål 1 og 2. Derimod har det stor betydning for analysens resultat, hvis behandlingslængden sættes til 8 cyklusser for patienter, der behandles med brentuximab vedotin + CHP. For klinisk spørgsmål 1 stiger de inkrementelle omkostninger fra ca. [redacted] DKK til ca. [redacted] DKK, og for klinisk spørgsmål 2 stiger de inkrementelle omkostninger fra ca. [redacted] til ca. [redacted] DKK. Det skyldes, at analysernes resultater i høj grad er drevet af lægemiddelomkostningerne for brentuximab vedotin.

Ansøger har forhandlet en betinget pris på brentuximab vedotin, som træder i kraft, såfremt brentuximab vedotin + CHP anbefales til begge populationer i klinisk spørgsmål 1 og 2. Den betingede pris har lille betydning for de inkrementelle omkostninger. Dog har det betydning i budgetkonsekvensanalysen for klinisk spørgsmål 1, hvis det antages, at brentuximab vedotin + CHP anbefales til patienter, der ellers ville have modtaget CHOP eller CHOEP. I dette scenarie, hvor den betingede pris indgår, stiger

budgetkonsekvenserne i år 5 fra ca. [redacted] DKK i hovedanalysen til ca. [redacted] DKK i år 5 i følsomhedsanalysen. Denne stigning hænger sammen med, at flere patienter forventes at sættes i behandling med brentuximab vedotin, hvis lægemidlet anbefales til både CHOP- og CHOEP-patienter. For klinisk spørgsmål 2 har den betingede pris minimal betydning for resultatet af budgetkonsekvenserne.

8. Referencer

1. Medicinrådets protokol for vurdering af brentuximab vedotin i kombination med doxorubicin og prednisolon til behandling af tidligere ubehandlet systemisk anaplastisk storcellet T- cellelymfom. :0–17.

2. Horwitz S, O'Connor OA, Pro B, Illidge T, Fanale M, Advani R, et al. Brentuximab vedotin with chemotherapy for CD30-positive peripheral T-cell lymphoma (ECHELON-2): a global, double-blind, randomised, phase 3 trial. Lancet. 2019;393(10168):229–40.

9. Versionslog

Versionslog		
Version	**Dato**	**Ændring**
1.0	24. februar 2021	Godkendt af Medicinrådet.

10. Bilag

10.1 Resultatet af ansøgers hovedanalyse

I ansøgers hovedanalyse for klinisk spørgsmål 1 bliver den inkrementelle omkostning pr. patient ca. [redacted] DKK over en tidshorisont på 30 år. Resultaterne fra ansøgers hovedanalyse er præsenteret i Tabel 21.

Tabel 21: Resultatet af ansøgers hovedanalyse for klinisk spørgsmål 1, DKK, diskonterede tal.

	Brentuximab vedotin + CHP	CHOEP	Inkrementelle omkostninger
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Hospitalsomkostninger	[redacted]	[redacted]	[redacted]
Bivirkningsomkostninger	[redacted]	[redacted]	[redacted]
Patientomkostninger	[redacted]	[redacted]	[redacted]
Efterfølgende behandling	[redacted]	[redacted]	[redacted]
Totale omkostninger	[redacted]	[redacted]	[redacted]

I ansøgers hovedanalyse for klinisk spørgsmål 2 bliver den inkrementelle omkostning pr. patient ca. [redacted] DKK over en tidshorisont på 30 år. Resultaterne fra ansøgers hovedanalyse er præsenteret i Tabel 22.

Tabel 22: Resultatet af ansøgers hovedanalyse for klinisk spørgsmål 2, DKK, diskonterede tal.

	Brentuximab vedotin + CHP	CHOP	Inkrementelle omkostninger
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Hospitalsomkostninger	[redacted]	[redacted]	[redacted]
Bivirkningsomkostninger	[redacted]	[redacted]	[redacted]
Patientomkostninger	[redacted]	[redacted]	[redacted]
Efterfølgende behandling	[redacted]	[redacted]	[redacted]
Totale omkostninger	[redacted]	[redacted]	[redacted]

10.2 Ansøgers budgetkonsekvensanalyse

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

Med de ovenstående antagelser om patientantal og markedsandel for klinisk spørgsmål 1 estimerer ansøger, at anvendelse af brentuximab vedotin + CHP vil resultere i budgetkonsekvenser på ca. [redacted] DKK i år 5. Ansøgers estimat af budgetkonsekvenserne fremgår af Tabel 23.

Tabel 23: Ansøgers hovedanalyse for totale budgetkonsekvenser for klinisk spørgsmål 1, 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]

Med de ovenstående antagelser om patientantal og markedsandel for klinisk spørgsmål 2 estimerer ansøger, at anvendelse af brentuximab vedotin + CHP vil resultere i budgetkonsekvenser på ca. [redacted] DKK i år 5. Ansøgers estimat af budgetkonsekvenserne fremgår af Tabel 24.

Tabel 24: Ansøgers hovedanalyse for totale budgetkonsekvenser for klinisk spørgsmål 2, 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	24.02.2021
Leverandør	Takeda
Lægemiddel	Adcetris (brentuximab vedotin)
Ansøgt indikation	Brentuximab vedotin i kombination med cyclophosphamid, doxorubicin og prednisolon til behandling af tidligere ubehandlet systemisk anaplastisk storcellet T-cellelymfom.

Forhandlingsresultat

Brentuximab vedotin er omfattet af et udbud, der løber fra 1. februar 2021 til 31. august 2021. Amgros har mulighed for at forlænge udbuddet 2x6 måneder. Amgros har gennem udbuddet opnået følgende pris på brentuximab vedotin:

Lægemiddel	Styrke/dosis	Pakningsstørrelse	AIP (kr)	Forhandlet SAIP (kr)	Rabatprocent ift. AIP
Brentuxumab vedotin	1,8 mg/kg	50 mg	21.088	[redacted]	[redacted]

Som en del af vurderingen af brentuximab vedotin til anaplastisk storcellet T-cellelymfom har Amgros forhandlet en yderligere rabat. **Denne er betinget af at brentuximab vedotin anbefales til standard ibrugtagning som alternativ til både CHOP og CHOEP (dvs. populationerne for begge kliniske spørgsmål).** Prisen reduceres dagen efter Medicinrådsmødet såfremt der anbefales til begge populationer. Den betingede pris ses i tabellen nedenfor.

Lægemiddel	Styrke/dosis	Pakningsstørrelse	AIP (kr)	Forhandlet SAIP (kr)	Rabatprocent ift. AIP
Brentuximab vedotin (betinget af en anbefaling)	1,8 mg/kg	50 mg	21.088	[redacted]	[redacted]

Vurdering af forhandlingsresultatet

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

[redacted]

Konklusion

Brentuximab vedotin er et lægemiddel forbundet med væsentlige meromkostninger sammenlignet med nuværende dansk klinisk praksis. En anbefaling til hele populationen vil sikre en lidt højere rabat, som vil modvirke en mindre andel af stigningen i omsætningen på lægemidlet. Amgros vurderer ikke det er muligt at opnå en højere rabat som en del af vurderingen til denne indikation.

Response to value categorization

A+CHP for first line treatment of sALCL patients

sALCL is a very rare cancer disease which globally predominantly is treated with CHOP
Current Danish Standard of Care, CHOEP, is based on low level, retrospective, evidence and have not conclusively been shown to lead to an OS advantage over CHOP
A+CHP shows unprecedented PFS and OS benefit over CHOP in a prospective head-to-head trial and is likely to be a valuable treatment alternative to CHOEP + HDT/SCT

Summary

Takeda is grateful for the opportunity to address the preliminary categorization of the added value of brentuximab vedotin (Adcetris) in combination with cyclophosphamide, doxorubicin and prednisone (A+CHP) as compared to current Danish Standard of Care.

In response to the current added value categorization of A+CHP vs. CHOP +/- HDT/SCT Takeda notes that

- The basis for *added value of unknow magnitude (Merværdi af ukendt størrelse)* of A+CHP vs. CHOP +/- HDT/SCT is **moderate added value**, but that the unpowered nature of the subgroup analysis in combination with immature OS data renders the Confidence Intervals broad in the study of the **first novel treatment to demonstrate superiority** over current global standard of care within the **rare cancer disease** sALCL.

In response to the current added value categorization of A+CHP vs. CHOEP + HDT/SCT Takeda notes that it has not been possible to attribute a value for A+CHP vs CHOEP + HDT/SCT **within the framework of the methods of the Medicines Council**.

Takeda further notes that

- The Scientific Committee (Fagudvalget) concludes that the OS benefit of CHOEP vs. CHOP as induction prior to HDT+SCT has not been conclusively demonstrated and that the evidence for CHOEP vs. CHOP is weak within the **rare cancer disease** sALCL [9].
- The OS and PFS benefits of A+CHP over CHOP have been conclusively demonstrated in a randomized, head-to-head, placebo-controlled, double-blinded, double-dummy, active comparator, global trial with more than 450 patients
- **New data,** generated in January 2021, supports a substantial added value for A+CHP + HDT/SCT vs. CHOEP + HDT/SCT.
- Patients induced with A+CHP rather than CHOEP prior to HDT + Stem Cell Transplant could be **spared significant toxicity without suffering a decrease in efficacy**.
- The above is recognized by payers in European countries where CHOEP + HDT/SCT historically was Standard of Care. Thus all these countries (**Germany, France, Austria, Czech Republic, Sweden, Finland**) have acknowledge the **practice changing** potential of A+CHP and **reimbursed A+CHP f**or patients historically treated with CHOEP + HDT/SCT.

In response to the current added value categorization of A+CHP vs. CHOP for ALK+ patients with favorable IPI score Takeda notes that it has not been possible to attribute a value within the framework of the methods of the Medicines Council as no data exists for this patient population.
Takeda further notes that

- There is no biological or pharmacological rationale for why a targeted agent that has proven to have an unprecedented efficacy in the past should not also induce deeper responses in this patient population.

Comments to added value categorizations

Induction with CHOP with and with-out HDT and stem cell transplant

Takeda notes that the added value category "added value of unknown magnitude" (*merværdi af ukendt størrelse*) means that the A+CHP is associated with *at least* small added value; possible medium or large added value.

Takeda also notes that the categorization is based on a preliminary (*foreløbig*) added value categorization for OS and PFS as *moderate*, but that this preliminary categorization is associated with a degree of uncertainty, as the data is considered immature since the median OS and PFS is not reached for the intervention arm.

Takeda wishes to re-emphasize that the analyses are unpowered and performed in the sALCL subgroup, rather than in the powered ITT population. This lack of power in the subgroup analysis results in wide confidence intervals as well as sensitivity to single events. Indeed, with an OS Hazard Ratio of 0.54 the confidence intervals spanned from 0.34 to 0.87.

Supporting the HR of 0.54, the supplementary outcome measures *differences in 2-years OS and PFS rates*, at 10,7% and 14,5% were **2 and 3 times larger** than the minimal clinically relevant difference of 5% stipulated in the protocol.

Such increases in efficacy could be offset by increases in toxicity or decreases in HRQoL. However, no such differences were observed; rather a decrease in discontinuation due to AEs of 5%, bordering on statistical significance with a RR of 0.40 (0.15; 1.05), was found, while no difference was found in HRQoL.

Specifically for the patients undergoing HDT and stem cell transplant, the Scientific Committee points out that the foundation for HDT and stem cell transplant is response, and response depth, to the induction therapy. In this context the differences in CR observed in the Echelon-2 trial **further supports a moderate or large added value**. Indeed, A+CHP was associated with a clinically relevant 12% improvement in CR rates (68% vs. 56%), resulting in more patients entering HDT + stem cell transplant in deep remission.

In sum, the significant increases in efficacy (OS, PFS, CR-rates), in combination with **no difference in toxicity or HRQoL** strongly argues that **the added value for A+CHP in the treatment of this rare cancer disease is at least moderate.**

High Dose Therapy (HDT) and autologous stem cell transplant following induction with CHOEP for young/fit ALK- sALCL patients

Takeda notes that it has not been possible to attribute an added value categorization to A+CHP vs. CHOEP + HDT and autologous stem cell transplant within the framework of the methods of the Medicines Council as

- No research has compared A+CHP directly with CHOEP
- The quality of the identified research did not allow an indirect comparison between A+CHP and CHOEP with CHOP as a common comparator.
- The Scientific Committee did not find that the literature comparing CHOP and CHOEP failed to conclusively argue that CHOEP is more efficacious than CHOP in younger sALCL patients.

Takeda further notes that the Scientific Committee mentions that the evidence for the superiority of CHOEP over CHOP is poorly demonstrated and that the evidence for using CHOEP in younger patients is weak (Page 8 in udkast til Medicinrådets Merværdivurdering: "***Disse retningslinjer baserer sig ikke på solid evidens***." [9]) and does not support an OS advantage (Page 8 in udkast til Medicinrådets Merværdivurdering: "*Den overordnede evidens på området er dog* ***overordnet set svag*** *og påviser således* ***ikke en afgørende forskel i overlevelsen ved brug af CHOEP.***" [9]). Indeed, the sum of the analyses identified through the systematic literature review supports this view, figure 2 in Background section below.

Takeda also notes that the **Scientific Committee conclude**s that it is **difficult to exclude A+CHP as a possible treatment alternative to CHOEP** based on the demonstrated **promising effects of A+CHP vs. CHOP on PFS and OS,** and the **lack of similar data for CHOEP vs. CHOP** (page 26 in udkast til Medicinrådets Merværdivurdering: **"***Selvom der ikke foreligger direkte sammenlignende studier mellem brentuximab vedotin + CHP og CHOEP er det* ***vanskeligt at underkende brentuximab vedotin + CHP som et muligt behandlingsalternativ til de yngre patienter som i dag tilbydes CHOEP****. ECHELON-2 studiet viser lovende OS- og PFS-data ved en sammenligning med CHOP.* ***De samme overbevisende data foreligger ikke for en sammenligning mellem CHOEP vs. CHOP****."* [9])

Takeda agrees with the position that A+CHP should not be ruled out as a treatment alternative to CHOEP as induction prior to HDT and Stem Cell Transplant.
Indeed, the value of A+CHP **could be substantial** for patients currently treated with CHOEP prior to HDT + Stem Cell Transplant.

In a holistic view of available evidence the sum of the arguments for a **substantial value** is:

1. Current evidence for superiority of CHOEP over CHOP is weak and does not demonstrate decisive OS benefits (fagudvalget; see Background section below for further).
2. Numerically, the 5-year PFS rate of the patients from Echelon-2 who received HDT + Stem Cell Transplant is longer than in any other reports Takeda is aware of, thus:
    a. [redacted] that ALK- sALCL patients from the A+CHP arm of the Echelon-2 trial who underwent HDT + Stem Cell Transplant after obtaining CR[1] have a **5-yr PFS rate of** [redacted] - [redacted] [10]
    b. The 5-yr PFS rate for ALK- sALCL patients in the Nordic NLG-T-01 trial testing CHOEP/CHOP followed by HDT + Stem Cell Transplant was **61%** [2].
    c. The 5-yr PFS rate for CHOEP/CHOP treated ALK- sALCL patients from the Swedish Registry Trial was **31.4%** [4]
3. A+CHP has been demonstrated in Echelon-2 to lead to a 12% increase in the number of patients who obtain a CR as compared to CHOP [11].
4. CHOEP is associated with significant added toxicity as compared to CHOP and/or A+CHP.

While such crude cross-trial comparisons as the ones above (2a/2b/2c) should be interpreted with caution[2], it is likely that patients currently receiving CHOEP as induction could be **spared significant toxicity without suffering a decrease in efficacy** (e.g. PFS & CR rates) if they received A+CHP rather than CHOEP as induction therapy prior to HDT + Stem Cell Transplant.

In sum:

- Current Standard of Care, CHOEP, is supported by low level evidence based on retrospective analyses and do not conclusively demonstrate an OS benefit over CHOP (see background below for further)
- The OS and PFS benefits of A+CHP over CHOP have been demonstrated in a randomized, head-to-head, placebo-controlled, double-blinded, double-dummy, active comparator, global trial with more than 450 patients (see Background section below for further)
- Patients induced with A+CHP rather than CHOEP prior to HDT + Stem Cell Transplant could be spared significant toxicity without suffering a decrease in efficacy

[1] HDT and transplantation was not mandated in the Echelon-2 trial, but was at the investigators discretion

[2] E.g. the Nordic trial transplanted patients who achieved CR and PR but only included patients up to the age of 67; Echelon-2 included patients up to the age of 85; it is unclear how many patients underwent stem cell transplant in the Swedish registry study etc.

Given the above, it is the position of Takeda that the true value of A+CHP as compared to CHOEP is likely substantial despite the impossibility of fitting the Global Echelon-2 study into the framework of the methods of the Danish Medicines Council.

Please see section "Background" below for detailed information on evidence level for CHOEP vs. CHOP, rationale for design of Echelon-2, and summary of recent reimbursement decisions in countries treating young/fit sALCL patients with CHOEP.

ALK+ sALCL patients with favorable IPI score

ALK+ sALCL patients with favorable IPI score were not enrolled in the Echelon-2 study and no evidence of the efficacy of A+CHP in this patient population exists from the clinical development program of brentuximab vedotin.
However, there is no reason to assume that favorable efficacy data from Echelon-2 is not extendable to this patient population, as the difference between A+CHP and CHOP is the targeted delivery of a microtubule disrupting agent (vedotin) to neoplastic cells, rather than untargeted systemic infusion of a microtubule disrupting agent (O, Vincristine).

Background

sALCL is a rare cancer disease; Global SoC is heterogenous and based on poor evidence

sALCL is a separate entity with-in the rare Peripheral T-Cell Lymphomas.
Indeed, with only 20-22 patients every year in Denmark, sALCL truly is a rare cancer disease.

As a consequence of the rarity of the disease, the evidence for the current treatment is based on low level of evidence such as **extrapolation from aggressive B-cell lymphoma trials** and **pooled retrospective analyses**.
The scientific committee mentions that current treatment is based on such low evidence several times, both in the protocol and in the preliminary added value categorization.

Due to this lack of high level evidence, the global treatment of sALCL/PTCL is heterogenous.
Indeed, 454 PTCL and sALCL treating hematologists have reported 8 different Standards of Care across the globe, including within the five big European countries Germany, France, Italy, Spain and UK, figure 1.

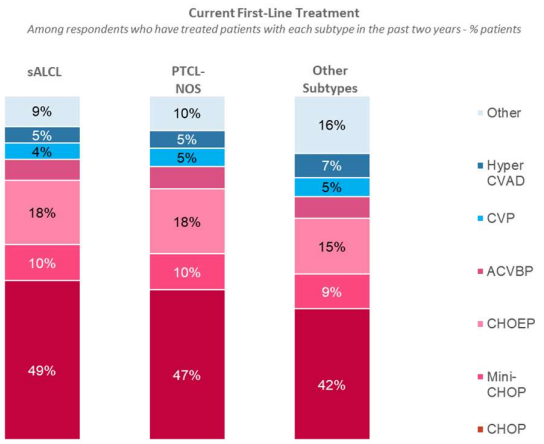


Figure 1: Current first line treatment of 454 hematologist from Japan, UK, France, Germany, Italy, Spain, Russia, Korea, and Brazil, who have treated the above PTCL subtypes within the last two years. 49% reported using CHOP as current first line therapy for sALCL. Takeda, data on file.

The Echelon-2 study provided unprecedented efficacy data and evidence level

Figure 1 shows that CHOP is the most widely used first line treatment in the world (49% of sALCL, 47% of PTCL-NOS etc). Consequently, CHOP was chosen as the control in the **global, multicenter, randomized, placebo-controlled, double-blinded and double-dummy, active comparator trial** Echelon-2.
It is worth to reiterate that Echelon-2, according to the FDA, is the first phase 3 trial to demonstrate superiority over CHOP, and that the PFS and OS improvements are unprecedented [12], and that the design of Echelon-2 makes the evidence level **uniquely high** within the sALCL/PTCL evidence pool.

Evidence for Danish Standard of Care

Danish SoC is CHOP to elderly/frail patients and CHOP with added etoposide (CHOEP) + stem cell transplant (SCT) to younger/fit patients. This SoC is based on a prospective non-controlled single arm phase 2 trial testing "up-front HDT+SCT [2] and retrospective analyses of European patients [1, 4, 6, 8] comparing CHOP vs CHOEP in various **heterogenous subgroups of sALCL/PTCL**.
Thus, among the four retrospective analyses mentioned above,

- Only one publication specifically analyzed sALCL patients; but **only ALK+ sALCL** patients (the rarest variant of sALCL). It found that
    - ALK+ sALCL patients aged 18-65, as a whole, benefitted from CHOEP as compared to CHOP
    - However, the benefit in the 18-65 year cohort was driven by PFS/OS improvement among patients aged 41-65, while patients aged 18-40 had **no PFS or OS benefit** of addition of etoposide [6]
- One analysis found that CHOEP favored PFS, **but not OS,** among 18-60 yrs old PTCL patients.
    - However, the CHOP/CHOEP groups had an uneven distribution of comorbidities favoring the CHOEP group [4].
- One analysis found an EFS (Event Free Survival) advantage, but **no OS advantage**, of CHOEP over CHOP in in 18-60 years old PTCL patients with specific clinical characteristics (LDH < 3 times Upper Limit of Normal) [1].
- One analysis of PTCL patients found a **PFS and OS benefit of etoposide** [8].
- Noteworthy, of the **599 PTCL** patients analyzed in the above four publications, only **130 were ALCL** patients further underscoring the heterogeneity of the evidence and extrapolation of evidence from other PTCL entities to sALCL.

Evidence for CHOEP vs. CHOP in sALCL/PTCL patients have reported conflicting outcomes; CHOEP for young/fit sALCL patients is not fully adopted across Europe despite ESMO guidelines

During the application process Takeda was given the opportunity to demonstrate that CHOEP and CHOP are associated with similar outcomes to allow an indirect comparison between the Echelon-2 study and CHOEP based induction of younger/fit patients. In accordance with the methods of the Medicines Council the systematic literature search was not confined geographically, but was global in scope.
The identified studies were heterogenous in regards to methods, patient populations and outcomes reported, and did not allow for a stringent comparison of CHOP vs. CHOEP.

A summary of the outcome identified analyses of CHOEP vs. CHOP is graphically presented in figure 2. Figure 2 demonstrates what appears to be an even distribution of analyses demonstrating less, more or no difference in efficacy when etoposide is added to CHOP. In the opinion of Takeda, this even distribution precludes a conclusive conclusion on the benefit of adding etoposide to CHOP.

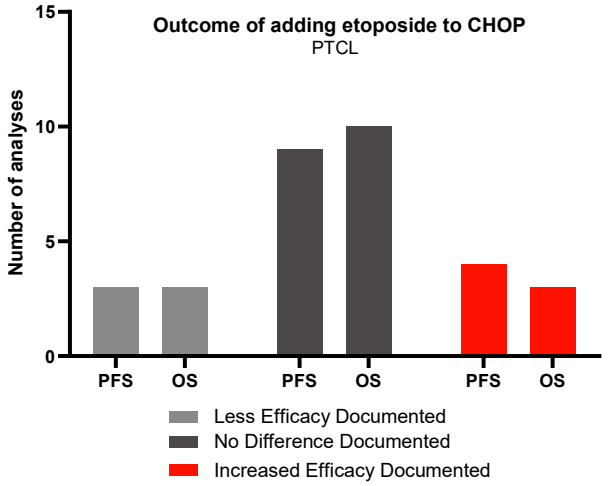


Figure 2: Distribution of outcome of analysis of the efficacy of CHOEP vs. CHOP in PTCL and ALCL patients. Based on [1-8]

The lack of apparent conclusive benefit of adding etoposide to CHOP means that CHOEP, despite being recommended by ESMO, have not gained full penetrance at a global, or European, level. Thus, physicians in Germany, Austria, France, Czech Republic and the Nordics, and to some extent Italy, follow the ESMO guidelines of CHOEP for selected (young/fit) sALCL patients, while physicians in UK, Spain, the Netherlands, Portugal, Greece, Belgium, and to some extent Italy, do not.

While the Scientific Committee acknowledged the heterogeneity in outcome demonstrated in figure 2, the committee felt that the comparatively consistent PFS benefit from the European studies presented in details above precluded an indirect comparison of A+CHP to CHOEP using CHOP as a common comparator in young/fit patients.

So far all reimbursement decisions rendered globally have been positive.

The unprecedented efficacy data and evidence quality provided by the Echelon-2 trial in combination with the recognized low level of evidence for other treatment regiments have so far led to reimbursement in all countries where decision have been rendered, **including countries where CHOEP for younger/fit sALCL patients is Standard of Care**.
Globally countries with reimbursement are: Canada, USA, Israel, Japan, Germany, UK, France, Austria, Netherlands, Czech Republic, Sweden, and Finland.
European countries favoring CHOEP to young/fit sALC patients where A+CHP is reimbursed are: Germany, France, Sweden, Finland, Austria, and the Czech Republic.

Summary of background

- Global Standard of Care is CHOP, figure 1
- Global evidence for the efficacy of CHOEP vs. CHOP is heterogenous and inconsistent, figure 2.
- Current Danish Standard of Care of sALCL differs from global Standard of Care and is based on studies providing sub-optimal evidence levels for a comparatively consistent PFS, but not OS, benefit [9]
- The Echelon-2 trial was designed using the most widely employed SoC (CHOP, figure 1) as control and have produced unprecedented efficacy data and evidence level for treatment of sALCL/PTCL [12]
- Given that the Echelon-2 trial design was global in scope, and that the historic evidence level within sALCL/PTCL, including Danish SoC, is poor and does not allow for stringent indirect comparisons, it is not possible for Takeda Denmark to lift the evidence burden for A+CHP vs. CHOEP within the framework of the methods of the Medicines Council – despite the unprecedented efficacy data generated by the Echelon-2 study.
- So far all reimbursement decisions rendered have been positive – including in Nordic and European countries traditionally using CHOEP for young and fit patients.

Comments to health economics

Exclusion of administration costs and patient costs for etoposide

Takeda's application states that treatment with CHOEP consists of doxorubicin 50 mg/m2, cyclophosphamide 750 mg/m2 , and vincristine 1.4 mg/m2 by intravenous infusion on day 1, etoposide 100 mg/m2 intravenously days 1–3, and oral prednisone days 1–5. Cycles are repeated every 3 weeks for a maximum of six to eight courses, dependent on the selection of the model.

Takeda notes that the feedback from the scientific committee states, that CHOEP will be administered biweekly, and not every third week as assumed in the application. However, as stated by the scientific committee, this does not change the outcome of the analysis due to the preset and limited number of cycles per treatment. Further, Takeda notes that dosage per cycle of etoposide has been adjusted from 100 mg/m2 to 200 mg/m2.

Takeda's application states that A+CHP and CHOEP are administrated intravenously at the outclinic. Patients receiving BV require a single infusion on Day 1 of each cycle. Doxorubicin and cyclophosphamide are administered on the same day as BV in patients receiving BV+CHP, and on the same day as vincristine/etoposide in patients receiving CHOEP. As a result, cost of administration is applied once per cycle for both treatments. However, the CHOEP regime is set to have an additional cost shown as a subsequent administration cost. The reason for the subsequent treatment cost is due to etoposide being administered on days 1-3 (three times in one cycle), therefore, resulting in the additional cost shown as subsequent administration cost.
Insights provide to Takeda, show that administration routes of CHOEP vary across Denmark. Thus, patients treated in Jutland and Fyn as a rule receives etoposide intravenously on day 1, 2, and 3. This is further substantiated by a treatment description published by Aalborg University hospital [13]. Patients treated on Zealand on the other hand are given etoposide intravenously on day 1, and orally on days 2 and 3 [14].

The secretariat has excluded the treatment cost of etoposide being administered intravenously, based on the assumption that all patients are given etoposide orally. However, by excluding costs associated with intravenous administration, costs will be underestimated for 55% of the patient population. To show the impact of excluding the intravenous administration cost, table 1 has been constructed.

Table 1 shows two scenarios. The first scenario shows the percentage change in incremental cost when etoposide is administered orally for all patients vs. when etoposide is administered intravenously for all patients. The result shows that the incremental difference increases by 16% when all patients are given etoposide orally. The second scenario shows the percentage difference in incremental cost when etoposide is administered partially orally and partially intravenous. The calculation is conducted by administering half of the doses orally, and the other half of the doses intravenously. The result shows, that the incremental difference increases by 7% compared to when all patients receive etoposide intravenously.

Table 1: Administration of etoposide

Scenario	Increase in incremental cost
Exclusion I.V. costs	16%
Partially exclusion of I.V. costs	7%

By excluding the cost of intravenous administration of etoposide, the costs of the CHOEP regime will be significantly underestimated. It is Takeda’s opinion that the cost analysis should reflect the variation in treatment practices across Denmark and therefore both included the practices of intravenous administration and oral administration of etoposide.

Distribution of patients given CHOP/CHOEP that receives SCT as consolidating treatment

Takeda notes that the Medicin Council has changed the percentage distribution of patients receiving SCT after CHOP and CHOEP treatment to 60%. Further, the distribution is changed to 65-70% for patients undergoing treatment with BV+CHP. The report from the Medicin council shows that the Scientific committee assesses that patients who are candidates for CHOEP are likely to achieve better response and therefore more patients might receive SCT compared to CHOP. However, due to uncertainty regarding the response of patients treated with CHOEP, the secretary chooses to set the distribution equivalent to patients treated with CHOP.

It is Takeda's opinion, that based on the statement above, patients undergoing treatment with CHOEP should be set at the distribution equivalent to the patients treated with BV+CHP (65-70%). Otherwise, the cost of the CHOEP regime will be underestimated, and the incremental difference in cost compared with BV+CHP will be inflated by approximately 12%.

References

1 Schmitz N, Trümper L, Ziepert M, Nickelsen M, Ho AD, Metzner B *et al*. Treatment and prognosis of mature T-cell and NK-cell lymphoma: an analysis of patients with T-cell lymphoma treated in studies of the German High-Grade Non-Hodgkin Lymphoma Study Group. *Blood* 2010; 116: 3418-3425.

2 d'Amore F, Relander T, Lauritzsen GF, Jantunen E, Hagberg H, Anderson H *et al*. Up-front autologous stem-cell transplantation in peripheral T-cell lymphoma: NLG-T-01. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2012; 30: 3093-3099.

3 Rattarittamrong E, Norasetthada L, Tantiworawit A, Chai-Adisaksopha C, Nawarawong W. CHOEP-21 chemotherapy for newly diagnosed nodal peripheral T-cell lymphomas (PTCLs) in Maharaj Nakorn Chiang Mai Hospital. *Journal of the Medical Association of Thailand = Chotmaihet thangphaet* 2013; 96: 1416-1422.

4 Ellin F, Landström J, Jerkeman M, Relander T. Real-world data on prognostic factors and treatment in peripheral T-cell lymphomas: a study from the Swedish Lymphoma Registry. *Blood* 2014; 124: 1570-1577.

5 Jia B, Hu S, Yang J, Zhou S, Liu P, Qin Y *et al*. Comparison of gemcitabin, cisplatin, and dexamethasone (GDP), CHOP, and CHOPE in the first-line treatment of peripheral T-cell lymphomas. *Hematology (Amsterdam, Netherlands)* 2016; 21: 536-541.

6 Cederleuf H, Bjerregård Pedersen M, Jerkeman M, Relander T, d'Amore F, Ellin F. The addition of etoposide to CHOP is associated with improved outcome in ALK+ adult anaplastic large cell lymphoma: A Nordic Lymphoma Group study. *British journal of haematology* 2017; 178: 739-746.

7 Kim YA, Byun JM, Park K, Bae GH, Lee D, Kim DS *et al*. Redefining the role of etoposide in first-line treatment of peripheral T-cell lymphoma. *Blood advances* 2017; 1: 2138-2146.

8 Janikova A, Chloupkova R, Campr V, Klener P, Hamouzova J, Belada D *et al*. First-line therapy for T cell lymphomas: a retrospective population-based analysis of 906 T cell lymphoma patients. *Annals of hematology* 2019; 98: 1961-1972.

9 Medicinrådets vurdering vedrørende brentuximab vedotin i kombination med cyclophosphamid, doxorubicin og prednisolon til behandling af tidligere ubehandlet systemisk anaplastisk storcellet T-cellelymfom, 2021.

10 Dong; C, Liu R. Takeda Data on File, 2021.

11 Horwitz S, O'Connor OA, Pro B, Illidge T, Fanale M, Advani R *et al*. Brentuximab vedotin with chemotherapy for CD30-positive peripheral T-cell lymphoma (ECHELON-2): a global, double-blind, randomised, phase 3 trial. *Lancet* 2019; 393: 229-240.

12 Richardson NC, Kasamon YL, Chen H, de Claro RA, Ye J, Blumenthal GM *et al*. FDA Approval Summary: Brentuximab Vedotin in First-Line Treatment of Peripheral T-Cell Lymphoma. *The oncologist* 2019; 24: e180-e187.

13 Behandling af lymfekræft med CHOEP-14. In: Hospital AU (ed): https://aalborguh.rn.dk/~/media/sxi/behandling-med-choep-14/behandling-med-choep-14-pdf.ashx.

14 [redacted]. In: Dydensborg A (ed), 2021.

Jesper Skov Neergaard

Fra: Jesper Skov Neergaard
Sendt: 9. februar 2021 11:33
Til: Dydensborg, Anders; Hilborg, Sigurd
Cc: Katrine Jürs; Snezana Djurisic; Jesper Skov Neergaard
Emne: Kvittering og svar til høringssvar

Kære Anders og Sigurd

Tak for jeres høringssvar vedrørende Medicinrådets vurdering af lægemidlets værdi for brentuximab vedotin og jeres høringssvar vedrørende den sundhedsøkonomiske afrapportering.

Vi har gennemgået jeres kommentarer til vurderingsrapporten og finder ikke anledning til at ændre den nuværende kategorisering. Som det også fremgår af vurderingsrapporten er Medicinrådet enig i, at den overordnede evidens for de nuværende rekommandationer for brugen af CHOEP og CHOP er svag. Medicinrådets vurdering er imidlertid, at den danske praksis på området og den gældende nationale guideline bygger på den aktuelt bedst tilgængelige evidens og derfor også skal udgøre grundlaget for sammenligning med ny eksperimentel behandling. De punkter som i øvrigt fremhæves i høringssvaret er elementer som har været drøftet i fagudvalget og inddraget i fagudvalgets samlede vurdering af brentuximab vedotin.

På baggrund af jeres kommentarer til den sundhedsøkonomiske afrapportering har sekretariatet ændret følgende i rapporten:
Vi inkluderer patient- og administrationsomkostninger til intravenøs etoposid for en andel af patienterne, idet vi medgiver at der er forskel i klinisk praksis på tværs af landet. Vi vælger derfor at ændre antagelsen i hovedanalysen, så det antages, at administration af etoposid på dag 2 og 3 er ligeligt fordelt mellem peroral og IV. Administrationsformen har betydning for doseringen af etoposid. Ved IV doseres 100 mg/m2 pr. administration, mens der ved peroral administration doseres 200 mg/m2. Dette ændres ligeledes i hovedanalysen.

Jeres høringssvar indgår i den videre behandling og bliver offentliggjort sammen med den endelige anbefaling. Den godkendte vurdering af lægemidlets værdi for brentuximab vedotin er offentliggjort på Medicinrådets hjemmeside.

Mvh
Jesper og Katrine

Jesper Skov Neergaard
Sundhedsvidenskabelig specialkonsulent og informationsspecialist
Cand.pharm, PhD
jne@medicinraadet.dk
+45 40 22 31 03

Medicinrådet
Dampfærgevej 27-29, 3. th.
2100 København Ø
+45 70 10 36 00
medicinraadet@medicinraadet.dk
www.medicinraadet.dk

Medicinrådet

Medicinrådets vurdering vedrørende brentuximab vedotin i kombination med cyclophosphamid, doxorubicin og prednisolon til behandling af tidligere ubehandlet systemisk anaplastisk storcellet T-cellelymfom

Version 1.0

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 bliver sammenfattet 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.

Dokumentoplysninger	
Godkendelsesdato	27. januar 2021
Dokumentnummer	99506
Versionsnummer	1.0

Indholdsfortegnelse

1. Medicinrådets konklusion

Medicinrådet vurderer, at brentuximab vedotin + CHP har en merværdi af ukendt størrelse sammenlignet med CHOP. Kategoriseringen gælder:

- ældre ≥ 60 år med tidligere ubehandlet systemisk anaplastisk storcellet T-cellelymfom, som kandiderer til HDT og ASCT.
- voksne (uanset alder) med tidligere ubehandlet systemisk anaplastisk storcellet T-cellelymfom, som ikke kandiderer til HDT og ASCT.

Medicinrådet finder, at den samlede værdi af brentuximab vedotin i kombination med CHP sammenlignet med cyclophosphamid, doxorubicin, vincristin, etoposid og prednisolon (CHOEP) ikke kan kategoriseres for voksne < 60 år med tidligere ubehandlet sALCL som kandiderer til HDT og ASCT.

Medicinrådet finder, at den samlede værdi af brentuximab vedotin i kombination med CHP sammenlignet med CHOP ikke kan kategoriseres for voksne med ALK-positiv sALCL og lav IPI-score.

Sprog: dansk
Format: pdf
Udgivet af Medicinrådet, 27. januar 2021

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

ALK: Anaplastisk lymfomkinase

ASCT: Autolog stamcelletransplantation

CD30: *Cluster of Differentiation 30*

CHOEP: Cyclophosphamid, doxorubicin, vincristin, etoposid og prednisolon

CHOP: Cyclophosphamid, doxorubicin, vincristin og prednisolon

CHP: Cyclophosphamid, doxorubicin og prednisolon

CI: Konfidensinterval

EMA: Det Europæiske Lægemiddelagentur (*European Medicines Agency)*

EPAR: *European Public Assessment Report*

GRADE: System til at vurdere evidens (*Grading of Recommendations, Assessment, Development and Evaluation*)

HDT: Højdosiskemoterapi

HR: *Hazard ratio*

IPI: International Prognostisk Index

ITT: *Intention to treat*

MMAE: Monomethyl auristatin E

OR: *Odds ratio*

PICO: Population, intervention, komparator og effektmål (*Population, Intervention, Comparator and Outcome)*

PP: *Per Protocol*

RCT: Randomiseret kontrolleret studie *(Randomised Controlled Trial)*

RR: Relativ risiko

sALCL: Systemisk anaplastisk storcellet T-cellelymfom

SMD *Standardized Mean Difference*

3. Introduktion

Formålet med Medicinrådets vurdering af brentuximab vedotin i kombination med cyclophosphamid, doxorubicin og prednisolon (CHP) til behandling af tidligere ubehandlet systemisk anaplastisk storcellet T-cellelymfom (sALCL) er at vurdere den værdi, lægemidlet har sammenlignet med dansk standardbehandling.

Vurderingen er udarbejdet, fordi Medicinrådet har modtaget en endelig ansøgning fra Takeda Pharma A/S. Medicinrådet modtog ansøgningen den 24. november 2020.

De kliniske spørgsmål er:

1. Hvilken værdi har brentuximab vedotin i kombination med cyclophosphamid, doxorubicin og prednisolon (CHP) sammenlignet med cyclophosphamid, doxorubicin, vincristin, etoposid og prednisolon (CHOEP) eller cyclophosphamid, doxorubicin, vincristin og prednisolon (CHOP) for tidligere ubehandlede patienter med sALCL, som kandiderer til højdosiskemoterapi (HDT) og autolog stamcelletransplantation (ASCT)?

2. Hvilken værdi har brentuximab vedotin i kombination med CHP sammenlignet med CHOP for tidligere ubehandlede patienter med sALCL, som ikke kandiderer til HDT og ASCT?

3.1 Systemisk anaplastisk storcellet T-celle lymfom

SALCL er et aggressivt lymfom, som hører til gruppen af perifere T-cellelymfomer. Perifere T-cellelymfomer er en heterogen gruppe af lymfekræftsygdomme, som udgør ca. 10-15 % af alle non-Hodgkin-lymfomer. SALCL er det tredje hyppigst forekommende perifere T-cellelymfom og udgør ca. 10-15 %. SALCL er næsten altid CD30-positiv (CD30+), hvilket betyder, at tumorcellerne næsten altid udtrykker receptoren CD30 i varierende grad [1]. Der diagnosticeres ca. 1.400 nye tilfælde af lymfekræft om året i Danmark, ca. 90 % af dem er non-Hodgkin lymfom, og ca. 10 % er Hodgkins lymfom. Fagudvalget skønner, at der diagnosticeres ca. 20 nye tilfælde af sALCL om året i Danmark.

SALCL har to overordnede undertyper, der defineres ved forekomsten af anaplastisk lymfomkinase (ALK) i de maligne celler. De to undertyper betegnes ALK-positiv og ALK-negativ. ALK-positiv sALCL udgør ca. 40 % og forekommer hyppigst blandt yngre patienter (medianalder 34 år), mens ALK-negativ udgør ca. 60 % og forekommer hyppigst blandt ældre patienter (medianalder 54-61 år). Begge har, sammenlignet med de øvrige perifere T-cellelymfomer, en relativ god prognose [1,2]. ALK-positiv sALCL har en 5-års overlevelse på 70-93 %, mens ALK-negativ sALCL har en 5-års overlevelse på 37-49 %. Hos yngre patienter (< 40 år) er der ikke observeret forskelle i overlevelse blandt ALK-positive og ALK-negative patienter [3]. Det er således uklart, hvorvidt forskel i prognose mellem ALK-positive og ALK-negative udelukkende skyldes forskel i aldersfordeling, eller om der er andre faktorer med indflydelse på prognosen.

Diagnosen stilles på baggrund af en histopatologisk vurdering af vævsmateriale fra en biopsi. Billeddiagnostik bruges på diagnosetidspunktet til stadieinddeling, men også under og efter behandlingsforløbet til vurdering af behandlingseffekt og sygdomskontrol. SALCL diagnosticeres oftest i et fremskredent stadium (stadie III og IV) med påviselig sygdom flere steder. Lokaliseret sygdom (stadie I-II) er sjælden. Sygdomsbyrden er derfor ofte stor med deraf følgende almensymptomer, herunder såkaldte B-symptomer (nattesved, ikke tilsigtet vægttab og feber uden anden forklaring). Sygdommen forekommer ofte i lymfeknuder (nodal sygdom), men kan dog også ses i regioner uden for det lymfatiske system (ekstranodal sygdom, herunder knoglemarv). Sygdommen opdages sædvanligvis på baggrund af hævede lymfeknuder og/eller almensymptomer. Patienter med sALCL kan inddeles i grupper med forskellig risiko for sygdomsforværring ved hjælp af det Internationale Prognostiske Index (IPI). IPI-scoren bestemmes ud fra fem risikofaktorer, som omfatter: alder, niveau af lactatdehydrogenase, sygdomsstadie, generel helbredsstatus og udbredelse af sygdommen. Scoren går fra 0-5, hvor en højere score er forbundet med en dårligere prognose. Inddelingen i forhold til risiko for dårlig prognose er således: lav (0-1), intermediær (2-3) og høj (4-5). Patienter med ALK-positiv sALCL og lav IPI har en markant bedre prognose end resten af gruppen af sALCL.

3.2 Brentuximab vedotin

Brentuximab vedotin er et antistoflægemiddelkonjugat bestående af et CD30-rettet monoklonalt antistof, som er kovalent bundet til antimikrotubulusmidlet monomethyl auristatin E (MMAE) [4]. Efter binding til CD30 optages brentuximab vedotin hurtigt i cellerne og transporteres til lysosomerne, hvor MMAE frigives og binder til tubulin. Som en konsekvens heraf dør cellerne [5].

Lægemidlet administreres som intravenøs infusion 1,8 mg/kg hver tredje uge i 6-8 serier. Denne vurdering vedrører en indikationsudvidelse til patienter med tidligere ubehandlet sALCL, hvor brentuximab vedotin gives i kombination med CHP.
Brentuximab vedotin er også indiceret til behandling af voksne patienter med:

- ikke tidligere behandlet CD30+ Hodgkin-lymfom stadie IV i kombination med doxorubicin, vinblastin og dacarbazin.
- CD30+ Hodgkin-lymfom med øget risiko for recidiv eller progression efter ASCT.
- recidiverende eller refraktært CD30+ Hodgkin-lymfom:
    - efter ASCT eller
    - efter mindst to tidligere behandlinger, når ASCT eller flerstofskemoterapibehandling ikke er en behandlingsmulighed.
- recidiverende eller refraktært sALCL.
- CD30+ kutant T-cellelymfom efter mindst 1 forudgående systemisk behandling.

Brentuximab vedotin har således allerede indikationen sALCL, blot i en senere behandlingslinje. Lægemidlet er blevet tildelt status som *orphan drug* hos EMA, men har ikke været i accelereret proces.

3.3 Nuværende behandling

De danske retningslinjer for behandling af sALCL er i overensstemmelse med retningslinjer fra ESMO [2]. Behandlingsmålet er helbredelse med samtidig fokus på at undgå uacceptabel toksicitet særligt hos ældre patienter og ved væsentlig komorbiditet.

Valg af behandling afhænger af alder, komorbiditet, om lymfomet er ALK-positivt eller ALK-negativt, samt risiko vurderet ud fra IPI-score. Patienter, som er ALK-negative og under 65 (-70) år uden markant komorbiditet, behandles med cyclophosphamid, doxorubicin, vincristin, etoposid og prednisolon (CHOEP), i alt 6 serier, som gives hver 14. dag (CHOEP-14). Opnås et tilfredsstillende respons, efterfølges dette af HDT og ASCT. Patienter, som er ALK-positive og under 65 (-70) år og som har en høj IPI-score, behandles på tilsvarende vis med CHOEP i 6 serier eventuelt efterfulgt af HDT og ASCT. Uafhængigt af ALK-status anbefales patienter over 60 år dog cyclophosphamid, doxorubicin, vincristin og prednisolon (CHOP) frem for CHOEP grundet toksicitet. Ved tilfredsstillende respons hos ældre mellem 60 - 70 år i god almen tilstand uden væsentlig komorbiditet efterfølges CHOP også af HDT og ASCT. HDT består af carmustin 300 mg/m^2 IV på dag 1, etoposid 100 mg/m^2 IV to gange dagligt på dag 2 til 5, cytarabin 200 mg/m^2 IV to gange dagligt på dag 2 til 5 og melphalan 140 mg/m^2 IV på dag 6 (kaldet BEAM).

Patienter, som ikke vurderes egnet til HDT og ASCT (ældre patienter > 65 (-70) år, og patienter med dårlig almen tilstand og/eller væsentlig komorbiditet) behandles med CHOP hver 14. eller 21. dag (CHOP-14 eller CHOP-21), i alt 6 serier [1]. Patienter, som er ALK-positive med lav IPI-score (0-1), har en markant bedre prognose, og her kan intensive strategier (CHOEP efterfulgt af HDT og ASCT) eventuelt udelades. Hos en mindre andel af patienter, som grundet meget høj alder og/eller markant komorbiditet vurderes som uegnet til CHOP, vil behandlingsvalget typisk være et mindre toksisk kemoregime.

Disse retningslinjer baserer sig ikke på solid evidens. Enkelte studier har vist en bedre *event free survival* (men ikke *overall survival*) med CHOEP frem for CHOP til patienter under 60 år [6]. Et studie fra den Nordiske Lymfomgruppe viste positive resultater med HDT og ASCT hos yngre patienter [7]. Sidstnævnte støttes af retrospektive populationsbaserede data [8]. Den overordnede evidens på området er dog overordnet set svag og påviser således ikke en afgørende forskel i overlevelsen ved brug af CHOEP. Imidlertid er responsraterne højere ved behandling med CHOEP, hvorfor man teoretisk antager, at det muliggør efterfølgende HDT og ASCT hos flere patienter, idet konsolidering med HDT forudsætter et forudgående respons.

4. Metode

Medicinrådets protokol for vurdering af brentuximab vedotin i kombination med CHP til behandling af tidligere ubehandlet sALCL beskriver sammen med *Håndbog for Medicinrådets proces og metode vedr. nye lægemidler og indikationsudvidelser*, hvordan Medicinrådet vil vurdere lægemidlets værdi for patienterne.

5. Resultater

5.1 Klinisk spørgsmål 1 og 2

Protokollen opdeler de kliniske spørgsmål i patienter, som kandiderer til HDT og ASCT, og patienter, som ikke kandiderer til HDT og ASCT. Da data fra ECHELON-2-studiet anvendes i besvarelsen af begge kliniske spørgsmål, gennemgås den identificerede evidens samlet nedenfor.

5.1.1 Litteratur

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

Ansøger har søgt litteratur med søgestrengen angivet i protokollen. Ansøger har ikke fundet studier, som muliggør en sammenligning mellem CHOEP og brentuximab vedotin + CHP baseret på statistiske metoder (direkte såvel som indirekte). Derfor har ansøger undersøgt, om der findes studier, som kan anvendes i en redegørelse for, om effekten af CHOP (komparator i ECHELON-2) er sammenlignelig med effekten af CHOEP, som også anvendes i dansk klinisk praksis.

Ansøger har inkluderet ECHELON-2-studiet, hvor brentuximab vedotin + CHP sammenlignes med CHOP hos voksne tidligere ubehandlede CD30-positive patienter med perifert T-cellelymfom [9].

ECHELON-2

I ECHELON-2-studiet er patienterne randomiseret 1:1 til enten at modtage brentuximab vedotin + CHP eller CHOP. Randomisering blev stratificeret for ALK-positiv sALCL versus alle andre histologier og IPI-score (0-1, 2-3 og 4-5). Studiet inkluderer 452 patienter, hvor af omtrent 70 % af patienterne havde sALCL (heraf ca. 1/3 ALK-positive og 2/3 ALK-negative). Studiet har ikke inkluderet tidligere ubehandlede ALK-positive patienter med lav IPI-score. Ca. 80 % af patienterne havde udbredt sygdom svarende til Ann Arbor stadie III-IV og ca. 75 – 80 % med IPI-score ≥ 2. Gennemsnitsalderen i den samlede studiepopulation var 58 år (fra 18 – 85 år), mens den var ca. 54-55 år (fra 18 – 85 år) for patienter med sALCL. Ca. 45 % af patienterne var ≥ 60 år (103 patienter i brentuximab vedotin + CHP-armen og 100 patienter i CHOP-armen), mens ca. 31 % var ≥ 65 år (69 patienter patienter i brentuximab vedotin + CHP-armen og 70 patienter i CHOP-armens).

Efter afslutning af forsøgsmedicinen modtog 50 patienter (22 %) konsoliderende ASCT i brentuximab vedotin + CHP-armen. I CHOP-armen modtog 39 patienter (17 %) konsoliderende ASCT. Beslutning om at give konsoliderende ASCT var op til den enkelte investigator.

Baselinekarakteristika for den fulde studiepopulation og for gruppen med sALCL er angivet i tabel 1.

Tabel 1. Baselinekarakteristika i ECHELON-2

	ITT-populationen		sALCL-populationen	
Patientkarakteristika	BV+CHP (n = 226)	CHOP (n = 226)	BV+CHP (n = 162)	CHOP (n = 154)
Medianalder (min-max)	58,0 (18 – 85)	58,0 (18 – 83)	55,0 (18 – 85)	54,0 (18 – 83)
Patienter (≥ 65 år)	69 (31)	70 (31)	38 (23)	36 (23)
Hankøn, n (%)	133 (59)	151 (67)	95 (59)	110 (71)
ECOG-status, n (%)				
0	84 (37)	93 (41)	58 (36)	53 (34)
1	90 (40)	86 (38)	62 (38)	61 (40)
2	51 (23)	47 (21)	41 (25)	40 (26)
Sygdomskarakteristika				
Diagnose, iht. Lokal vurdering, n (%)				
sALCL	162 (72)	154 (68)	162 (100)	154 (100)
ALK-positiv	49 (22)	49 (22)	49 (30)	49 (32)
ALK-negativ	113 (50)	105 (46)	113 (70)	105 (68)
Perifert T-celle-lymfom	29 (13)	43 (19)	NA	NA
Angioimmunoblastisk T-celle-lymfom	30 (13)	24 (11)	NA	NA
Adult T-celle-leukæmi/lymfom	4 (2)	3 (1)	NA	NA
Enteropati-associeret T-celle-lymfom	1 (0)	2 (1)	NA	NA
Mediantid fra diagnose til første dosis, måneder (interval)	0,8 (0 – 19)	0,9 (0 – 10)	0,8 (0 – 19)	0,9 (0 – 10)
Sygdomstade ved indledende diagnose, n (%)				
Stadie I	12 (5)	9 (4)	12 (7)	7 (5)
Stadie II	30 (13)	37 (16)	22 (14)	27 (18)
Stadie III	57 (25)	67 (30)	29 (18)	46 (30)
Stadie IV	127 (56)	113 (50)	99 (61)	74 (48)
IPI-score				
0	8 (4)	16 (7)	7 (4)	14 (9)
1	45 (20)	32 (14)	34 (21)	18 (12)

	ITT-populationen		sALCL-populationen	
2	74 (33)	78 (35)	58 (36)	60 (39)
3	66 (29)	66 (29)	37 (23)	40 (26)
4	29 (13)	25 (11)	22 (14)	16 (10)
5	4 (2)	9 (4)	4 (2)	6 (4)
Ekstranodal involvering på diagnosetidspunkt, n (%)				
≤ 1 sted	142 (63)	146 (65)	94 (58)	92 (62)
> 1 sted	84 (37)	80 (35)	68 (42)	59 (38)
Knoglemarvsbiopsi-lymfominvolvering ved baseline, n (%)				
Ja	30 (13)	34 (15)	15 (9)	13 (8)
Nej	196 (87)	192 (85)	147 (91)	141 (92)

Samlet set er studiepopulationens mediane alder (ITT-populationen, tabel 2) i overensstemmelse med den mediane alder i dansk klinisk praksis. Hovedparten af patienterne har som omtalt ovenfor udbredt sygdom og intermediær til høj IPI-risikoprofil, hvilket også stemmer overens med den danske population.

Fagudvalget vurderer, at der er visse uoverensstemmelser mellem gruppen af patienter med sALCL og den danske population, som kan have klinisk betydning i vurderingen af, om patienterne i dansk kontekst ville blive tilbudt standardbehandling med CHOP som i ECHELON-2. I Danmark er patienternes alder og almentilstand afgørende for behandlingsvalget, hvilket ikke er afspejlet i ECHELON-2, hvor komparator er CHOP uanfægtet patienternes alder og almentilstand. Fagudvalget vurderer ud fra baselinekarakteristika, at en betydelig del af patienterne med sALCL ville være blevet tilbudt behandling med CHOEP efterfulgt af konsoliderende HDT og ASCT i dansk klinisk praksis. Derfor har fagudvalget, som diskuteret nedenfor, kun fundet grundlag for at anvende data fra ECHELON-2 til en kategorisering i forhold til patienter, som i dansk klinisk praksis vil blive tilbudt behandling med CHOP. I Danmark tilbydes CHOP-behandling primært til patienter over 60 år og efterfølges for en mindre del også af konsoliderende HDT og ASCT (patienter mellem 60-70 år i god almen tilstand). Denne ældre undergruppe udgør kun en mindre del af sALCL-populationen i studiet (patienter over 60 år udgør ca. 36 % af patienterne med sALCL, og patienter over 65 år udgør under ¼ af patienterne med sALCL (23 %)). Det betyder, at studiepopulationen i ECHELON-2 samlet set må forventes at have en bedre prognose end de patienter, som i dansk klinisk praksis behandles med CHOP. Fagudvalget kan ikke vurdere, om dette har betydning for effektforholdet mellem brentuximab vedotin + CHP og CHOP, men det bidrager med usikkerhed i forhold til den eksterne validitet af studieresultaterne.

Fagudvalget vurderer desuden, at konsolidering med HDT og ASCT er en prognostisk betydende parameter. I dansk praksis afsluttes behandlingen med HDT, hvis patienten har opnået et tilfredsstillende respons på CHOP eller CHOEP. HDT anses for toksisk til patienter over 70 år og/eller hvis patienten har betydende komorbiditet. Evidensen bygger på retrospektive opgørelser og et større Nordisk studie uden randomisering, som tyder på at prognosen (overlevelse) forbedres sammenlignet med induktionsbehandling (CHOP eller CHOEP) alene. I ECHELON-2 var det op til den enkelte investigator, hvorvidt man ønskede at højdosisbehandle. Kun et mindretal af patienterne blev højdosisbehandlet antagelig som udtryk for, at det i flere lande ikke anses som standardpraksis. Da konsoliderende HDT og ASCT antages at være forbundet med en bedre prognose, kan effekten af brentuximab vedotin + CHP teoretisk være underestimeret i studiet sammenlignet med dansk klinisk praksis. Forskellen i anvendelsen af HDT mellem dansk praksis og ECHELON-2 vanskeliggør dog en overførsel af studieresultaterne til dansk klinisk praksis. Imidlertid er det velkendt ved aggressive lymfomtyper, at responsdybden før HDT er en betydningsfuld prognostisk faktor. Den prognostiske forbedring, brentuximab vedotin + CHP måtte give, vil derfor kunne antages også at forbedre prognosen efter HDT samt muliggøre, at flere patienter opnår et tilstrækkeligt respons, som muliggør HDT.

CHOEP vs. CHOP

Ansøger har inkluderet otte studier i deres redegørelse for, om effekten af CHOP er sammenlignelig med effekten af CHOEP, som også anvendes i dansk klinisk praksis. Studierne er angivet i listen nedenfor.

Tabel 2. Studier, som indgår i den narrative sammenligning mellem CHOP og CHOEP.

Forfatter, reference	Titel	Studiedesign
Schmitz N, Trümper L, Ziepert M et al. 2010 [6]	Treatment and prognosis of mature T-cell and NK-cell lymphoma: an analysis of patients with T-cell lymphoma treated in studies of the German High-Grade Non-Hodgkin Lymphoma Study Group	Retrospektiv analyse baseret på en række prospektive fase-II og III-studier. Herunder NHL-B1 (CHOP vs. CHOEP hos yngre ≤ 60) og NHL-B2 (CHOP vs. CHOEP hos ældre > 60). NHL-B1 og NHL-B2 inkluderer hovedsageligt patienter med b-celle lymfom
d'Amore F, Relander T, Lauritzsen GF et al. 2012 [7]	Up-Front Autologous Stem-Cell Transplantation in Peripheral T-Cell Lymphoma: NLG-T-01.	Prospektivt fase-II-studie
Kim YA, Byun JM, Park K et al. 2017 [10]	Redefining the role of etoposide in first-line treatment of peripheral T-cell lymphoma.	Retrospektivt kohortestudie (enkelt hospital) og nationalt registerstudie
Ellin F, Landström J, Jerkeman M et al. 2014 [8]	Real-world data on prognostic factors and treatment in peripheral T-cell lymphomas: a study from the Swedish Lymphoma Registry.	Retrospektivt registerbaseret kohortestudie
Cederleuf H, Bjerregård Pedersen M et al. 2017 [11]	The addition of etoposide to CHOP is associated with improved outcome in ALK+ adult anaplastic large cell lymphoma: A Nordic Lymphoma Group study.	Retrospektivt registerbaseret kohortestudie

Forfatter, reference	Titel	Studiedesign
Janikova A, Chloupkova R, Campr V et al. 2019 [12]	First-line therapy for T cell lymphomas: a retrospective population-based analysis of 906 T cell lymphoma patients.	Retrospektivt registerbaseret kohortestudie
Jia B, Hu S, Yang J et al. 2016 [13]	Comparison of gemcitabin, cisplatin, and dexamethasone (GDP), CHOP, and CHOPE in the first-line treatment of peripheral T-cell lymphomas.	Retrospektivt kohortestudie (to hospitaler)
Rattarittamrong E, Norasetthada L, Tantiwo-rawit A et al. 2013 [14]	CHOEP-21 chemotherapy for newly diagnosed nodal peripheral T-cell lymphomas (PTCLs) in Maharaj Nakorn Chiang Mai Hospital.	Retrospektivt kohortestudie (enkelt hospital)

Ansøger fremhæver, at der er en række forhold, som udfordrer studiernes sammenlignelighed og anvendelighed. Dette diskuteres yderligere i afsnit 5.1.2.

5.1.2 Databehandling og analyse

I dette afsnit er ansøgers datagrundlag, databehandling og analyse for hvert effektmål beskrevet.

Ansøger har indsendt et datagrundlag, som er i overensstemmelse med protokollen. Der indgår data for alle de ønskede effektmål. Ansøger har på baggrund af de identificerede studier i tabel 3 ikke fundet grundlag for at konkludere, at tilføjelse af etoposid til CHOP resulterer i betydelige forskelle i OS, PFS eller livskvalitet. Ansøger påpeger samtidig en række forhold ved den identificerede litteratur, som påvirker tiltroen til resultaterne, og anser det derfor for rimeligt at antage, at effekten af CHOEP er sammenlignelig med effekten af CHOP.

CHOP er ikke en repræsentativ komparator for hele populationen med sALCL i Danmark

Som tidligere nævnt, er der i Danmark tradition for at anvende det mere intensive CHOEP-regime efterfulgt af HDT og ASCT hos yngre patienter (< 60 år). Denne strategi er rekommanderet som standardbehandling hos yngre patienter i retningslinjen fra Dansk Lymfomgruppe og den europæiske behandlingsvejledning fra ESMO [1,2]. Anbefalingerne har afsæt i et ikke-randomiseret fase II-studie fra den Nordiske Lymfomgruppe, som viste positive resultater med HDT og ASCT [7]. Effektforholdet mellem CHOEP og CHOP er endnu ikke undersøgt i et prospektivt randomiseret forsøg hos patienter med perifert T-cellelymfom. Fagudvalget er enig med ansøger i, at den evidens, der foreligger for sammenligningen mellem CHOEP og CHOP, er usikker, og tolkbarheden derfor er udfordret. Imidlertid finder fagudvalget, at CHOEP til yngre patienter baseres på bedste foreliggende evidens og danner grundlag for anbefalet dansk praksis. Derfor bør CHOEP være sammenligningsgrundlag til patienter under 60 år.

Evidensgrundlaget for sammenligningen af CHOP og CHOEP består hovedsageligt af retrospektive observationelle studier. En oversigt over studierne inkl. resultater findes i

bilag 1. Der indgår generelt meget få patienter med sALCL i studierne. I flere studier er der risiko for selektionsbias, da der observeres forskelle på flere væsentlige prognostiske faktorer (f.eks. alder, IPI-score) mellem grupperne. Der er også stor heterogenitet mellem studierne, som inkluderer forskellige typer af perifert T-cellelymfom. Der er samtidig forskel i alder og risikoprofil (IPI-score og sygdomsstadie) på tværs af studierne. Studiernes forskelligheder giver stor variation i de rapporterede resultater. Nogle studier viser en gevinst på PFS (eller *event-free survival*) og i mindre grad OS ved behandling med CHOEP hos yngre, men det kan ikke udelukkes, at en del af effekten skyldes confounding. Modsat er der også flere studier, som ikke viser forskel i PFS og OS. I et enkelt koreansk studie ses en forbedret PFS og OS ved CHOP sammenlignet med CHOEP. De europæiske studier virker dog konsistente, hvad angår gevinst på PFS ved CHOEP behandling hos yngre (< 60 år) [6,8,11,12].
Da ansøger ikke i tilstrækkeligt omfang har sandsynliggjort, at CHOP og CHOEP er ligeværdige behandlinger, anser fagudvalget CHOEP, i overensstemmelse med dansk klinisk praksis og gældende nationale og europæiske retningslinjer, som den rette komparator hos yngre patienter med sALCL. Fagudvalget vurderer derfor, at ECHELON-2-studiet kun kan danne grundlag for en vurdering af brentuximab vedotin + CHP til patienter med sALCL, som i dansk klinisk praksis behandles med CHOP. Det vil sige CHOP kandidater i klinisk spørgsmål 1 (patienter over 60 år i god almen tilstand uden væsentlig komorbiditet som kandiderer til HDT og ASCT) og populationen i klinisk spørgsmål 2 (voksne som ikke kandiderer til HDT og ASCT). Fagudvalget har ikke fundet grundlag for at anvende de identificerede studier med CHOEP til en sammenligning med brentuximab vedotin + CHP. Derfor er det ikke muligt at kategorisere en værdi af brentuximab vedotin + CHP i forhold til CHOEP.

Analyser fra ECHELON-2

Alle analyser er subgruppeanalyser baseret på data fra ECHELON-2-studiet. Den eneste analyse, hvor det er rimeligt at antage, at randomiseringen er bevaret, er for subgruppen ALK+ sALCL, som indgår som stratifikationsfaktor i randomiseringen. For de øvrige subgrupper, inkl. ansøgningens hovedanalyse, baserer analyserne sig på populationer, som ikke entydigt består af hele strata fra randomiseringen. Som ansøger også konstaterer, er flere af subgruppeanalyserne desuden gennemført med udgangspunkt i få patienter (og lave observerede hændelsesrater) og vil derfor være sårbare overfor tilfældige udslag.

Ansøgningens hovedanalyse inkluderer alle patienter med sALCL. På trods af, at der er tale om en subgruppeanalyse, og randomiseringen derfor ikke med sikkerhed er bevaret, vurderer fagudvalget ikke, at det giver anledning til bekymring. Fagudvalget vurderer, at risiko for bias ift. randomisering er minimal, da patient- og sygdomskarakteristika hos patienter behandlet med henholdsvis brentuximab vedotion + CHP og CHOP i subgruppen med sALCL er velbalanceret (tabel 2).

Data i ansøgningen fra ECHELON-2-studiet baserer sig på data fra data-cut-off den 15. august 2018, som svarer til det prædefinerede tidspunkt for analysen af det primære effektmål (*primary efficacy analysis*). I forbindelse med sagsbehandlingen er sekretariatet blevet bekendt med en opdateret analyse for effektmålet OS, som baserer

sig på et senere data-cut-off (september 2019). Sekretariatet har været i dialog med ansøger om dette. Ansøger har angivet, at den seneste analyse udelukkende er lavet som en supplerende analyse på opfordring fra EMA, og at data derfor ikke har gennemgået samme rigide dataoprensning og kvalitetssikring (herunder *survival sweep),* som tilfældet er, når der er foretaget en formel *database lock*. Derfor vil effektestimaterne fra det første data-cut-off danne grundlag for kategoriseringen af den foreløbige kategori for dette effektmål, mens analysen ved det senere data cut-off inddrages som støtte i den samlede vurdering for effektmålet OS.

I forbindelse med sagsbehandlingen har ansøger indsendt 5-års data for OS og PFS fra ECHELON-2-studiet. Data blev præsenteret ved den årlige konference afholdt af *American Society of Hematology* i december 2020. OS-data for populationen med sALCL er ikke publiceret, mens PFS-data og data fra studiets ITT-population er offentliggjort i et abstract fra konferencen [15]. I lighed med ovenstående inddrages 5-års data som støtte i den samlede vurdering af effektmålene OS og PFS.

5.1.3 Evidensens kvalitet

Medicinrådet har anvendt GRADE til at foretage en systematisk og transparent vurdering af kvaliteten af evidensen. Den fuldstændige GRADE-vurdering og begrundelserne er samlet i en GRADE-profil (bilag 2).

Evidensens kvalitet er meget lav, hvilket betyder, at nye studier med høj sandsynlighed kan ændre konklusionen.

Vurdering af risikoen for bias fremgår af bilag 2.

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 sammenligning mellem brentuximab vedotin + CHP og CHOP i klinisk spørgsmål 1 og 2.

Tabel 3. Resultater for sammenligning af brentuximab vedotin + CHP vs. CHOP i klinisk spørgsmål 1 og 2

Effektmål	Målenhed (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 OS i måneder (6 måneder)	Kritisk	Ikke nået	Kan ikke kategoriseres	HR 0,54 (0,34; 0,87)	Moderat merværdi	Merværdi af ukendt størrelse
	Andel af patienter, der opnår 2-års overlevelse (5 %-point)		[redacted]	Kan ikke kategoriseres			
Progressionsfri overlevelse (PFS)	Median PFS i måneder (6 måneder)	Kritisk	1,48 måneder	Kan ikke kategoriseres	HR 0,59 (0,42; 0,84)	Moderat merværdi	Moderat merværdi
	Andel af patienter, der opnår 2-års PFS (5 %-point)		14,5 %-point	Kan ikke kategoriseres			
Livskvalitet	Gennemsnitlig ændring fra baseline på EORTC QLQ-C30 til efter endt behandling (10 point)	Vigtig	[redacted]	Kan ikke kategoriseres			Kan ikke kategoriseres
	Gennemsnitlig ændring fra baseline på EORTC QLQ-C30 til efter endt opfølgning (10 point)		[redacted]	Kan ikke kategoriseres			
Uønskede hændelser	Andel, som ophører behandlingen pga. uønskede hændelser (behandlingsophør) (5 %-point)	Vigtig	[redacted]	Ingen dokumenteret merværdi	[redacted]	Ingen dokumenteret merværdi	Ingen dokumenteret merværdi
	Andel patienter med uønskede hændelser grad 3 og grad 4 (10 %-point)		[redacted]	Kan ikke kategoriseres	[redacted]	Ingen dokumenteret merværdi	
Konklusion							
Samlet kategori for lægemidlets værdi	Merværdi af ukendt størrelse						
Kvalitet af den samlede evidens	Meget lav						

CI = konfidensinterval, HR = Hazard Ratio, OR = Odds Ratio, RR = relativ risiko

Samlet overlevelse (OS)

Som beskrevet i protokollen er effektmålet OS kritisk for vurderingen af lægemidlets værdi for patienterne, fordi det belyser patientpopulationens levetid og dermed den potentielle overlevelsesgevinst ved interventionen.

Punktestimatet for den absolutte forskel mellem OS-raterne efter 2 år afspejler en klinisk relevant forskel, da forskellen på [redacted] er større end den mindste klinisk relevante forskel på 5 %-point. Andelen af patienter, som er i live efter 2 år, var [redacted] i brentuximab vedotin-armen mod [redacted] i CHOP-armen. Der er ikke noget konfidensinterval omkring forskellen på 2-års OS, hvorfor den foreløbige værdi ikke kan kategoriseres. Den absolutte forskel for 2-års OS er afbildet i figur 1 nedenfor.

Patienterne i studiet er ikke fulgt tilstrækkelig længe til, at den mediane OS er nået. Derfor kan den foreløbige værdi ikke kategoriseres for forskellen i median OS.

[redacted]

Baseret på den relative effektforskel ved data-cut-off i august 2018 (HR 0,54 (0,34; 0,87)), som fremgår af tabel 3, har brentuximab vedotin i kombination med CHP foreløbigt en moderat merværdi vedr. OS. I EMAs vurderingsrapport foreligger desuden OS-data fra et senere opfølgningstidspunkt (data-cut-off: september 2019). Den relative effektforskel er her opgjort til HR 0,63 (0,40; 0,99). Ansøger har desuden fremsendt 5-års data, som viser en relativ effektforskel på HR [redacted]. Punktestimaterne og de øvre grænser i konfidensintervallerne ved de senere opfølgningstidspunkter indikerer, at der er en tendens til, at effekten er svagt faldende. Der kan være flere årsager til dette, bl.a. anvendelse af brentuximab vedotin i de efterfølgende behandlingslinjer, som

ikke er balanceret mellem de to arme. I ITT-populationen har 22 % af patienterne efterfølgende modtaget brentuximab vedotin i CHOP-armen mod 10 % i brentuximab vedotin + CHP-armen [9]. Fagudvalget vurderer, at det er et udtryk for, at data er umodne og dermed skal tolkes med en vis forsigtighed.

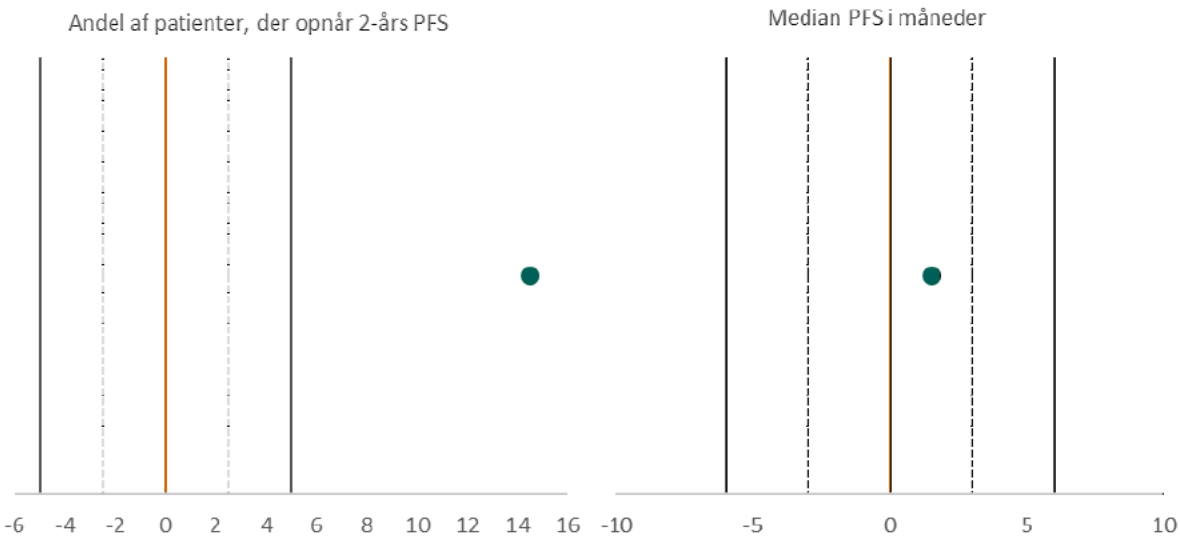
Fagudvalget vurderer, at brentuximab vedotin i kombination med CHP aggregeret har en merværdi af ukendt størrelse vedr. OS. Dette begrundes med den moderate merværdi for den relative effektforskel og forskellen mellem OS-raterne efter 2 år, som afspejler en klinisk relevant forskel mellem grupperne. Som forventet foreligger der ikke data for median OS, og data kan derfor ikke betragtes som modne. Samtidig bidrager data ved de senere opfølgningstidspunkter også med usikkerhed i forhold til kategoriseringen for dette effektmål.

Progressionsfri overlevelse (PFS)
Som beskrevet i protokollen er effektmålet PFS vigtigt for vurderingen af lægemidlets værdi for patienterne, fordi det er et udtryk for graden og længden af sygdomskontrol, som opnås ved og efter 1. linjebehandling. Det komplementerer OS, idet OS kan være påvirket af de efterfølgende behandlingslinjer.

Punktestimatet for den absolutte forskel mellem PFS-raterne efter 2 år afspejler en klinisk relevant forskel, da forskellen på 14,5 %-point er større end den mindste klinisk relevante forskel på 5 %-point. Andelen uden progression efter 2 år var 68,4 % (60,4; 75,2) i brentuximab vedotin-armen og 53,9 % (45,5; 61,5) i CHOP-armen. Der er ikke noget konfidensinterval omkring forskellen på 2-års PFS, hvorfor den foreløbige værdi ikke kan kategoriseres.

Punktestimatet for den absolutte forskel i median PFS afspejler ikke en klinisk relevant forskel, da forskellen på 1,5 måneder er mindre end den mindste klinisk relevante forskel på 6 måneder. Den mediane PFS i brentuximab vedotin-armen var 55,7 måneder, mens den var 54,2 måneder i CHOP-armen. Der er ikke noget konfidensinterval omkring forskellen i median PFS, hvorfor den foreløbige værdi ikke kan kategoriseres.
[redacted]

De absolutte forskelle er afbildet i figur 2 nedenfor.



Figur 2. Punktestimat og 95 % konfidensinterval for de absolutte forskelle i 2-års PFS (til venstre) og median PFS (til højre). 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.

Baseret på den relative effektforskel (HR 0,59 (0,42; 0,84)), som fremgår af tabel 3, har brentuximab vedotin i kombination med CHP foreløbigt en moderat merværdi vedr. PFS. Data efter 5-års opfølgning bekræfter kategoriseringen af PFS, idet den relative effektforskel er HR 0,55 (0,39; 0,78).

Fagudvalget vurderer, at brentuximab vedotin i kombination med CHP aggregeret har en moderat merværdi vedr. PFS. Dette begrundes med en moderat merværdi for den relative effektforskel og forskellen i PFS-raterne ved 2 år, som afspejler en klinisk relevant forskel mellem grupperne. Den mindste klinisk relevante forskel på 14,5 %-point ligger noget højere end den mindste klinisk relevante forskel på 5 %-point. Fagudvalget har lagt mindre vægt på median PFS, da forskellen i median vurderes at være usikker grundet manglende modenhed i data. Medianerne ved det første opfølgningstidspunkt opnås først efter ca. 4,5 år, og der observeres et betydeligt antal censureringer på Kaplan-Meier kurverne inden dette tidspunkt.

[redacted]

Livskvalitet

Som beskrevet i protokollen er effektmålet livskvalitet vigtigt for vurderingen af lægemidlets værdi for patienterne, fordi både sygdomsbyrde og toksicitet af behandlingen kan have markant indflydelse på patienternes livskvalitet.

Fagudvalget har ønsket livskvalitet opgjort som ændring fra baseline på den globale EORTC QLQ-C30 livskvalitetsskala frem til endt behandling og endt opfølgning.

Punktestimatet for de absolutte effektforskelle afspejler ikke klinisk relevante effektforskelle. Konfidensintervallerne er brede og indeholder både negative og positive værdier. Derfor kan de foreløbige værdier af brentuximab vedotin i kombination med CHP vedr. livskvalitet efter endt behandling og efter endt opfølgning ikke kategoriseres efter Medicinrådets metoder.

De absolutte forskelle er afbildet i figur 3 nedenfor.

Idet der er tale om et kontinuert effektmål, findes der ikke data på den relative effektforskel, og effektmålet kategoriseres derfor udelukkende på baggrund af de absolutte effektforskelle.

På aggregeret niveau vurderer fagudvalget, at værdien af brentuximab vedotin i kombination med CHP ikke kan kategoriseres vedr. livskvalitet, fordi konfidensintervallerne for de absolutte forskelle indeholder klinisk betydende positive og negative værdier. Data tyder ikke på, at der er en livskvalitetsgevinst ved behandling med brentuximab vedotin i kombination med CHP sammenlignet med CHOP. Omvendt er der heller ikke noget, der tyder på, at behandling med brentuximab vedotin i kombination med CHP forringer patienternes livskvalitet sammenlignet med CHOP.

Uønskede hændelser
Som beskrevet i protokollen er effektmålet uønskede hændelser vigtigt for vurderingen af lægemidlets værdi for patienterne, fordi eventuelle bivirkninger har stor betydning for den enkelte patients livskvalitet og vilje til at forblive i en behandling over længere tid.

Punktestimatet for den absolutte effektforskel for andelen af patienter, som ophører med behandling på grund af uønskede hændelser, afspejler en klinisk relevant effektforskel. I brentuximab vedotin-armen er der [redacted] uf ad 160 patienter, som ophører med behandling på grund af en uønsket hændelse, mens det tilsvarende tal i CHOP-armen er [redacted] ud af 154. Den øvre grænse for konfidensintervallet er tættere på 0 (ingen effekt) end på en klinisk relevant forskel til fordel for CHOP. Derfor er den foreløbige værdi af brentuximab vedotin i kombination med CHP ingen dokumenteret merværdi.

Punktestimatet for den absolutte effektforskel for andelen af patienter med uønskede hændelser grad 3 og grad 4 afspejler ikke en klinisk relevant effektforskel. I brentuximab vedotin-armen oplevede [redacted] af patienterne en grad 3 eller 4 uønsket hændelse. Det tilsvarende tal i CHOP-armen var [redacted]. Den øvre grænse for konfidensintervallet ligger tættere på en klinisk relevant forskel til fordel for CHOP end på 0 (ingen effektforskel). Derfor kan den foreløbige værdi af brentuximab vedotin i kombination med CHP ikke kategoriseres efter Medicinrådets metoder.

Den absolutte forskel er afbildet i figur 4 nedenfor.

[redacted]

Baseret på de relative effektforskelle på RR [redacted] og RR [redacted], som fremgår af tabel 3, har brentuximab vedotin i kombination med CHP foreløbigt ingen dokumenteret merværdi vedr. uønskede hændelser.

Kvalitativ gennemgang af bivirkninger

Brentuximab vedotin har en velkendt bivirkningsprofil. De rapporterede uønskede hændelser fra ECHELON-2 stemmer overens med den kendte bivirkningsprofil. Blandt de kendte og hyppigst forekommende bivirkninger kan nævnes infektioner, neutropeni, perifer sensorisk og motorisk neuropati samt de gastrointestinale bivirkninger som kvalme, obstipation, opkastning, diarré, abdominalsmerter og stomatit. I studiet er sikkerhedsprofilen overordnet ens på tværs af alle histologiske undertyper, og de mest almindelige uønskede hændelser forekom med tilsvarende frekvenser i alle undertyper. I studiet var forekomst, type og sværhedsgrad af uønskede hændelser i brentuximab vedotin-armen sammenlignelige med CHOP-armen. Toksiciteten af brentuximab vedotin + CHP betragtes generelt som håndterbar.

Fagudvalget vurderer, at brentuximab vedotin i kombination med CHP aggregeret har ingen dokumenteret merværdi vedr. uønskede hændelser. Dette begrundes med sammenlignelige frekvenser af behandlingsophør grundet uønskede hændelser og grad 3-4 hændelser ved de to behandlinger. Toksiciteten af brentuximab vedotin + CHP betragtes som håndterbar og i øvrigt sammenlignelig med CHOP.

Det er fagudvalgets erfaring, at tilføjelse af etoposid til CHOP giver en kraftigere knoglemarvspåvirkning, tendens til hyppigere infektion, hyppigere træthed og stomatit. Disse bivirkninger ved CHOEP er tidligere observeret i to store randomiserede studier hos patienter med aggressive lymfomer (primært b-celle lymfomer) [16,17].

5.1.5 Fagudvalgets konklusion

Klinisk spørgsmål 1

Sammenligning med CHOP

Samlet set vurderer fagudvalget, at brentuximab vedotin + CHP jf. Medicinrådets metoder har en merværdi af ukendt størrelse i sammenligning med CHOP hos voksne ≥ 60 år med tidligere ubehandlet systemisk anaplastisk storcellet T-cellelymfom, som kandiderer til HDT og ASCT.

Dette er begrundet med en merværdi af ukendt størrelse på det kritiske effektmål OS, som viser en mindre dødelighed hos patienter behandlet med brentuximab vedotin i kombination med CHP sammenlignet med CHOP. I kategoriseringen af OS er der inddraget upubliceret data med længere opfølgningstid. Effekten på OS understøttes også af effekten på PFS, som viser en moderat merværdi og dermed reduceret risiko for progression og en betydelig højere andel af patienter uden progression efter 2 år. Data for OS og PFS er behæftet med en vis usikkerhed, da data forsat er umodne. Der foreligger endnu ikke data for median OS, og data for median PFS må anses for at være meget usikkert.

[redacted]

[redacted] Der er ikke tegn på forskelle i livskvalitet og uønskede hændelser ved behandling med brentuximab vedotin i kombination med CHP sammenlignet med CHOP. Det betyder, at brentuximab vedotin i kombination med CHP samlet set giver en gevinst på overlevelse uden at påvirke patienternes livskvalitet og uden at give flere bivirkninger.

Sammenligning med CHOEP

Fagudvalget finder ikke grundlag for at ekstrapolere effekten af brentuximab vedotin + CHP overfor CHOP med henblik på at kategorisere værdien af brentuximab vedotin + CHP overfor CHOEP. Dette er begrundet med, at CHOEP er standardpraksis i Danmark på baggrund af bedst foreliggende evidens. Den eksisterende evidens på området, der er svag, består af ukontrollerede og/eller observationelle studier, som indikerer, at behandling med CHOEP giver bedre PFS end behandling med CHOP hos yngre patienter. Værdien af brentuximab vedotin + CHP overfor CHOEP kan derfor ikke kategoriseres jf. Medicinrådets metoder for voksne < 60 år med tidligere ubehandlet systemisk anaplastisk storcellet T-cellelymfom, som kandiderer til HDT og ASCT.

Klinisk spørgsmål 2
Samlet set vurderer fagudvalget, at brentuximab vedotin + CHP jf. Medicinrådets metoder har en merværdi af ukendt størrelse i sammenligning med CHOP for voksne med tidligere ubehandlet systemisk anaplastisk storcellet T-cellelymfom, som ikke kandiderer til HDT og ASCT.

Dette er begrundet med en merværdi af ukendt størrelse på det kritiske effektmål OS, som viser en mindre dødelighed hos patienter behandlet med brentuximab vedotin i kombination med CHP sammenlignet med CHOP. I kategoriseringen af OS er der inddraget upubliceret data med længere opfølgningstid. Effekten på OS understøttes også af effekten på PFS, som viser en moderat merværdi og dermed reduceret risiko for progression og en betydelig højere andel af patienter uden progression efter 2 år. Data for OS og PFS er behæftet med en vis usikkerhed, da data forsat er umodne. Der foreligger endnu ikke data for median OS, og data for median PFS må anses for at være meget usikkert.

[redacted] Der er ikke tegn på forskelle i livskvalitet og uønskede hændelser ved behandling med brentuximab vedotin i kombination med CHP sammenlignet med CHOP. Det betyder, at brentuximab vedotin i kombination med CHP samlet set giver en gevinst på overlevelse uden at påvirke patienternes livskvalitet og uden at give flere bivirkninger.

Tidligere ubehandlede ALK-positive voksne med lav IPI-score er ikke inkluderet i ECHELON-2-studiet og værdien af brentuximab vedotin + CHP kan derfor ikke kategoriseres for denne gruppe af patienter.

6. Andre overvejelser

6.1 Opgørelse af effekt for ALK-ekspression, IPI og alder

Ansøger har indsendt data for OS og PFS stratificeret efter ALK-status (ALK-negativ og ALK-positiv), IPI-score (lav (0-1), intermediær (2-3) og høj IPI-score (> 3)) og alder (≤ 60 år og > 60 år).

Fagudvalget vurderer, at data for de forskellige subgrupper understøtter den effekt, som observeres i den samlede population af patienter med sALCL. Der observeres ikke tendenser til, at effekten skulle være forbeholdt specifikke subgrupper. Data skal tolkes med varsomhed, da flere af analyserne tager udgangspunkt i få patienter (og lave observerede hændelsesrater) og vil derfor være sårbare overfor tilfældige udslag. Det kan heller ikke med sikkerhed antages, at randomiseringen er opretholdt for subgruppeanalyserne, og det må derfor betragtes som ikke-randomiserede sammenligninger.

Se nedenstående tabel 4 over subgruppedata.

Tabel 4. Resultater stratificeret efter vigtige prognostiske faktorer.

Subgruppe	Events/N, BV+CHP	Events/N, CHOP	OS, Hazard ratio (95 % CI)	Median OS, måneder	2-års OS, %-point	Events/N, BV+CHP	Events/N, CHOP	PFS, Hazard ratio (95 % CI)	Median PFS, måneder	2-års PFS, %-point
Samlet population										
sALCL	29/162	44/154	0,54 (0,34; 0,87)	Ikke nået	[redacted]	56/163	73/151	0,59 (0,42; 0,84)	1,48	14,5
ALK-status										
ALK+	4/49	10/49	0,38 (0,12; 1,22)	[redacted]	[redacted]	5/49	16/49	0,29 (0,11; 0,79)	[redacted]	[redacted]
ALK-	25/113	34/105	0,58 (0,35; 0,98)	[redacted]	[redacted]	50/113	60/105	0,65 (0,44; 0,95)	[redacted]	[redacted]
IPI-score										
IPI 0-1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IPI 2-3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IPI 4-5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alder										
< 60 år	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥ 60 år	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ALK-status og IPI										
ALK+ / IPI 0-1					Ikke inkluderet i studiet					
ALK+ / IPI 2-3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ALK+ / IPI 4-5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ALK- / IPI 0-1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ALK- / IPI 2-3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ALK- / IPI 4-5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

6.2 Efterfølgende behandlingslinjer

Brug af brentuximab vedotin som monoterapi er en potentiel behandlingsstrategi for patienter med tilbagefald.

Ifølge ansøger bør brentuximab vedotin overvejes som en potentiel behandlingsstrategi i anden linje, selv efter anvendelse i første linje. Dette baseres på objektive responsrater hos et mindretal af patienter i ECHELON-2-studiet (n = 23), som efter behandling i første linje, er behandlet med brentuximab vedotin i anden linje. Ansøger fremhæver desuden et andet tidligere studie, hvor 8 patienter med recidiverende sALCL er forsøgt genbehandlet med brentuximab vedotin monoterapi [18].

Fagudvalget vurderer ikke, at brentuximab vedotin vil være et relevant behandlingsvalg i anden linje, hvis det allerede er anvendt i første linje.

7. Fagudvalgets samlede konklusion

Fagudvalget vurderer, at brentuximab vedotin + CHP jf. Medicinrådets metoder har en merværdi af ukendt størrelse sammenlignet med CHOP. Dette indbefatter:

- ældre ≥ 60 år med tidligere ubehandlet systemisk anaplastisk storcellet T-cellelymfom, som kandiderer til HDT og ASCT.
- voksne (uanset alder) med tidligere ubehandlet systemisk anaplastisk storcellet T-cellelymfom, som ikke kandiderer til HDT og ASCT.

Denne patientpopulation vurderes af fagudvalget at inkludere ca. 5-10 patienter om året.

Værdien af brentuximab vedotin + CHP kan ikke kategoriseres jf. Medicinrådets metoder når det sammenlignes med:

- CHOEP hos voksne < 60 år som kandiderer til HDT og ASCT.
- CHOP til voksne med ALK-positiv sALCL med lav IPI-score.

Selvom der ikke foreligger direkte sammenlignende studier mellem brentuximab vedotin + CHP og CHOEP er det vanskeligt at underkende brentuximab vedotin + CHP som et muligt behandlingsalternativ til de yngre patienter som i dag tilbydes CHOEP. ECHELON-2 studiet viser lovende OS- og PFS-data ved en sammenligning med CHOP. De samme overbevisende data foreligger ikke for en sammenligning mellem CHOEP vs. CHOP.

8. Relation til behandlingsvejledning

Der findes ikke en relevant behandlingsvejledning fra Medicinrådet på området.

9. Referencer

1. Dansk Lymfomgruppe. ANBEFALINGER FOR DIAGNOSTIK OG BEHANDLING AF PERIFERE T-CELLE LYMFOMER (PTCL). 2017;
2. d'Amore F, Gaulard P, Trümper L, Corradini P, Kim W-S, Specht L, et al. Peripheral T-cell lymphomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2015;26:v108–15.
3. Sibon D, Fournier M, Brière J, Lamant L, Haioun C, Coiffier B, et al. Long-Term Outcome of Adults With Systemic Anaplastic Large-Cell Lymphoma Treated Within the Groupe d'Étude des Lymphomes de l'Adulte Trials. J Clin Oncol. 2012;30(32):3939–46.
4. EMA- European Medicines Agency. Produktresumé Adcetris. London; 2018.
5. Francisco JA, Cerveny CG, Meyer DL, Mixan BJ, Klussman K, Chace DF, et al. cAC10-vcMMAE, an anti-CD30-monomethyl auristatin E conjugate with potent and selective antitumor activity. Blood. 2003;102(4):1458–65.
6. Schmitz N, Trümper L, Ziepert M, Nickelsen M, Ho AD, Metzner B, et al. Treatment and prognosis of mature T-cell and NK-cell lymphoma: an analysis of patients with T-cell lymphoma treated in studies of the German High-Grade Non-Hodgkin Lymphoma Study Group. Blood. 2010;116(18):3418–25.
7. d'Amore F, Relander T, Lauritzsen GF, Jantunen E, Hagberg H, Anderson H, et al. Up-Front Autologous Stem-Cell Transplantation in Peripheral T-Cell Lymphoma: NLG-T-01. J Clin Oncol. 2012;30(25):3093–9.
8. Ellin F, Landström J, Jerkeman M, Relander T. Real-world data on prognostic factors and treatment in peripheral T-cell lymphomas: a study from the Swedish Lymphoma Registry. Blood. 2014;124(10):1570–7.
9. Horwitz S, O'Connor OA, Pro B, Illidge T, Fanale M, Advani R, et al. Brentuximab vedotin with chemotherapy for CD30-positive peripheral T-cell lymphoma (ECHELON-2): a global, double-blind, randomised, phase 3 trial. Lancet. 2019;393(10168):229–40.
10. Kim YA, Byun JM, Park K, Bae GH, Lee D, Kim DS, et al. Redefining the role of etoposide in first-line treatment of peripheral T-cell lymphoma. Blood Adv. 2017;1(24):2138–46.
11. Cederleuf H, Bjerregård Pedersen M, Jerkeman M, Relander T, D'Amore F, Ellin F. The addition of etoposide to CHOP is associated with improved outcome in ALK+ adult anaplastic large cell lymphoma: A Nordic Lymphoma Group study. Br J Haematol. 2017;178(5):739–46.
12. Janikova A, Chloupkova R, Campr V, Klener P, Hamouzova J, Belada D, et al. First-line therapy for T cell lymphomas: a retrospective population-based analysis of 906 T cell lymphoma patients. Ann Hematol. 2019;98(8):1961–72.
13. Jia B, Hu S, Yang J, Zhou S, Liu P, Qin Y, et al. Comparison of gemcitabin, cisplatin, and dexamethasone (GDP), CHOP, and CHOPE in the first-line treatment of peripheral T-cell lymphomas. Hematology. 2016;21(9):536–41.
14. Rattarittamrong E, Norasetthada L, Tantiworawit A, Chai-Adisaksopha C, Nawarawong W. CHOEP-21 chemotherapy for newly diagnosed nodal peripheral T-cell lymphomas (PTCLs) in Maharaj Nakorn Chiang Mai Hospital. J Med Assoc Thai. 2013;96(11):1416–22.
15. Horwitz S, O'Connor OA, Pro B, Illidge T, Iyer S, Advani R, et al. The Echelon-2 Trial: 5-Year Results of a Randomized, Double-Blind, Phase 3 Study of Brentuximab Vedotin and CHP (A+CHP) Versus CHOP in Frontline Treatment of Patients with CD30-Positive Peripheral T-Cell Lymphoma. I: 62nd ASH Annual Meeting and Exposition. 2020. s. Abstract #1150.
16. Pfreundschuh M, Trümper L, Kloess M, Schmits R, Feller AC, Rudolph C, et al. Two-weekly or 3-weekly CHOP chemotherapy with or without etoposide for the

treatment of young patients with good-prognosis (normal LDH) aggressive lymphomas: results of the NHL-B1 trial of the DSHNHL. Blood. 2004;104(3):626–33.
17. Pfreundschuh M, Trümper L, Kloess M, Schmits R, Feller AC, Rübe C, et al. Two-weekly or 3-weekly CHOP chemotherapy with or without etoposide for the treatment of elderly patients with aggressive lymphomas: results of the NHL-B2 trial of the DSHNHL. Blood. 2004;104(3):634–41.
18. Bartlett NL, Chen R, Fanale MA, Brice P, Gopal A, Smith SE, et al. Retreatment with brentuximab vedotin in patients with CD30-positive hematologic malignancies. J Hematol Oncol. 2014;7:24.

10. Sammensætning af fagudvalg og kontaktinformation til Medicinrådet

Medicinrådets fagudvalg vedrørende lymfekræft (lymfomer)

Sammensætning af fagudvalg	
Formand	**Indstillet af**
Lars Møller Pedersen *Forskningsansvarlig overlæge*	Lægevidenskabelige Selskaber og udpeget af Region Hovedstaden
Medlemmer	**Udpeget af**
Jakob Madsen *Ledende overlæge*	Region Nordjylland
Paw Jensen *Overlæge*	Region Nordjylland
Ida Blok Sillesen *Afdelingslæge*	Region Midtjylland
Jacob Haaber Christensen *Overlæge, ph.d.*	Region Syddanmark
Dorte Maegaard Tholstrup *Afdelingslæge, ph.d.*	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
Tidligere medlemmer, som har bidraget til arbejdet	**Udpeget af**
Peter Kamper *Overlæge, ph.d.*	Region Midtjylland

Sammensætning af fagudvalg	
Øvrige medlemmer, som ikke har bidraget til arbejdet	**Udpeget af**
Torsten Holm Nielsen *Speciallæge i hæmatologi, afdelingslæge*	Region Hovedstaden
Rikke Bech *Afdelingslæge*	Dansk Dermatologisk Selskab
Maria Kamstrup *Afdelingslæge*	Dansk Dermatologisk Selskab

Medicinrådets sekretariat

Medicinrådet
Dampfærgevej 27-29, 3.th.
2100 København Ø
+45 70 10 36 00
medicinraadet@medicinraadet.dk

11. Versionslog

Versionslog		
Version	**Dato**	**Ændring**
1.0	27. januar 2021	Godkendt af Medicinrådet

12. Bilag 1: Oversigt over studier, der sammenligner CHOEP med CHOP

Studie, år, land	Baselinekarakteristika							Effektmål				Kommentar
	Alder	IPI		Sygdomsstadie		Andel sALCL		PFS		OS		
		CHOP	CHOEP	CHOP	CHOEP	CHOP	CHOEP	CHOP	CHOEP	CHOP	CHOEP	
Schmitz, 2010, Tyskland	Median: 50 år (18 – 78) < 60 år: 70 % (224/320)	0-1: 51 % (163) 2-3: 40 % (128) 4-5: 9 % (29)		III-IV: 51 % (163)		60 % (191/320) ALK+: 24 % (78) ALK-: 35 % (113)		Yngre < 60 år 3-års EFS: 51,0 % (35,7; 66,3)	Yngre < 60 år 3-års EFS: 75,4 % (62,1; 88,7)	IA	IA	Gælder yngre (< 60 år) EFS: p = 0,003, OS ikke forskellig (p = 0,176). Intensivering af tidsintervallet fra 3 til 2 uger (CHOP-21 vs CHOP-14), administration af 8 i stedet for 6 serier CHOP-14 eller tilføjelse af etoposid (CHOEP) havde ingen mereffekt hos ældre. Stor andel med IPI 0-1.
d'Amore, 2012, Danmark	Samlet: Median: 57 år (22-67) CHOP: Median 64 år (61 – 67) CHOEP: IA	0-1: 10 % (4/42) 2-3: 50 % (21/42) 4-5:	IA	III-IV: 81 % (129)		19 % (31/160) ALK+: 0 % ALK-: 19 % (31)		5-års PFS: 34 %	5-års PFS: 39 %	5-års OS: 45 %	5-års OS: 39 %	Effekt CHOP (Alder 61 - 67 år) vs. CHOEP (Alder 55 – 60 år) er ens.

Studie, år, land	Baselinekarakteristika							Effektmål				Kommentar
	Alder	IPI		Sygdomsstadie		Andel sALCL		PFS		OS		
		CHOP	CHOEP	CHOP	CHOEP	CHOP	CHOEP	CHOP	CHOEP	CHOP	CHOEP	
		40 % (17/42)										
Kim, 2017, Korea	Kohorte 1: Median 59 år (20 – 89) Kohorte 2: Median 58 år (20 – 91)	IA	IA	Kohorte 1: I-II: 20 % (26/131) III-IV: 80 % (105/131) Kohorte 2: I-II: 26 % (511/1933) III-IV: 35 % (674/1933) Ukendt: 39 % (748/1933)		Kohorte 1: 21 % (48/131) ALK+: IA ALK-: IA Kohorte 2: 17 % (326/1933) ALK+: IA ALK-: IA		Kohorte 1: Median 11 måneder Kohorte 2: 6,5 måneder	Kohorte 1: Median 9 måneder Kohorte 2: 4,9 måneder	Kohorte 1: 5-års OS 18,2 % Kohorte 2: 5-års OS 27,1 %	Kohorte 1: 5-års OS 5,0 % Kohorte 2: 5-års OS 17,9 %	Der fremgår ikke karakteristika for CHOP vs. CHOEP. Analyse af to kohorter. Kohorte 1: SNUH og kohorte 2: KCCR. I kohorte 1 blev der ikke fundet forskelle i OS eller PFS mellem CHOP (N = 77) og CHOEP (N = 20). I kohorte 2 ses en OS- og PFS-fordel for patienter behandlet med CHOP (N = 646) vs. CHOEP (N = 609).
Ellin, 2014, Sverige	CHOP: Median 65 år (18 – 70) CHOEP: Median 52 år (24 – 69)	0-1: 37 % (39/107) 2-3: 53 % (57/107) 4-5: 7 % (7/107)	0-1: 23 % (32/145) 2-3: 54 % (76/145) 4-5: 23 % (32/145)	I: 14 % (20) II: 19 % (27) III: 25 % (36) IV: 42 % (61)	I: 9 % (10) II: 24 % (26) III: 21 % (22) IV: 46 % (49)	17 % (25) ALK+: 0 % ALK-: 17 % (25)	25 % (27) ALK+: 0 % ALK-: 25 % (27)	5-års PFS: 23 %	5-års PFS: 40 %	5-års OS: 30 %	5-års OS: 47 %	Hos patienter < 60 år ses en gavnlig virkning på PFS ved tilføjelse af etoposid. Kan muligvis forklares med færre komorbiditeter hos patienter behandlet med CHOEP. Hvis analysen inkluderede patienter op til 70 år, var der ikke længere nogen effekt ved tilføjelse af etoposid. <u>18 – 70 år</u> OS: HR: 0,78; P = 0,288 PFS: HR: 0,84; P = 0,424 <u>18 – 60 år</u> OS: HR: 0,58 (0,33; 1,01); P = 0,052 PFS: HR: 0,49 (0,29; 0,83); P = 0,008

Studie, år, land	Alder	Baselinekarakteristika						Effektmål				Kommentar
		IPI		Sygdomsstadie		Andel sALCL		PFS		OS		
		CHOP	CHOEP	CHOP	CHOEP	CHOP	CHOEP	CHOP	CHOEP	CHOP	CHOEP	
Cederleuf, 2017, Danmark/ Sverige	Median: 40 år CHOP: Median 48 år (19 – 85) CHOEP: Median 42 år (18 – 66)	0-1: 53 % (68/122) 2-5: 47 % (54/122)		III-IV: 54 % (65/122)		100 % (122) ALK+: 100 % (122) ALK-: 0 %		CHOEP vs. CHOP Ikke-justeret HR: 0,48 (0,24; 0,95); P = 0,034 <u>Alder 41-65 år</u> HR: 0,45 (0,18; 1,15) Justeret for køn: HR: 0,37 (0,14; 0,94) Justeret for LDH: HR 0,31 (0,11; 0,88) Justeret for IPI 2-5: HR 0,32 (0,11; 0,92)		CHOEP vs. CHOP Ikke-justeret HR: 0,34 (0,16; 0,75); P = 0,008 <u>Alder 41-65 år</u> HR: 0,38 (0,14; 0,99) Justeret for køn: HR: 0,29 (0,11; 0,79) Justeret for LDH: HR 0,27 (0,09; 0,80) Justeret for IPI 2-5: HR 0,25 (0,08; 0,76)		Alder og IPI i CHOP vs. CHOEP er ikke signifikant forskellig. Effekt opretholdt ved justering for køn, LDH og IPI. <u>Effekt i aldersgrupper</u> 18 - 40 år: Ingen forskel i OS, men CHOEP-gruppen var prognostisk dårligere stillet.
Janikova, 2019, Tjekkiet	CHOP: Median 49 år (21 – 59) CHOEP: Median 51 år (19 – 59)	0-1: 47 % (49/104) 2-3: 45 % (47/113) 4-5: 8 % (8/104)	0-1: 46 % (31/67) 2-3: 46 % (31/67) 4-5: 7 % (5/67)	I: 9 % (10) II: 24 % (26) III: 24 % (26) IV: 43 % (47)	I: 18 % (12) II: 22 % (15) III: 28 % (19) IV: 32 % (22)	25 % (17/68) ALK+: 0 % ALK-: 19 % (13) ukendt: 6 % (4)	27 % (30/113) ALK+: 0 % ALK-: 16 % (18) ukendt: 11 % (12)	5-års PFS: 32,9 % (24,0; 41,7)	5-års PFS: 59,0 % (47,0; 71,0)	5-års OS: 47,6 % (38,2; 57,1)	5-års OS: 65,6 % (53,9; 77,4)	PFS: p = 0,001; OS: p = 0,008 Resultaterne blev også bekræftet i multivariat analyse med IPI-score som mulig confounder. Grupperne var ens, med undtagelse af statistisk flere patienter med forhøjet LDH (72,1 % vs. 52, 3%) og B-symptomer (55,2 % vs. 39,6 %) i CHOEP-armen.
Jia, 2016, Kina	CHOP: ≤ 60 år: 70 % (28/40) > 60 år: 30 % (12/40)	0-1: 37,5 % (15/40) 2-5: 62,5 % (25/40)	0-1: 47,6 % (20/42) 2-5: 52,4 % (22/42)	I-II: 30 % (12/40) III-IV: 70 % (28/42)	I-II: 35,7 % (15/42) III-IV: 64,3 % (27/42)	14 % (13/93) ALK+: 0 % ALK-: IA		1-års PFS: 35,0 % Median: 6,0 måneder	1-års PFS: 54,8 % Median:	1-års OS: 65,0 %	1-års OS: 83,3 %	OS: P = 0,030 Meget få med ALCL. Der rapporteres ingen forskel i de hyppigste grad 3-4 uønskede

Studie, år, land	Baselinekarakteristika							Effektmål				Kommentar
	Alder	IPI		Sygdomsstadie		Andel sALCL		PFS		OS		
		CHOP	CHOEP	CHOP	CHOEP	CHOP	CHOEP	CHOP	CHOEP	CHOP	CHOEP	
	CHOEP: ≤ 60 år: 76 % (32/42) > 60 år: 24 % (10/42)								15,3 måneder			hændelser, som bl.a. inkluderer trombocytopeni, neutropeni og leukopeni.
Rattarit-tamrong, 2013, Thailand	CHOP: Median 48,4 år (25 – 60) CHOEP: Median 48,9 år (18 – 60)	0-1: 38 % (9/24) 2-3: 50 % (12/24) 4-5: 12 % (3/24)	0-1: 54 % (6/11) 2-3: 27 % (3/11) 4-5: 18 % (2/11)	IV: 63 % (15/24)	IV: 36 % (4/11)	3 % (1/35)		2-års EFS: 51,4 %	2-års EFS: 37,6 %	2-års OS: 51,9 %	2-års OS: 54,4 %	Kun 1 patient med ALK- ALCL, ellers ingen ALCL-patienter.

13. Bilag 2: Evidensens kvalitet

13.1 Cochrane – risiko for bias

Vurdering af risiko for bias ved Cochrane risk of bias tool 2.0.

Tabel 5. Vurdering af risiko for bias Horwitz et al., 2019, ECHELON-2, NCT01777152

Bias	Risiko for bias	Uddybning
Risiko for bias i randomiserings-processen	**Forbehold**	sALCL udgør en undergruppe på 75 % af den samlede ITT-population. Randomiseringen vurderes kun at være opretholdt for ALK+ sALCL. Der er dog ikke væsentlige forskellige i baselinekarakteristika. Der observeres højere andel kvinder i BV+CHP-armen (andel mænd: 95 (59) vs. 110 (71)) og numerisk flere med stadie IV-sygdom i BV+CHP-armen og tilsvarende mindre med stadie III – samlet er stadie III+IV sammenlignelige. Fordelingen af IPI-score er velbalanceret.
Effekt af tildeling til intervention	**Lav**	
Manglende data for effektmål	**Lav**	
Risiko for bias ved indsamlingen af data	**Lav**	
Risiko for bias ved udvælgelse af resultater, der rapporteres	**Lav**	
Overordnet risiko for bias	**Lav**	På trods af,at randomiseringen ikke med sikkerhed er opretholdt i sALCL-populationen, vurderes det ikke at have betydning, da baseline-karakteristika overordnet set er velbalanceret.

13.2 GRADE

Klinisk spørgsmål 1 og 2 – brentuximab vedotin + CHP sammenlignet med CHOP til behandling af sALCL

Tabel 6. GRADE evidensprofil for klinisk spørgsmål 1 og 2

Sikkerhedsvurdering							Antal patienter		Effekt			
Antal studier	Studie-design	Risiko for bias	Inkonsistens	Indirekthed	Unøjagtighed	Andre overvejelser	BV+CHP	CHOP	Relativ (95 % CI)	Absolut (95 % CI)	Sikkerhed	Vigtighed
Samlet overlevelse (OS), median OS i måneder												
1	RCT	Ikke alvorlig	Alvorlig[a]	Alvorlig[b]	Ikke alvorlig	Ingen	162	154	HR: 0,54 (0,34; 0,87)	NE	⨁⨁◯◯ LAV	KRITISK
Samlet overlevelse (OS), andel af patienter, der opnår 2-års overlevelse												
1	RCT	Ikke alvorlig	Alvorlig[a]	Alvorlig[b]	Alvorlig[c]	Ingen	162	154	-	[redacted]	⨁◯◯◯ MEGET LAV	KRITISK
Progressionsfri overlevelse (PFS), median PFS i måneder												
1	RCT	Ikke alvorlig	Alvorlig[a]	Alvorlig[b]	Ikke alvorlig	Ingen	162	154	HR: 0,59 (0,42; 0,84)	1,48 måneder	⨁⨁◯◯ LAV	VIGTIGT
Samlet overlevelse (PFS), andel af patienter, der opnår 2-års PFS												
1	RCT	Ikke alvorlig	Alvorlig[a]	Alvorlig[b]	Alvorlig[c]	Ingen	163	151	-	14,5 %-point	⨁◯◯◯ MEGET LAV	VIGTIGT

Sikkerhedsvurdering							Antal patienter		Effekt			
Antal studier	Studie-design	Risiko for bias	Inkonsistens	Indirekthed	Unøjagtighed	Andre overvejelser	BV+CHP	CHOP	Relativ (95 % CI)	Absolut (95 % CI)	Sikkerhed	Vigtighed
Livskvalitet, gennemsnitlig ændring fra baseline på EORTC QLQ-C30 til efter endt behandling												
1	RCT	Ikke alvorlig	Alvorlig[a]	Alvorlig[b]	Alvorlig[d]	Ingen	[redacted]	[redacted]	-	[redacted]	⨁◯◯◯ MEGET LAV	VIGTIGT
Livskvalitet, gennemsnitlig ændring fra baseline på EORTC QLQ-C30 til efter endt opfølgning												
1	RCT	Ikke alvorlig	Alvorlig[a]	Alvorlig[b]	Alvorlig[d]	Ingen	[redacted]	[redacted]	-	[redacted]	⨁◯◯◯ MEGET LAV	VIGTIGT
Uønskede hændelser, andel, som ophører behandlingen pga. uønskede hændelser												
1	RCT	Ikke alvorlig	Alvorlig[a]	Alvorlig[b]	Alvorlig[d]	Ingen	[redacted]	[redacted]	[redacted]	[redacted]	⨁◯◯◯ MEGET LAV	VIGTIGT
Uønskede hændelser, andel patienter med uønskede hændelser grad 3 og grad 4												
1	RCT	Ikke alvorlig	Alvorlig[a]	Alvorlig[b]	Alvorlig[d]	Ingen	[redacted]	[redacted]	[redacted]	[redacted]	⨁◯◯◯ MEGET LAV	VIGTIGT
Kvalitet af den samlede evidens	MEGET LAV[e]											

[a] Der er nedgraderet ét niveau, da der kun var ét studie.
[b] Der er nedgraderet, da der er forskelle mellem studiepopulationen og den danske population.
[c] Der er nedgraderet, da der ikke findes et estimat for usikkerheden for overlevelses/PFS-raterne efter 2 år.
[d] Øvre og nedre konfidensgrænse kan give anledning til forskellige umiddelbare konklusioner.
[e] Den samlede evidenskvalitet er vurderet ud fra den laveste kvalitet af de kritiske effektmål.

Medicinrådet

Application for the assessment of brentuximab vedotin in combination with cyclophosphamide, doxorubicin and prednisolon for treatment of previously untreated systemic Anaplastic Large Cell Lymphoma

Contents

Figures

Tables

1 Basic information

Table 1 Contact information

Name	Sigurd Due Hilborg
Title	Market Access Manager
Area of responsibility	Health Economy
Phone	+45 60944922
E-mail	Sigurd.hilborg@takeda.com
Name	Anders Bondo Dydensborg
Title	Medical Advisor
Area of responsibility	Clinical/Medical
Phone	+45 24885993
E-mail	Anders-bondo.dydensborg@takeda.com

Table 2 Overview of the pharmaceutical

Proprietary name	Adcetris
Generic name	Brentuximab Vedotin
Marketing authorization holder in Denmark	Takeda Pharma a/s Delta Park 45 2655 Vallensbæk Strand Denmark
ATC code	L01XC12
Pharmacotherapeutic group	3
Active substance(s)	Brentuximab Vedotin
Pharmaceutical form(s)	Powder for concentrate for solution for infusion.
Mechanism of action	ADCETRIS is an antibody-drug conjugate composed of a CD30-directed monoclonal antibody that is covalently linked to the antimicrotubule agent monomethyl auristatin E (MMAE).
Dosage regimen	The recommended dose in combination with chemotherapy (cyclophosphamide [C], doxorubicin [H] and prednisone [P] [CHP]) is 1.8 mg/kg administered as an intravenous infusion over 30 minutes every 3 weeks for 6 to 8 cycles
Therapeutic indication relevant for assessment (as defined by the European Medicines Agency, EMA)	ADCETRIS in combination with cyclophosphamide, doxorubicin and prednisone (CHP) is indicated for adult patients with previously untreated systemic anaplastic large cell lymphoma (sALCL).
Other approved therapeutic indications	Hodgkin lymphoma ADCETRIS is indicated for adult patients with previously untreated CD30+ Stage IV Hodgkin lymphoma (HL) in combination with doxorubicin, vinblastine and dacarbazine (AVD). ADCETRIS is indicated for the treatment of adult patients with CD30+ HL at

	increased risk of relapse or progression following autologous stem cell transplant (ASCT). ADCETRIS is indicated for the treatment of adult patients with relapsed or refractory CD30+ Hodgkin lymphoma (HL): 1. following ASCT, or 2. following at least two prior therapies when ASCT or multi-agent chemotherapy is not a treatment option. Systemic anaplastic large cell lymphoma ADCETRIS is indicated for the treatment of adult patients with relapsed or refractory sALCL. Cutaneous T-cell lymphoma ADCETRIS is indicated for the treatment of adult patients with CD30+ cutaneous T-cell lymphoma (CTCL) after at least 1 prior systemic therapy.
Will dispensing be restricted to hospitals?	Yes
Combination therapy and/or co-medication	In combination with cyclophosphamide, doxorubicin and prednisolone. Primary prophylaxis with GCS-F is recommended when given in combination.
Packaging – types, sizes/number of units, and concentrations	Vials. Each vial contains 50 mg of brentuximab vedotin.
Orphan drug designation	Yes

2 Abbreviations

ADR	Adverse Drug Reactions
AEs	Adverse Events
ALCL	Anaplastic Large Cell Lymphoma
ALK	Anaplastic Lymphoma Kinase
ASCT	Autologous Stem Cell Transplant
CHOEP	Cyclophosphamid, doxorubicin, vincristin, etoposid, and prednisolon
CHOP	Cyclophosphamid, doxorubicin, vincristin, and prednisolon
CHP	Cyclophosphamid, doxorubicin, and, prednisolon
CI	Confidence Interval
CR	Complete Response
EMA	*European Medicines Agency*
EPAR	*European Public Assessment Report*
HDT	High Dose Therapy
HR	Hazard Ratio
HRQoL	Health Related Quality of Life
IPI	International Prognostic Index
ITT	Intention To Treat
KM	Kaplan-Meier (curve)
LDH	Lactate Dehydrogenase
ORR	Objective Response Rate
OS	Overall Survival
PFS	Progression Free Survival
PICO	*Population, Intervention, Comparator and Outcome*
PR	Partial Response
PTCL	Peripheral T Cell Lymphoma
RR	Relative Risk
sALCL	Systemic Anaplastic Large Cell Lymphoma
SCT	Stem Cell Transplant

SOC	Standard Of Care
ULN	Upper Limit of Normal
Yr	Year
Yrs	Years

3 Summary

This application concerns the use of brentuximab vedotin (Adcetris) in the treatment of sALCL first-line patients.
Systemic Anaplastic Large Cell Lymphoma (sALCL) is an aggressive, life-threatening malignancy that is part of the nodal Peripheral T-Cell lymphomas (PTCLs).
Globally, first line treatment is predominantly CHOP or CHOP with the addition of etoposide, CHOEP, and consolidative HDT and SCT for patients with good performance status and poor prognosis. The prognosis of sALCL is generally poor but is dependent on IPI-score and ALK-status. Currently, 5-year survival is between 23% and 50% for higher risk patients. Aim of current treatment is to avoid relapse, as relapse historically is associated with an abysmal prognosis. Data on PFS and OS after first relapse thus show median values of 5.2 months and 9.1 months, respectively (Morel et al. 2017). Recently, the introduction of Adcetris in the treatment of RR ALCL has prolonged the 5-yrs PFS and OS rates of RR ALCL patients to 39% and 60%, respectively (Pro et al. 2017).

The literature search conducted according to the instruction given by the Medicines Council only found one head-to-head study comparing BV vs CHOP, whereas no head-to-head studies were identified that either compared BV against CHOEP or even CHOP vs CHOEP in sALCL or PTCL patients. High-level evidence to support documentation of BV vs CHOEP is therefore lacking.

Nine publications did contain comparisons of CHOP vs CHOEP from retrospective studies, meta-analysis, or single arm trials allowing usage of both CHOP and CHOEP. These studies fulfilled the criteria defined in the protocol provided by the Medicines Council for a naïve, narrative, comparison of CHOP vs. CHOEP in support of a direct comparison of A+CHP and CHOP in lieu of a comparison of A+CHP and CHOEP.

A naïve, literature based, narrative comparison of CHOP and CHOEP revealed inconsistent results that did not support an evidence-based conclusion of superiority of CHOEP over CHOP at the level of OS, PFS, HRQoL or AE. In accordance with the protocol, the comparison of CHOEP/CHOP against A+CHO (transplant eligible patients) was therefore done as a comparison of A+CHP vs. CHOP.
For patients who are candidates for CHOEP/CHOP treatment followed by HDT and SCT, the hazard ratios for death (OS) and PFS were 0,54 (95% CI: 0.337-0.876, P=0.0096) and 0.59 (95% CI: 0.42-0.84, P=0.0031), respectively. [redacted].
For patients who are not candidates for HDT and SCT, the hazard ratio for death (OS) and PFS were 0,54 (95% CI: 0.337-0.876, P=0.0096) and 0.59 (95% CI: 0.42-0.84, P=0.0031), respectively. [redacted].

CONCLUSION: considering the totality of the available literature, no evidence for a superiority of CHOEP over CHOP could be demonstrated. [redacted]

4 Literature search

4.1 Databases and search strategy for Clinical Question 1.

Please see appendix 1.

4.2 Articles for statistically valid indirect comparison of A+CHP and CHOEP; General considerations

The literature searches for Clinical Question 1 were conducted according to the specifications in the protocol (table 1 and 2, appendix 1).

The literature searches were conducted on 10-JUL-2020 using Google Chrome and yielded 208 records. This number was reduced to 12 articles following removal of duplicate records and screening of titles (see PRISMA diagram in appendix, section 8.1.3).

Of the remaining 12 article, 11 were excluded from an attempt to perform a statistically valid indirect comparison between CHOEP and Adcetris+CHP (A+CHP), table A, section 4.3, below, in the absences of randomized clinical trials comparing CHOP and CHOEP.

The 11 excluded articles were based on retrospective, observational studies resulting in substantial inter-study heterogeneity, treatment and selection bias within the individual studies, as well as a lack of reporting of OS, PFS, AE, and HRQOL data at a HR or Kaplan-Meier level (Table A). Furthermore, the overall level of information that could be extracted from the publications were limited and insufficient to perform statistically valid comparisons. Information such as patient numbers per study arm, absolute and relative outcomes, and confidence intervals was inconsistently reported; frequently conclusions were reported at the level of “no difference was observed”.

Finally, analyses that addressed issues from the current application (efficacy of CHOP vs. CHOEP) was frequently not performed at the ITT level, but only at patient groups for whom the authors had sufficient information to delineate what specific treatment the patients had received (i.e. CHOP/CHOEP/GDP etc), further downgrading the overall level of evidence.

The final article retained from the literature search was the publication describing a comparison of brentuximab vedotin + CHP to CHOP in the treatment of previously untreated mature CD30+ T-cell lymphoma (Horwitz et al. 2019). This publication reports the results of a randomized, global, placebo- and double-dummy controlled phase 3 study; Echelon-2 and represents the first randomized placebo-controlled trial which have shown superiority over CHOP with-in the PTCL patient population.

4.3 Articles for narrative indirect comparison of CHOEP and CHOP; General considerations

As per protocol, the applicant proceeds to give a narrative account for whether the efficacy of CHOP is comparable to CHOEP using a subset of the 11 articles that were excluded at the full text level from the statistically valid indirect comparison.

The criteria set up for inclusion in the narrative indirect comparison of CHOEP and CHOP were:

Inclusion:

- assessed for eligibility at the full text level following the systematic literature search stipulated in the protocol.

Exclusion

- no comparison of CHOEP and CHOP (reporting of only one treatment modality)
- no reporting of outcomes relevant to this application (OS, PFS, HRQoL, AEs)
- no attempts at correcting outcomes for differences in underlying patient characteristics

Of the 11 excluded (at full text level) articles from the literature search described above, three articles were further excluded for the narrative comparison: one article reported no attempts at correcting for underlying patient differences (IPI, age etc) (Liu et al. 2019), and one did not address any outcomes specified in the protocol (Cederleuf, Hjort Jakobsen, et al. 2017). The final excluded article was a metaanalysis of studies already included in the identified literature as well as two other articles not identified in the literature search: one article was in Chinese, the other could not be identified via MEDLINE or CENTRAL.
The meta-analysis reported response- and AE-rates, but not OS, PFS or HRQoL. For the application-relevant endpoint AE, the meta-analysis arrived at the same conclusion as Kim et al., 2017, as this study dominated he meta-analysis. The meta-analysis was therefore excluded as it was felt it did not bring any added information to the overall analysis.
The narrative indirect comparison of CHOEP and CHOP was thus conducted using a total of eight articles, table A, below.

Table A: Articles that were 1) excluded from the attempt to perform a statistically valid indirect comparison of CHOEP with Adcetris+CHP (see section 4.2) and 2) carried over to form the basis of a naïve comparison of CHOP and CHOEP or further excluded from the naïve comparison (see section 4.3)

Reference	Reason for exclusion from indirect comparison of A+CHP vs CHOEP	Carried over to naïve comparison of CHOP vs. CHOEP	Reason for exclusion from naïve comparison of CHOP vs. CHOEP
Schmitz N, Trümper L, Ziepert M, Nickelsen M, Ho AD, Metzner B, et al. Treatment and prognosis of mature T-cell and NK-cell lymphoma: an analysis of patients with T-cell lymphoma	Retrospective study. Outcome data for OS or PFS not reported in a format sustaining a statistical comparison (i.e. no HR or	Yes	

treated in studies of the German High-Grade Non-Hodgkin Lymphoma Study Group. Blood. 2010;116(18):3418-25.	Kaplan-Meier curve between treatment arms)		
d'Amore F, Relander T, Lauritzsen GF, Jantunen E, Hagberg H, Anderson H, et al. Up-front autologous stem-cell transplantation in peripheral T-cell lymphoma: NLG-T-01. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2012;30(25):3093-9.	Single arm study. Outcome data for OS or PFS not reported in a format sustaining a statistical comparison (i.e. no HR or Kaplan-Meier curve between treatment arms)	Yes	
Rattarittamrong E, Norasetthada L, Tantiworawit A, Chai-Adisaksopha C, Nawarawong W. CHOEP-21 chemotherapy for newly diagnosed nodal peripheral T-cell lymphomas (PTCLs) in Maharaj Nakorn Chiang Mai Hospital. Journal of the Medical Association of Thailand = Chotmaihet thangphaet. 2013;96(11):1416-22.	Retrospective study. Prospective single arm study with historic control (secondary analysis). Heterogenous distribution of male/:female ratio, no correction made. No ALK+ ALCL patients. ALCL ALK- patients are not reported separately.	Yes	
Jia B, Hu S, Yang J, Zhou S, Liu P, Qin Y, et al. Comparison of gemcitabin, cisplatin, and dexamethasone (GDP), CHOP, and CHOPE in the first-line treatment of peripheral T-cell lymphomas. Hematology (Amsterdam, Netherlands). 2016;21(9):536-41.	Not the right patient population; ALCL patients are not reported separately.	Yes	
Cederleuf H, Bjerregård Pedersen M, Jerkeman M, Relander T, d'Amore F, Ellin F. The addition of etoposide to CHOP is associated with improved outcome in ALK+ adult anaplastic large cell lymphoma: A Nordic Lymphoma Group study. British journal of haematology. 2017;178(5):739-46.	Retrospective study covering only ALK+ ALCL patients. Only 5 out of 122 patients received auto-SCT.	Yes	
Cederleuf H, Hjort Jakobsen L, Ellin F, de Nully Brown P, Stauffer Larsen T, Bøgsted M, et al. Outcome of peripheral T-cell lymphoma in first complete remission: a Danish-Swedish population-based study. Leukemia & lymphoma. 2017;58(12):2815-23.	Does not adress outcomes in the protocol from the Medicines Council.	No	Does not adress outcomes in the protocol from the Medicines Council
Deng S, Lin S, Shen J, Zeng Y. Comparison of CHOP vs CHOEP for treatment of peripheral T-cell lymphoma: a meta-analysis. OncoTargets and therapy. 2019;12:2335-42	Meta-analysis of Response Rates (CR, PR, ORR) and AEs in PTCL patients. No separate reporting of ALCL patients. No reporting of how many	No	Does not report OS, PFS, or HrQoL. AE section was based on 3 articles; one of

	patients inlcuded. No reporting of OS or PFS.		which is already presented in this analysis; one in Chinese and one that could not be found. The result of the meta-analysis was identical to the results in the article already presented in this application.
Janikova A, Chloupkova R, Campr V, Klener P, Hamouzova J, Belada D, et al. First-line therapy for T cell lymphomas: a retrospective population-based analysis of 906 T cell lymphoma patients. Annals of hematology. 2019;98(8):1961-72.	Retrospective study. No separate reporting of ALCL patients. ALCL ALK+ patients not part of the analysis. No usable outcome data for OS or PFS (i.e. no HR or Kaplan-Meier curve between treatment arms)	Yes	
Liu X, Yang M, Wu M, Zheng W, Xie Y, Zhu J, et al. A retrospective study of the CHOP, CHOPE, and CHOPE/G regimens as the first-line treatment of peripheral T-cell lymphomas. Cancer chemotherapy and pharmacology. 2019;83(3):443-9.	Retrospective study with no correction for differences in age or IPI scores. CHOEP treated patients were younger and had significantly lower IPI-score than CHOP-treated patients ALK+ ALCL patients not included in the study.	No	No correction was made for age or IPI difference, so the differences in outcome are likely caused by underlying patient characteristics.
Kim YA, Byun JM, Park K, Bae GH, Lee D, Kim DS, et al. Redefining the role of etoposide in first-line treatment of peripheral T-cell lymphoma. Blood advances. 2017;1(24):2138-46.	High likelyhood of treatment bias based on differential prognostics of ALK+ and ALK- ALCL patients.	Yes	
Ellin F, Landström J, Jerkeman M, Relander T. Real-world data on prognostic factors and treatment in peripheral T-cell lymphomas: a study from the Swedish Lymphoma Registry. Blood. 2014;124(10):1570-7.	High likelyhood of treatment bias based on differential prognostics of ALK+ and ALK- ALCL patients.	Yes	

4.4 Relevant studies for the naïve comparison of CHOP vs. CHOEP and the head-to-head comparison of A+CHP vs. CHOP.

Table B: Relevant studies included in the naïve comparison of CHOP vs. CHOEP and the comparison of CHOP and A+CHP

Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)	Relevant for clinical question <x>*
Brentuximab vedotin with chemotherapy for CD30-positive peripheral T-cell lymphoma (ECHELON-2): a global, double-blind, randomised, phase 3 trial. Horwitz S, O'Connor OA, Pro B, Illidge T, Fanale M, Advani R, et al. The Lancet. 2019;393(10168):229-40.	Echelon-2	NCT01777152	Start: January 2013 End: August 2020	1 & 2
Schmitz N, Trümper L, Ziepert M, Nickelsen M, Ho AD, Metzner B, et al. Treatment and prognosis of mature T-cell and NK-cell lymphoma: an analysis of patients with T-cell lymphoma treated in studies of the German High-Grade Non-Hodgkin Lymphoma Study Group. Blood. 2010;116(18):3418-25.		NA	NA	1
d'Amore F, Relander T, Lauritzsen GF, Jantunen E, Hagberg H, Anderson H, et al. Up-front autologous stem-cell transplantation in peripheral T-cell	A Nordic Phase II Study of PTCL Based on Dose-intensive Induction and High-dose	NCT00791947	Start: august 2001 End: august 2010	1

lymphoma: NLG-T-01. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2012;30(25):3093-9.	Consolidation With ASCT			
Kim YA, Byun JM, Park K, Bae GH, Lee D, Kim DS, et al. Redefining the role of etoposide in first-line treatment of peripheral T-cell lymphoma. Blood advances. 2017;1(24):2138-46.		NA	NA	1
Ellin F, Landström J, Jerkeman M, Relander T. Real-world data on prognostic factors and treatment in peripheral T-cell lymphomas: a study from the Swedish Lymphoma Registry. Blood. 2014;124(10):1570-7.		NA	NA	1
Cederleuf H, Bjerregård Pedersen M, Jerkeman M, Relander T, d'Amore F, Ellin F. The addition of etoposide to CHOP is associated with improved outcome in ALK+ adult anaplastic large cell lymphoma: A Nordic Lymphoma Group study. British journal of haematology. 2017;178(5):739-46.		NA	NA	1
Liu X, Yang M, Wu M, Zheng W, Xie Y, Zhu J, et al. A retrospective study of the CHOP, CHOPE, and CHOPE/G regimens as the first-		NA	NA	1

line treatment of peripheral T-cell lymphomas. Cancer chemotherapy and pharmacology. 2019;83(3):443-9.				
Janikova A, Chloupkova R, Campr V, Klener P, Hamouzova J, Belada D, et al. First-line therapy for T cell lymphomas: a retrospective population-based analysis of 906 T cell lymphoma patients. Annals of hematology. 2019;98(8):1961-72.		NA	NA	1
Jia B, Hu S, Yang J, Zhou S, Liu P, Qin Y, et al. Comparison of gemcitabin, cisplatin, and dexamethasone (GDP), CHOP, and CHOPE in the first-line treatment of peripheral T-cell lymphomas. Hematology (Amsterdam, Netherlands). 2016;21(9):536-41.		NA	NA	1
Rattarittamrong E, Norasetthada L, Tantiworawit A, Chai-Adisaksopha C, Nawarawong W. CHOEP-21 chemotherapy for newly diagnosed nodal peripheral T-cell lymphomas (PTCLs) in Maharaj Nakorn Chiang Mai Hospital. Journal of the Medical		NA	NA	1

Association of Thailand = Chotmaihet thangphaet. 2013;96(11):1416-22.				
**when multiple clinical questions are defined in the protocol*				

4.5 Main characteristics of included studies for comparative analysis of A+CHP vs. CHOP

Echelon-2 was a global phase 3 study of A+CHP vs. CHOP as first line treatment of systemic Anaplastic Large Cell Lymphoma. The study was placebo- and double-dummy controlled. Patients were randomized (1:1) to either A+CHP+"vincristine-placebo" or CHOP+"Adcetris-Placebo" with respective dummy procedures. All participants (investigators, patients, review committee, Takeda Employees etc) were blinded to the treatment.

Please see table A2 in appendix for full description of the study.

5 Clinical questions

5.1 What is the clinical value of brentuximab vedotin in combination with cyclophosphamide, doxorubicin and prednisolone (CHP) compared with cyclophosphamide, doxorubicin, vincristine, etoposide, and prednisolone (CHOEP) or cyclophosphamide, doxorubicin, vincristine, and prednisolone (CHOP) for previously untreated patients with sALCL who are candidates for HDT and ASCT?

5.1.1 General Comments

The studies identified in the systematic literature review met the inclusion criteria. However, the following should be taken into consideration when assessing the literature and the reported data:

- No studies compared A+CHP to CHOEP
- With-in the specified patient population, no prospective randomized studies compared CHOEP to CHOP.
- The retrospective studies used for comparing CHOEP and CHOP are associated with large degree of uncertainty as:
    - The retrospective nature of the studies introduces a large risk of selection bias
    - Outcomes are reported at different levels (relative and/or absolute values) and with varying degree of details.
    - The reporting of baseline characteristics varied from study to study.
    - The population composition differs across the studies (PTCL, ALCL, ALK+/- ALCL).
    - The included patient populations span a large spectrum of size, from very small (N=35 (Rattarittamrong et al. 2013) to very large (N=1200+) (Kim et al. 2017).
- Only one randomized, prospective head-to-head trial was identified: the ECHELON-2 trial comparing A+CHP to CHOP.

5.1.2 Presentation of relevant studies

5.1.2.1 Brentuximab vedotin with chemotherapy for CD30-positive peripheral T-cell lymphoma (ECHELON-2): a global, double-blind, randomized, phase 3 trial.

Echelon-2 was a randomized, double-blind, double-dummy and placebo-controlled, phase 3 study of brentuximab vedotin and CHP (A+CHP vs. CHOP) in the 1. Line treatment of patients with CD30-positive mature T-cell lymphoma.
Regulatory requirements from EMA stipulated that a minimum of 70% of the enrolled patients had to be sALCL patients. This requirement was met.

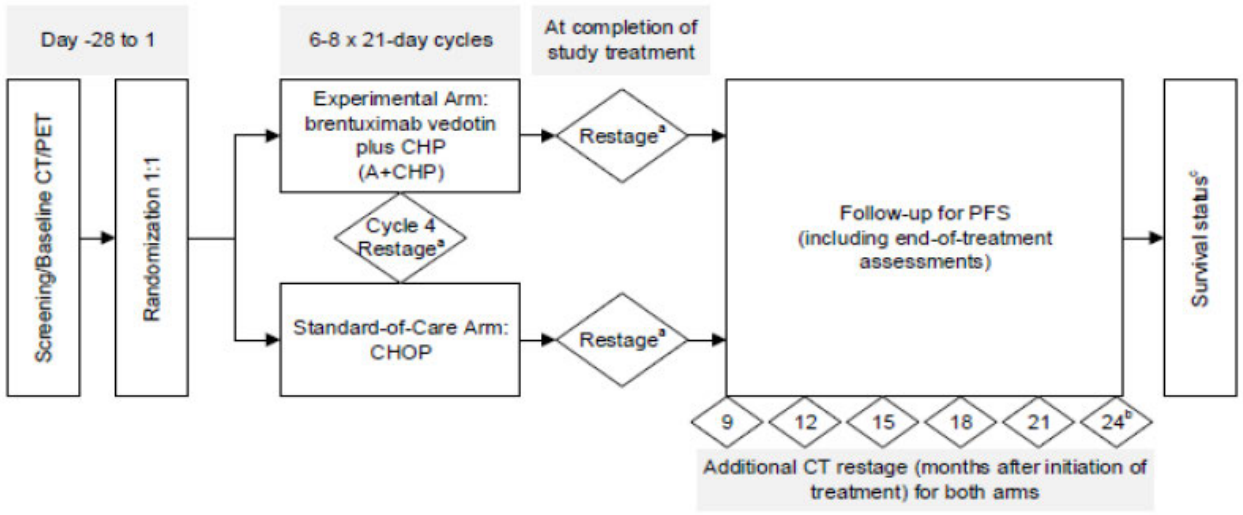


FIGURE A. STUDY DESIGN OF ECHELON-2.

The trial was conducted as a superiority trial with the aim of showing a PFS benefit of A+CHP over CHOP. All efficacy analyses were performed by an Independent Review Committee, to ensure stringency and consistency of efficacy evaluations.

PFS was defined as time from randomization to the date of first documented progression, death, or receipt of subsequent anticancer chemotherapy to treat residual or progressive disease, whichever occurred first.

See table A2a for a summary of further details.

5.1.2.2 Indirect comparison of CHOP and CHOEP

5.1.2.3 General considerations

A systematic literature search was conducted in accordance with the search criteria laid out by the protocol. No literature was found that enabled performing a statistically valid indirect comparison, as the

studies were retrospective, had heterogenous patient populations and/or did not report data specifically for ALCL patients (see table A, p.13).

Relevant studies from the systematic literature search were therefore included in a protocol-stipulated presentation of the evidence supporting an efficacy difference between CHOP and CHOEP.

In total eight studies presenting data addressing the efficacy of CHOP vs. CHOEP in PTCL/ALCL patients were identified:

- Six retrospective studies (Cederleuf, Bjerregård Pedersen, et al. 2017; Ellin et al. 2014; Janikova et al. 2019; Jia et al. 2016; Kim et al. 2017; Schmitz et al. 2010)
- One prospective phase II trial (d'Amore et al. 2012)
- One prospective phase II trial comparing CHOEP to historic CHOP controls (Rattarittamrong et al. 2013).

The overall aim of all the studies presented below is to describe the outcomes for PTCL patients.
However, the retrospective nature of the majority of the studies means that large interstudy heterogeneity between the studies exists.
This heterogeneity is at the level of patients included (I.e. ALK+ ALCL only (Cederleuf, Bjerregård Pedersen, et al. 2017), or PTCL at large (Kim et al. 2017; Janikova et al. 2019; Jia et al. 2016)), single centers (Jia et al. 2016), national registries of all patients treated within a specific time period (Cederleuf, Bjerregård Pedersen, et al. 2017; Ellin et al. 2014; Kim et al. 2017), retrospective annalysis of patients previously enrolled in clinical trials (Schmitz et al. 2010), or prospective enrollment of selected patients in a clinical trial (d'Amore et al. 2012). Such differences results in unavoidable patient heterogeneity which is further exacerbated by the differences in information level available across institutional and national registries from divergent countries such as Sweden, Germany, South-Korea, and China.

The majority of the studies report data in patient populations that are outside the scope of the present application. Only subsets of the data from these studies are therefore relevant for the application. Only the relevant data will be presented.

5.1.2.4 Treatment and prognosis of mature T-cell and NK-cell lymphoma: an analysis of patients with T-cell lymphoma treated in studies of the German High-Grade Non-Hodgkin Lymphoma Study Group. Blood. 2010;116(18):3418-25.

The study retrospectively looked at 320 German PTCL patients enrolled in eight DSHNHL trials between 1993 and 2007. 25% and 35% of the patients had ALK+ and ALK- ALCL, respectively.
Both the total study population and the subgroup of ALCL patients were dominated by patients with low IPI-score. Specifically, 58% and 57% of the ALK+ and ALK- ALCL patients were IPI 0-1, while only 15% and 20% were IPI 3-5, respectively, table C, below.
While a total of 320 patients were included in the study, the differences in treatment between the eight trials that formed the foundation for the study meant that only 42 and 41 patients received standard CHOEP and CHOP regiments respectively. The analyses presented in the result section 5.1.3.3 are derived from these patients.

TABLE C: BASELINE CHARACTERISTICS OF THE APPLICATION RELEVANT PATIENTS IN STUDY (SCHMITZ ET AL. 2010).

	All (n = 320)	ALK+ (n = 78)	ALK− (n = 113)
Sex			
Male	197 (61.6%)	44 (56.4%)	69 (61.1%)
Female	123 (38.4%)	34 (43.6%)	44 (38.9%)
Median age, y (range)	50 (18, 78)	37 (18, 74)	50 (18, 77)
Age > 60 y	96 (30.0%)	11 (14.1%)	39 (34.5%)
LDH > UNV	121 (37.8%)	21 (26.9%)	41 (36.3%)
ECOG > 1	53 (16.6%)	11 (14.1%)	16 (14.2%)
Stage III, IV	163 (50.9%)	41 (52.6%)	49 (43.4%)
More than 1 extranodal site	61 (19.1%)	16 (20.5%)	16 (14.2%)
IPI			
0, 1	163 (50.9%)	45 (57.7%)	64 (56.6%)
2	80 (25.0%)	21 (26.9%)	27 (23.9%)
3	48 (15.0%)	10 (12.8%)	14 (12.4%)
4, 5	29 (9.1%)	2 (2.6%)	8 (7.1%)
B symptoms	139 (43.4%)	42 (53.8%)	39 (34.5%)
Bulky disease	82 (25.6%)	23 (29.5%)	35 (31.0%)

5.1.2.5 The addition of etoposide to CHOP is associated with improved outcome in ALK+ adult anaplastic large cell lymphoma: A Nordic Lymphoma Group study.

In this study a total of 122 ALK+ ALCL patients from Swedish and Danish registries were retrospectively analyzed for prognostic factors (Cederleuf, Bjerregård Pedersen, et al. 2017). The study does thus not report any data for ALK- ALCL patients.
The patients were diagnosed between 2000 and 2010.
The patient population was predominantly IPI score 0-1 (53%), 15% had > 1 extranodal involvement, 15% had Bulky Disease and 39% had LDH > UNL (Cederleuf, Bjerregård Pedersen, et al. 2017).

Full baseline characteristics are presented in table D, below.

The authors analyzed patients aged 18-40 (N=79) and patients aged 41-65 (N=43). Baseline characteristics of the patient group aged 41-65 yrs are presented in table E, further below.

TABLE D. PATIENT CHARACTERISTICS FROM (CEDERLEUF, BJERREGÅRD PEDERSEN, ET AL. 2017).

Table I. Patient characteristics and prognostic factors.

Variable	$N = 122$	Missing
Age (per year)		
Aged 18–40 years (ref)	61 (50)	0
Aged 41–60 years	38 (31)	0
Aged > 60 years	23 (19)	0
IPI score 2–5	54 (47)	7
Male gender	71 (58)	0
LDH > UNL	45 (39)	6
WHO PS > 1	26 (21)	0
Ann Arbor stage III–IV	65 (54)	2
CHOEP (ref: CHOP)		
Anaemia (Hb < 120 g/l)	44 (46)	26
Lymphopenia $<1{\cdot}0 \times 10^9$/l	18 (23)	42
β_2 microglobulin > UNL	9 (25)	86
Albumin < 35 g/l	39 (43)	32
Bulky disease	17 (15)	11
B symptoms	66 (55)	3
Extranodal involvement >1	19 (15)	2
Muscle involvement	10 (8·2)	0
Bone involvement	12 (9·8)	0
Pulmonary involvement	9 (7·4)	0
GI involvement	5 (4·1)	0
BM involvement	10 (8·3)	2
Liver involvement	5 (4·1)	0

TABLE E. PATIENT CHARACTERISTICS, AGES 41-65 YRS (CEDERLEUF, BJERREGÅRD PEDERSEN, ET AL. 2017)

Table II. Prognostic factors and characteristics of ALK+ ALCL patients aged 41–65 years.

	Characteristic			PFS			OS		
Variable	CHOP	CHOEP	*P*-value	HR	95% CI	*P*-value	HR	95% CI	*P*-value
Extranodal involvement >1	3 (19%)	1 (3·8%)	0·11	0·42	0·55–3·14	0·40	0·56	0·074–4·24	0·58
Ann Arbor stage III–IV	8 (50)	13 (48)	0·91	1·77	0·71–4·42	0·22	1·56	0·61–3·97	0·35
WHO PS > 1	3 (19)	7 (26)	0·59	1·03	0·37–2·85	0·96	1·09	0·39–3·09	0·87
LDH > UNL	3 (21)	8 (31)	0·53	2·28	0·86–6·03	0·097	1·44	0·52–3·97	0·48
IPI 2–5	5 (36)	11 (44)	0·61	2·19	0·81–5·89	0·12	1·71	0·62–4·72	0·30
Albumin <35 g/l	6 (43)	6 (33)	0·58	3·06	1·01–9·29	0·049	2·42	0·77–7·63	0·13
Male gender	8 (50)	18 (67)	0·28	2·64	0·95–7·34	0·063	2·25	0·80–6·32	0·13
B symptoms	9 (56)	16 (62)	0·74	1·47	0·55–3·92	0·44	1·40	0·52–3·79	0·51
Anaemia (Hb <120 g/l)	7 (50)	8 (40)	0·56	1·61	0·55–4·67	0·39	1·40	0·46–4·27	0·56
Lymphopenia ($<1{\cdot}0 \times 10^9$/l)	2 (18)	2 (12)	0·64	1·68	0·36–7·91	0·51	1·81	0·37–8·80	0·46
Bulky disease	0 (0)	5 (20)	0·096	0·35	0·045–2·69	0·31	0·46	0·059–3·53	0·45
Liver involvement	1 (6·3)	1 (3·7)	0·70	1·89	0·25–14·4	0·54	2·84	0·37–22·0	0·32

5.1.2.6 Redefining the role of etoposide in first-line treatment of peripheral T-cell lymphoma.

In this very large retrospective study of 1.557 PTCL patients, two PTCL populations were analyzed for differences in outcome between epotopside containing regiments; predominantly CHOEP and CHOP.
First, data from a cohort from a single center (large University Hospital) suggested that addition of etoposide to first line treatment was not associated with better outcomes. Following this initial analysis, the authors validated the conclusion by expanding the study into a national cohort covering 646 and 609 CHOP and CHOEP treated patients, respectively.
Both cohorts were from South Korea and spanned the years 2002-2010; baseline characteristics are summarized in table below.
The most relevant data for this application originates from subgroup analysis of differences of OS and PFS in CHOP and CHOEP treated patients with PTCL and ALCL as well as PTCL patients <45 yrs of age.
Patient numbers as well as outcome of analysis of the above mentioned cohorts are summarized in tables A3e-i and in section 5.1.3.5.
It is unclear from the baseline characteristics, table F, below, whether there were differences in patient characteristics between the CHOP (group 1) or CHOEP (group 2) treated patients.

OS and PFS were estimated using Kaplan-Meier methods.
Univariate and multivariate proportional hazards regression models were used to identify independent risk factors of survival by Cox proportional hazards models. Predictors achieving $P < 0.1$ in univariate analysis were sequentially preceded to multivariable models. Differences between groups were assessed using the Student t-test or 1 way analysis of variance for continuous variables and Pearson Chi-square test for categorical variables. All analyses were performed using SAS.

TABLE F. BASELINE CHARACTERISTICS OF PATIENTS FROM SINGLE CENTER AND NATIONAL COHORTS (KIM ET AL. 2017). GROUP 1: CHOP OR CHOP-LIKE REGIMEN; GROUP 2: CHOEP OR CHOEP LIKE REGIMEN, GROUP 3: OTHER REGIMENT PLUS ETOPOSIDE; GROUP 4: OTHER REGIMEN (KIM ET AL. 2017).

Table 1. Baseline characteristics

Characteristic	SNUH, n (%)	KCCR, n (%)
Total patients	131	1933
Median (range) age, y	59 (20-89)	58 (20-91)
Male sex	82 (62.6)	1194 (61.8)
CCI, points		
1-3	120 (91.6)	1719 (88.9)
≥4	11 (8.4)	214 (11.1)
Pathologic subtype		
PTCL-NOS	46 (35.1)	1075 (55.6)
AITL	48 (36.6)	445 (23.0)
ALCL	27 (20.6)	326 (16.9)
EATL	7 (5.3)	40 (2.1)
SPTCL	3 (2.3)	38 (2.0)
HSTCL	0	9 (0.5)
Stage		
1-2	26 (19.8)	511 (26.3)
3-4	105 (80.2)	674 (34.7)
Unknown	0	748 (38.7)
First-line chemotherapy group		
1	106 (80.9)	748 (38.7)
2	23 (17.6)	678 (35.1)
3	2 (1.5)	113 (5.9)
4	0	394 (20.3)
HSCT		
Yes	22 (16.8)	273 (11.6)
Autologous HSCT	21 (95.5)	171 (62.6)
Upfront	8 (38.0)	NA
Salvage	13 (61.9)	NA
Allogeneic HSCT	1 (4.5)	22 (8.1)
Upfront	0	NA
Salvage	1 (100)	NA
Cord	0	80 (29.3)
No	109 (83.2)	1660 (85.9)

HSCT, hematopoietic stem-cell transplantation; HSTCL, hepatosplenic T-cell lymphoma; NA, not available; SNUH, Seoul National University Hospital.

5.1.2.7 *Real-world data on prognostic factors and treatment in peripheral T-cell lymphomas: a study from the Swedish Lymphoma Registry*

This retrospective study looked at all PTCL patients treated in Sweden from 2000-2010, including 68 ALK+ and 115 ALK- ALCL patients.
The ALK+ patients were predominantly IPI 0-1 (53%), while the ALK- patients predominantly presented with IPI 3-5 (63%) (Ellin et al. 2014), table G, below.

TABLE G: BASELINE CHARACTERISTICS (ELLIN ET AL. 2014)

Table 1. Distribution of histologic subtypes and clinical characteristics in the entire cohort (N = 755)

Clinical characteristics	All patients (N = 755)	ALCL, ALKpos (n = 68)	ALCL, ALKneg (n = 115)	ALCL, ALKu (n = 36)	PTCL NOS (n = 256)	AITL (n =104)	EATL (n = 68)	TCL U (n = 57)	NK/T, nt (n = 33)	SPTCL (n = 12)	HSTCL (n = 8)
Age (y), median (range)	67 (18-96)	41 (18-81)*	67 (19-93)	69 (31-89)	69 (18-96)	70 (33-88)	68 (35-88)	72 (30-94)	62 (26-91)	58 (20-73)†	47 (18-72)
Male	445 (59)	37 (54)	80 (70)	21 (58)	148 (58)	59 (57)	40 (59)	34 (60)	20 (61)	6 (50)	4 (50)
Female	310 (41)	31 (46)	37 (30)	14 (42)	108 (42)	45 (43)	28 (41)	25 (40)	13 (39)	6 (50)	4 (50)
B symptoms	444 (59)	40 (59)	61 (52)	20 (57)	155 (61)	74 (71)‡	37 (54)	31 (53)	15 (46)	6 (50)	6 (75)
Stage III-IV	490 (65)	33 (49)	68 (59)	18 (50)	184 (72)	93 (89)§	28 (41)	40 (70)‖	14 (42)	7 (58)	7 (88)
BM	154 (20)	6 (9)¶	16 (13)	6 (17)	56 (22)	37 (36)#	1 (2)	26 (44)	1 (3)	—	5 (63)
Extranodal involvement >1	110 (15)	5 (7)**	17 (15)	4 (11)	35 (14)	12 (12)	16 (24)¶	12 (20)	6 (18)	1 (8)	3 (38)
WHO PS >1	267 (35)	16 (24)¶	40 (34)	8 (29)	92 (36)	35 (35)	24 (38)	26 (47)	6 (18)	4 (33)	4 (50)
Bulky disease (>10 cm)	81 (11)	11 (16)††	18 (15)	3 (8)	27 (11)	5 (5)	7 (10)	6 (10)	1 (3)	1 (8)	2 (25)
LDH > ULN	441 (54)	31 (46)	61 (52)	19 (54)	162 (63)	77 (74)‡‡	16 (24)§§	39 (66)‖‖	17 (52)	11 (92)	8 (100)
IPI 0-1	170 (23)	36 (53)¶¶	37 (32) n	11 (31)##	41 (16)***	4 (4)†††	25 (37)	5 (9)†††	9 (27)	2 (17)	—
IPI 2-3	386 (51)	26 (38)##	46 (40)‡‡‡	14 (39)§§§	141 (55)‖‖‖	68 (65)‖‖‖	26 (38)	35 (61)‖‖‖	17 (52)	8 (67)	6 (75)
IPI 4-5	139 (18)	4 (6)¶¶¶	26 (23) p	6 (17)	58 (23)†††	26 (25)###	8 (12)	6 (11)	1 (3)	2 (17)	2 (25)
5-y OS (%)	34.1	79.4	38.4	27.8	28.1	31.6	20.4	24.6	20.5	58.3	42.9
5-y PFS (%)	25.7	63.2	31.4	25.0	21.3	20.4	17.6	15.1	13.8	40.0	20.0

Factors were analyzed in univariable analysis, and all factors with P < .1 were retained in a multivariable model. All P values were 2 sided.
A univariable analysis of the differences in efficacy between CHOP and CHOEP treated ALK- ALCL, AITL, PTCL-NOS, EATL and TCL U patients with an upper age limit of 70 was performed. In the patient population of this analysis the CHOP treated patients had a higher fraction of IPI 4-5 (23% vs. 7%, P < 0.001) and a higher median age (65 vs. 52, P < 0.001), table H below.

TABLE H BASELINE CHARACTERISTICS OF ALK- ALCL, AITL, TCL U, AND EATL PATIENTS ≤ 70 YRS (ELLIN ET AL. 2014).

Table 3. Clinical characteristics among 252 patients with ALKneg ALCL, AITL, TCL U, and EATL up to age 70 treated with CHOP/CHOEP

	Auto-SCT ITT (n = 128)	Non–auto-SCT (n = 124)	P	CHOEP (n = 107)	CHOP (n = 145)	P
Median age (range), y	57 (24-68)	65 (18-70)	<.001	52 (24-69)	65 (18-70)	<.001
Male	87 (70)	87 (68)	.707	72 (67)	102 (70)	.604
B symptoms	83 (67)	79 (62)	.536	72 (67)	90 (62)	.414
Ann Arbor I	6 (5)	24 (19)		10 (9)	20 (14)	
II	35 (28)	18 (14)		26 (24)	27 (19)	
III	30 (24)	28 (22)	.999*	22 (21)	36 (25)	.867*
IV	53 (43)	57 (45)		49 (46)	61 (42)	
BM	22 (18)	29 (23)	.332	20 (19)	31 (21)	.600
Extranodal involvement >1	19 (15)	18 (14)	.778	17 (16)	20 (14)	.642
WHO PS >0	71 (57)	82 (64)	.176	63 (59)	90 (62)	.574
Bulky disease (>10 cm)	9 (7)	14 (11)	.292	7 (7)	16 (11)	.223
LDH > ULN	83 (69)	74 (60)	.233	67 (64)	90 (64)	.797
IPI 0-1	43 (35)	28 (22)	.024	39 (37)	32 (23)	.012
IPI 2-3	62 (50)	71 (56)	.385	57 (53)	76 (54)	.893
IPI 4-5	16 (13)	23 (18)	.266	7 (7)	32 (23)	.001
CHOP	42 (34)	103 (80)	<.001	—	—	—
CHOEP	82 (66)	25 (20)	—	—	—	—
PTCL NOS	44 (34)	65 (52)	—	41 (38)	68 (47)	—
ALKneg ALCL	31 (24)	21 (17)	—	27 (25)	25 (17)	—
AITL	27 (21)	20 (16)	—	18 (17)	29 (20)	—
EATL	20 (16)	14 (11)	—	17 (16)	17 (12)	—
TCL U	2 (2)	8 (6)	—	4 (4)	6 (4)	—
5-y OS (%)	48	26	—	47	30	—
5-y PFS (%)	41	20	—	40	23	—

A second multivariable analysis was performed for patients aged 18-60. Baseline characteristics of the patients in this analysis was not reported.

No separate data was reported for ALCL patients.

5.1.2.8 Up-front autologous stem-cell transplantation in peripheral T-cell lymphoma: NLG-T-01.

This prospective, unblinded, single arm study assessed the utility of treating 18 to 67 years old PTCL patients with CHOEP (18-60) or CHOP (61-67) followed by up-front autologous stem-cell transplantation. The study was conducted at a total of 24 centers in Denmark, Finland, Norway and Sweden.

The objective of the study was to describe the outcome of up-front autologous stem cell transplant following induction with CHOEP or CHOP for patients aged 18-60 and 61-67 years of age, respectively.

Inclusion criteria were newly diagnosed systemic PTCL, excluding primary cutaneous lymphomas, and primary leukemic subtypes, as well as ALK+ ALCL. Additional inclusion criteria were PS < 4, no severe comorbidity or concomitant malignancy, HIV negativity, no uncontrolled infections, no pregnancy or lactation.
Thirty-one (19%) of the 166 patients were ALK- ALCL patients.
Seventy-two % of the patients had IPI > 2, IPI distribution across the major diagnoses (including ALCL) did not differ statistically significantly (d'Amore et al. 2012).
Eighty-one % of patients presented with advanced stage disease, 59% had B-symptoms, and 62% had elevated LDH, table I below.

TABLE I: BASELINE CHARACTERISTICS (D'AMORE ET AL. 2012).

Table 1. Pretherapeutic Clinicopathologic Patient Characteristics (n = 160)

Characteristic	Patients	
	No.	%
Age, years		
Median	57	
Range	22-67	
Sex		
Male	107	67
Female	53	33
B symptoms	94	59
Elevated sLDH	99	62
PS 2	46	29
Bulk	26	17
Clinical stage III to IV	129	81
BM involvement	41	26
IPI 2	115	72
Histologic subtype		
PTCL-NOS	62	39
ALK-negative ALCL	31	19
AILT	30	19
EATL	21	13
Panniculitis like	6	4
T/NK nasal type	5	3
Hepatosplenic	5	3

Abbreviations: AILT, angioimmunoblastic T-cell lymphoma; ALCL, anaplastic large-cell lymphoma; ALK, anaplastic lymphoma kinase; BM, bone marrow; EATL, enteropathy-associated T-cell lymphoma; IPI, International Prognostic Index; PS, performance score; PTCL-NOS, peripheral T-cell lymphoma, not otherwise specified; sLDH, serum lactate dehydrogenase; T/NK, T cell/natural killer.

According to WHO scale 0 to 4.

A separate outcome (OS, PFS, ORR, and CR) analysis was performed for the CHOP-treated patients (N= 42, aged 61-67) and the "elderly" (N=50, 55-60) CHOEP treated patients.
Among the CHOP treated patients the median age was 64. 10%, 24%, 26%, and 40% of the patients had low, low-intermediate, intermediate-high, and high IPI respectively.

5.1.2.9 First-line therapy for T cell lymphomas: a retrospective population-based analysis of 906 T cell lymphoma patients

A secondary objective of this retrospective non-randomized study was to compare the outcome of 1. Line treatment of 113 CHOP treated patients vs. 68 CHOEP treated PTCL patients (Janikova et al. 2019).
18 and 13 CHOP and CHOEP treated ALK- ALCL patients were included in the analysis; no ALK+ ALCL patients were included (Janikova et al. 2019).
Baseline characteristics showed a higher proportion of patients with LDH < ULN and b-symptoms among the CHOEP treated patients, table J, below.
PFS and OS were estimated using KM-method and the comparison of outcomes according to subgroups (i.e. CHOP and CHOEP treated patients) was performed by means of the log-rank test.
Univariable and multivariable Cox proportional hazard model were used to evaluate the effect of all

potential prognostic factors on the survival measures. Statistical significance of HR was assessed by means of the Wald test.

TABLE J. BASELINE CHARACTERISTICS OF CHOP AND CHOEP TREATED PTCL PATIENTS (JANIKOVA ET AL. 2019).

Table 4 Baseline characteristics according to first-line chemotherapy

Characteristics[a], *n* (%)		Chemotherapy treatment		
		CHOEP (*n* = 68)	CHOP (*n* = 113)	*p*[b]
Sex	Male	44 (64.7)	77 (68.1)	0.745
	Female	24 (35.3)	36 (31.9)	
Age at diagnosis [years]	median (min-max)	51 (19–59)	49 (21–59)	0.763
B symptoms	Yes	37 (55.2)	44 (39.6)	0.046
	No	30 (44.8)	67 (60.4)	
Stage at diagnosis	I	12 (17.6)	10 (9.2)	0.265
	II	15 (22.1)	26 (23.9)	
	III	19 (27.9)	26 (23.9)	
	IV	22 (32.4)	47 (43.1)	
Bone marrow involvement	Yes	8 (11.9)	23 (20.4)	0.160
	No	59 (88.1)	90 (79.6)	
Extranodal involvement	0	29 (42.6)	42 (37.2)	0.530
	≥ 1	39 (57.4)	71 (62.8)	
ECOG PS	PS 0	33 (49.3)	45 (40.9)	0.595
	PS1	20 (29.9)	39 (35.5)	
	PS 2 or higher	14 (20.9)	26 (23.6)	
Bulky disease	≤ 10 cm	52 (91.2)	78 (85.7)	0.440
	> 10 cm	5 (8.8)	13 (14.3)	
LDH	≤ ULN	19 (27.9)	51 (47.7)	0.011
	> ULN	49 (72.1)	56 (52.3)	
IPI	Low risk	31 (46.3)	49 (47.1)	0.994
	Low-intermediate risk	20 (29.9)	29 (27.9)	
	High-intermediate risk	11 (16.4)	18 (17.3)	
	High risk	5 (7.5)	8 (7.7)	
Time from diagnosis to first-line treatment initiation (days)	median (mean)	17 days (24)	26 days (27)	0.260
First-line auto-SCT	Yes	20 (29.9)	19 (17.0)	0.061
	No	47 (70.1)	93 (83.0)	
Type of T cell lymphoma	PTCL-NOS	34 (50.0)	46 (41.4)	0.422
	ALCL ALK-	13 (19.1)	18 (16.2)	
	ALCL ALKu	4 (5.9)	12 (10.8)	
	C-ALCL	2 (2.9)	2 (1.8)	
	AITL	1 (1.5)	11 (9.9)	
	T-NHL	4 (5.9)	7 (6.3)	
	MF or SS	1 (1.5)	1 (0.9)	
	NK/T nasal	7 (10.3)	9 (8.1)	
	EATL	2 (2.9)	5 (4.5)	
5-years OS	% (95% CI)	65.6 (53.9–77.4)	47.6 (38.2–57.1)	0.008
5-years PFS	% (95% CI)	59.0 (47.0–71.0)	32.9 (24.0–41.7)	0.001

[a] All characteristics are known in more than 92% of patients, with exception of Bulky disease (81%)

[b] Fisher exact test, Mann-Whitney test or log-rank test

5.1.2.10 Comparison of gemcitabin, cisplatin, and dexamethasone (GDP), CHOP, and CHOPE in the first-line treatment of peripheral T-cell lymphomas (Jia et al. 2016).

Ninety-three consecutively treated PTCL patients (including 13 ALK- ALCL, but no ALK+ ALCL patients) diagnosed between 2003 and 2014 and treated at two Beijing hospitals were included in this retrospective analysis. 40 and 42 patients received CHOP and CHOEP, respectively, while 11 patients received GDP. Patients were only included if they did not receive subsequent stem cell transplant.
Patient characteristics were well balanced between the CHOP, CHOEP, and GDP populations, table K, below.

TABLE K. BASELINE CHARACTERISTICS OF CHOP AND CHOEP TREATED PTCL PATIENTS (JIA ET AL. 2016).

Table 1 Clinical characteristics of all PTCL patients

Patients	CHOP ($n = 40$)	CHOPE ($n = 42$)	GDP ($n = 11$)	*P* Value
Age (years)				0.612
≤60	28 (70.0%)	32 (76.2%)	7 (63.6%)	
>60	12 (30.0%)	10 (23.8%)	4 (36.4%)	
Sex				0.780
Male	25 (62.5%)	29 (69.0%)	8 (72.7%)	
Female	15 (37.5%)	13 (31.0%)	3 (27.3%)	
Ann Arbor Stage				0.820
I/II	12 (30.0%)	15 (35.7%)	3 (36.4%)	
III/IV	28 (70.0%)	27 (64.3%)	6 (63.6%)	
ECOG				0.176
0–1	32 (80.0%)	38 (90.5%)	11 (100%)	
≥2	8 (20.0%)	4 (9.5%)	0 (0%)	
IPI				0.417
0–1	15 (37.5%)	20 (47.6%)	3 (27.3%)	
≥2	25 (62.5%)	22 (52.4%)	8 (72.7%)	
PIT				0.685
0–1	29 (72.5%)	34 (81.0%)	9 (81.8%)	
≥2	11 (27.5%)	8 (19.0%)	2 (18.2%)	
Median chemotherapy cycles	4	5	6	0.078
Radiotherapy				0.891
No	31 (77.5%)	31 (73.8%)	8 (72.7%)	
Yes	9 (22.5%)	11 (26.2%)	3 (27.3%)	

PTCL, peripheral T-cell lymphomas; ECOG, Eastern Cooperative Oncology Group; IPI, international prognostic index; PIT, Prognostic Index for T-cell lymphoma

Comparisons of clinical characteristics and response rate between different groups were performed using χ2 test and Wilcoxon Rank-Sum test. Survival analysis was estimated by the Kaplan–Meier method, and differences between curves were analyzed using the log-rank test. The Cox proportional hazards model was used for multivariate analysis. $P < 0.05$ was considered statistically significant and all P values correspond to two-sided significance tests (Jia et al. 2016).

5.1.2.11 CHOEP-21 Chemotherapy for Newly Diagnosed Nodal Peripheral T-Cell Lymphomas (PTCLs) in Maharaj Nakorn Chiang Mai Hospital

24 consecutive 18-60-year-old PTCL patients were treated with CHOEP-21 and compared to 11 historic CHOP treated control patients in this study. Most of the patients were PTCL-NOS (64% in each arm); ALK+ sALCL patients were not included.

Besides gender, the baseline characteristics were well balanced, table L, below.

TABLE L. BASELINE CHARACTERISTICS OF CHOP AND CHOEP TREATED PATIENTS (RATTARITTAMRONG ET AL. 2013).

Table 1. Comparison between CHOEP and CHOP historical control patient characteristics and outcome

Parameter	CHOEP-21	CHOP-21	p-value
Number of patients	24	11	-
Age, mean ± SD y (range)	48.9±9.9 (18-60)	48.4±10.3 (25-60)	0.683
Sex (male:female ratio)	20:4	5:6	0.041
Histologic subtype, No. patients (%)			
PTCL, NOS	16 (64)	7 (64)	1.000
Non-PTCL, NOS (ALCL, ALK-negative: AITL)	8 (1:7; 36%)	4 (0:4; 36%)	
Ann Arbor stage IV, No. patients (%)	15 (63)	4 (36)	0.273
B symptoms, No. patients (%)	12 (50)	4 (36)	0.257
Bone marrow involvement, No. patients (%)	6 (25)	1 (9)	0.392
Elevated LDH serum level, No. patients (%)	14 (58)	7 (64)	1.000
Bulky disease (%)	0 (0)	0 (0)	-
IPI score at least 2, No. patients (%)	15 (72)	5 (46)	0.467
0-1	9 (38)	6 (54)	
2-3	12 (50)	3 (27)	
4-5	3 (12)	2 (18)	
CR (%)	10 (42)	8 (72)	0.146
Overall response rate; CR + PR (%)	14 (58)	8 (72)	0.709
Relapse/refractory (%)	12 (50)	5 (45)	1.000

CHOEP = cyclophosphamide, doxorubicin, vincristine etoposide and prednisolone; CHOP = cyclophosphamide, doxorubicin, vincristine and prednisolone; PTCL, NOS = peripheral T-cell lymphoma, not otherwise specified; ALK-negative ALCL = anaplastic lymphoma kinase-negative large cell lymphoma; AITL = angioimmunoblastic T-cell lymphoma; LDH = lactate dehydrogenase; IPI = international prognostic index; CR = complte response; PR = partial response

The primary end-point was EFS, OS was the secondary endpoint.
EFS and OS curves were calculated according to the Kaplan-Meier method.
The patient characteristics were compared between the 2 treatment arms using the Fisher's exact test or the Pearson Chi-square test in cases of discrete variables, or the Wilcoxon rank sum test in cases of continuous variables. The response end points were compared between the two treatment arms using logistic regression and EFS and OS were compared according to the Kaplan-Meier method (Rattarittamrong et al. 2013).

5.1.3 Results per study

5.1.3.1 Brentuximab vedotin with chemotherapy for CD30-positive peripheral T-cell lymphoma (ECHELON-2): a global, double-blind, randomized, phase 3 trial.

OS

With a median follow-up time of 36.3 months, the median OS was not reached for either treatment arm; the estimated 2-yr OS was [redacted] The Kaplan-Meier derived Hazard Ratio for OS was 0.54 (95% CI: 0.34-0.87, p=0.0096) (CHMP 2020b), figure B. It is noteworthy that the two curves separate 2 months after randomization and that the prolonged flatness of the A+CHP arm suggest a sustainable effect of A+CHP.

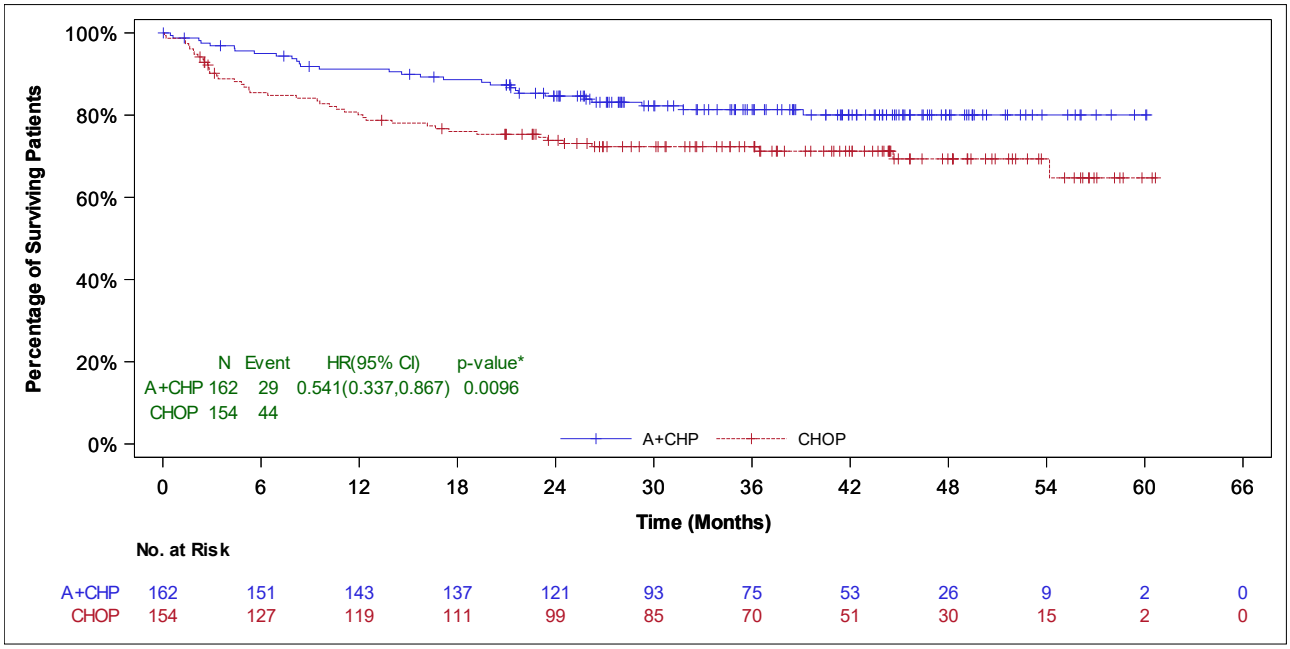


FIGURE B. OVERALL SURVIVAL IN SALCL PATIENTS. MEDIAN FOLLOW-UP: 36.3 MONTHS (TAKEDA 2019).

PFS

With a median follow-up time of 36.3 months, the median PFS was 55.7 and 54.2 for the A+CHP and CHOP arms respectively.

While the median PFS is numerically similar between the two treatment arms, the Kaplan-Meier curves, figure C, below, show a markedly different picture of the PFS-events of the sALCL population. The two arms separate very early and stay separated for > 2 yrs.
Thus, the 25% percentile PFS is 15.6 months and 4.6 months for A+CHP and CHOP, respectively (CHMP 2020b) while the (estimated) 2-yrs PFSs were 68.4% (95% CI: 60.4%-75.2%) and 53.9% (95% CI: 45.5%-61.5%), respectively.
However, the flattening of the curves occurs slightly before the median PFS is reached in either arm, figure C, below, and extends to a timepoint (54 months) where only 5 patients remain at risk in either arm. The sudden large drop of both curves at 54 months, is thus an artifact of the low number of patients at risk in either arm at this late timepoint. This sudden drop creates an inconstant course of the curves resulting in

numerically similar median PFS despite the clear differences in PFS kinetics between the two arms. Indeed, the Hazard Ratio for PFS, which takes the course of the entire curves into consideration, was 0.59 (95% CI: 0.42-0.84, p=0.0031), figure C, below, supporting that the PFS of the A+CHP arm is significantly favored over the CHOP arm.

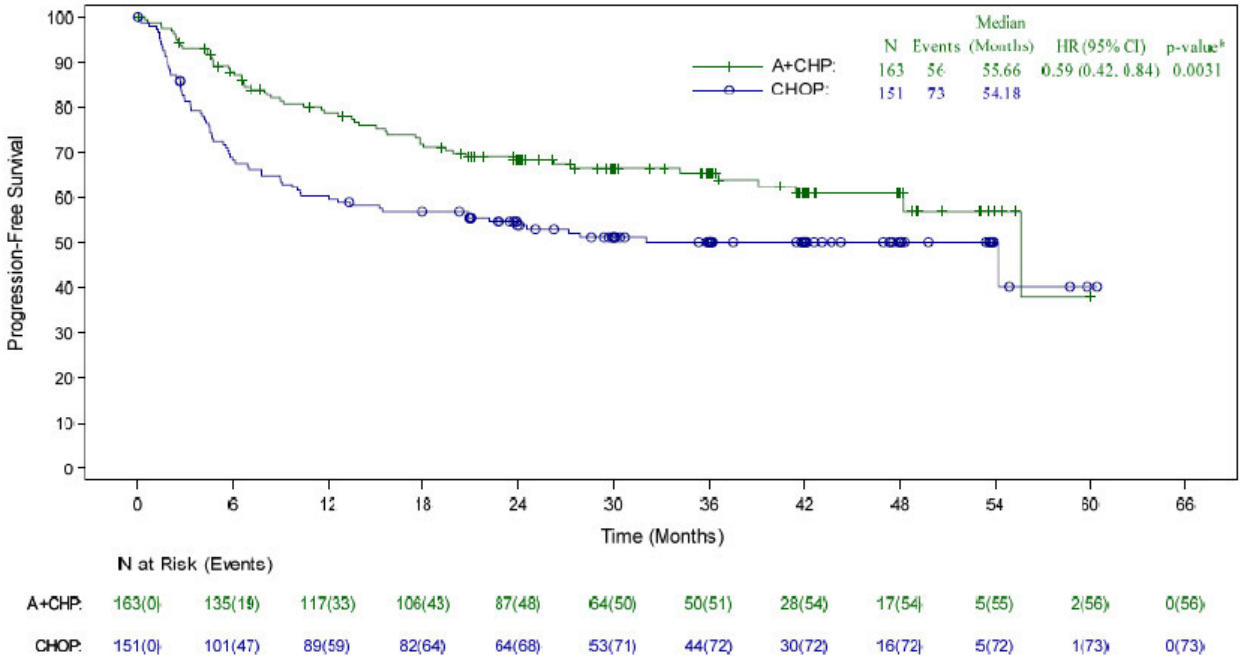


FIGURE C. PROGRESSION FREE SURVIVAL IN THE SALCL PATIENT POPULATION, FROM (CHMP 2020B).

Data marked in yellow are unpublished and confidential.

Health Related Quality of Life

[redacted] (Takeda 2019).

[redacted] (Takeda 2019).

[redacted] (Takeda 2019).

Adverse Events

A+CHP substitutes the microtubule disrupting agent Vincristine (O) from CHOP with targeted microtubule disrupting agent Adcetris (A). The overall Adverse Event profile between A+CHP and CHOP is therefore relatively comparable.

[redacted] (Takeda 2019).

[redacted] (Takeda 2019).

All data are summarized in table A3a

5.1.3.2 General considerations for studies addressing the efficacy of CHOP vs. CHOEP

In the following account of results from the presented studies, all outcomes have been defined the same way: PFS: the time from diagnosis to death or progressive disease (whichever came first), OS: the time from diagnosis to death, EFS: time to death, time to progressive disease or start of different anti-cancer treatment (whichever came first).
Data is presented as reported in the publications with the limitations this entails.

5.1.3.3 Treatment and prognosis of mature T-cell and NK-cell lymphoma: an analysis of patients with T-cell lymphoma treated in studies of the German High-Grade Non-Hodgkin Lymphoma Study Group

While a total of 320 patients were included in the study, the differences in treatment between the eight trials that formed the foundation for the study meant that only 42 and 41 patients received CHOEP and CHOP respectively. The analyses presented in below are derived from these patients.

OS
For patients < 60 yrs with normal LDH values, no difference was found between CHOP and CHOEP, p=0.176.

EFS
The study found that for patients < 60 yrs, with normal LDH values, addition of etoposide to CHOP led to longer Event-Free-Survival in the total PTCL population (3-yr EFS: 75.4% (95% CI: 62.1-88.7%) vs. 51.0% (95% CI: 35.7%-66.3%), P=0.003.

HRQOL: Not reported.

AEs: Not reported.

In summary: No effects were seen in the ITT population, but secondary subgroup analysis found an EFS effect with the addition of etoposide within the younger patients with normal LDH-values.

Table A3b summarizes outcomes relevant for this application.

5.1.3.4 The addition of etoposide to CHOP is associated with improved outcome in ALK+ adult anaplastic large cell lymphoma: A Nordic Lymphoma Group study.

OS

For younger patients (18-40 yrs, N=79)), no difference in OS was found between CHOP and CHOEP.
For older patients (41-65 yrs, N = 16 and 27 for CHOP and CHOEP, respectively), addition of etoposide was associated with statistically significant improvements of OS, the magnitude of which varied according to which clinical parameter (IPI2-5, gender, LDH) the authors corrected data for, table M, below (Cederleuf, Bjerregård Pedersen, et al. 2017).

TABLE M. PROGNOSTIC FACTORS AND CHARACTERISTICS OF ALK+ ALCL PATIENTS AGED 41-65 YRS (CEDERLEUF, BJERREGÅRD PEDERSEN, ET AL. 2017)

Table II. Prognostic factors and characteristics of ALK+ ALCL patients aged 41–65 years.

	Characteristic			PFS			OS		
Variable	CHOP	CHOEP	*P*-value	HR	95% CI	*P*-value	HR	95% CI	*P*-value
Extranodal involvement >1	3 (19%)	1 (3·8%)	0·11	0·42	0·55–3·14	0·40	0·56	0·074–4·24	0·58
Ann Arbor stage III–IV	8 (50)	13 (48)	0·91	1·77	0·71–4·42	0·22	1·56	0·61–3·97	0·35
WHO PS > 1	3 (19)	7 (26)	0·59	1·03	0·37–2·85	0·96	1·09	0·39–3·09	0·87
LDH > UNL	3 (21)	8 (31)	0·53	2·28	0·86–6·03	0·097	1·44	0·52–3·97	0·48
IPI 2–5	5 (36)	11 (44)	0·61	2·19	0·81–5·89	0·12	1·71	0·62–4·72	0·30
Albumin <35 g/l	6 (43)	6 (33)	0·58	3·06	1·01–9·29	0·049	2·42	0·77–7·63	0·13
Male gender	8 (50)	18 (67)	0·28	2·64	0·95–7·34	0·063	2·25	0·80–6·32	0·13
B symptoms	9 (56)	16 (62)	0·74	1·47	0·55–3·92	0·44	1·40	0·52–3·79	0·51
Anaemia (Hb <120 g/l)	7 (50)	8 (40)	0·56	1·61	0·55–4·67	0·39	1·40	0·46–4·27	0·56
Lymphopenia (<1·0 × 10^9/l)	2 (18)	2 (12)	0·64	1·68	0·36–7·91	0·51	1·81	0·37–8·80	0·46
Bulky disease	0 (0)	5 (20)	0·096	0·35	0·045–2·69	0·31	0·46	0·059–3·53	0·45
Liver involvement	1 (6·3)	1 (3·7)	0·70	1·89	0·25–14·4	0·54	2·84	0·37–22·0	0·32
Treatment analysis									
CHOEP (ref: CHOP)	16 (37)	27 (63)		0·45	0·18–1·15	0·096	0·38	0·14–0·99	0·047
CHOEP adjusted for gender				0·37	0·14–0·94	0·037	0·29	0·11–0·79	0·016
CHOEP adjusted for LDH				0·31	0·11–0·88	0·027	0·27	0·092–0·80	0·018
CHOEP adjusted for IPI 2–5				0·32	0·11–0·92	0·034	0·25	0·082–0·76	0·014

95% CI, 95% confidence interval; CHOEP, CHOP + etoposide; CHOP, cyclophosphamide, doxorubicin, vincristine and prednisone; Hb, Haemoglobin; HR, Hazard ratio; IPI, international prognostic index; LDH, Lactate dehydrogenase; OS, Overall survival; PFS, Progression-free survival; UNL, Upper normal limit; WHO PS, World Health Organization performance status.

PFS

For younger patients (18-40 yrs), no difference in PFS was found between CHOP and CHOEP.
For older patients (41-65 yrs), addition of etoposide was associated with statistically significant improvements of PFS, the magnitude of which varied according to which clinical parameter (IPI2-5, gender, LDH) the authors corrected data for, table above (Cederleuf, Bjerregård Pedersen, et al. 2017).

HRQOL: Not Reported.

AEs: Not reported.

In summary: Subgroup analysis found an OS and PFS effect with the addition of etoposide within older ALK+ ALCL (Cederleuf, Bjerregård Pedersen, et al. 2017).

Table A3c-d summarizes outcomes relevant for this application.

5.1.3.5 *Redefining the role of etoposide in first-line treatment of peripheral T-cell lymphoma*

OS

PTCL

In the single center cohort no differences in OS was found between CHOP (N=77) and CHOEP (N=20) treated patients, P=0.654 (Kim et al. 2017).
However, in the national database, a clear OS disadvantage was identified for patients treated with CHOEP (N=609) vs. patients treated with CHOP (N=646), P<0.001, (Kim et al. 2017). A multivariate analysis using Cox Regression confirmed this finding, identifying addition of etoposide in first line treatment as an adverse prognostic factor for OS, HR: 0.746 (95% CI: 0.59-0.95, P= 0.016).

PTCL < 45 yrs

In the national database addition of etoposide led to a statistically worse OS-outcome (P<0.001, N=476 in total); no difference was found in the single center analysis (P=0.777, N=25 in total) (Kim et al. 2017).

ALCL

In the single center cohort no differences in OS was found between CHOP (N=NR) and CHOEP (N=NR[1]) treated patients, P=0.240 (Kim et al. 2017).
However, in the national database, a clear OS disadvantage was identified for patients treated with CHOEP (N=NR) vs. patients treated with CHOP (N=NR), P=0.030 (Kim et al. 2017).

PFS:

PTCL

In the single center cohort no differences in PFS was found between CHOP (N=77) and CHOEP (N=20) treated patients, P=0.383 (Kim et al. 2017).
However, in the national database, a clear PFS disadvantage was identified for patients treated with CHOEP (N=609) vs. patients treated with CHOP (N=646), P<0.001 (Kim et al. 2017). A multivariate analysis using Cox Regression confirmed this finding, identifying addition of etoposide in first line treatment as an adverse prognostic factor for PFS, HR: 0.474 (95% CI: 0.25-0.88, P= 0.019).

PTCL < 45 yrs

In the national database addition of etoposide led to a statistically worse PFS-outcome (P=0.003)(Kim et al. 2017).

ALCL

In the single center cohort no differences in PFS was found between CHOP (N=NR[2]) and CHOEP (N=NR[2]) treated patients, P=0.944 (Kim et al. 2017).
However, in the national database, a clear PFS disadvantage was identified for patients treated with CHOEP (N=NR) vs. patients treated with CHOP (N=NR), P=0.041 (Kim et al. 2017).

HRQOL:

Not reported.

[1] Not Reported
[2] Not Reported

AEs
Addition of etoposide led to greater incidence of transfusion requirements and multivariate analysis identified addition of etoposide as an adverse prognostic factor in the national database (Kim et al. 2017).

A similar analysis performed in the smaller single center cohort found no differences (Kim et al. 2017).

Tables A3e-i summarizes relevant study data.

5.1.3.6 Real-world data on prognostic factors and treatment in peripheral T-cell lymphomas: a study from the Swedish Lymphoma Registry

5-yrs OS
ITT PTCL patients
The ITT population was not analyzed for the impact of addition of etoposide

ALK- ALCL, AITL, PTCL-NOS, EATL and TCL U patients (18-70 yrs)
No difference was found for OS between CHOP and CHOEP treated PTCL patients (HR: 0.78, P=0.288) (Ellin et al. 2014).
ALK- ALCL, AITL, PTCL-NOS, EATL and TCL U patients (18-60 yrs)
No difference was found for OS between CHOP and CHOEP treated PTCL patients in a subsequent multivariable model (HR: 0.58, P=0.052) (Ellin et al. 2014).

5-yrs PFS
ALK- ALCL, AITL, PTCL-NOS, EATL and TCL U patients (18-70 yrs)
No difference was found for PFS between CHOP and CHOEP treated PTCL patients (HR: 0.84, P=0.424) (Ellin et al. 2014).
ALK- ALCL, AITL, PTCL-NOS, EATL and TCL U patients (18-60 yrs).
A subsequent multivariable model analysis found a better PFS for CHOEP treated patients (HR: 0.49, 95% CI: 0.29-0.83, P=0.008) among younger patients (Ellin et al. 2014).

HRQOL
Not Reported

AEs

Not Reported

Tables A3j-k summarizes relevant data.

5.1.3.7 Up-front autologous stem-cell transplantation in peripheral T-cell lymphoma: NLG-T-01

This single arm prospective phase II trial constitutes one of the largest pieces of evidence for the efficacy of CHOEP (followed by up-front autologous stem-cell transplant) in the 1. Line treatment setting of PTCL (excluding ALK+ ALCL). However, all patients aged 61-67 yrs were, per protocol, treated with CHOP rather than CHOEP. This enables a naïve comparison of OS, PFS, CR, and ORR between near aged-matched 55-60

yrs (N=50) and 61-67 yrs (N=42) treated with CHOEP and CHOP, respectively, as well as the overall CHOP/CHOEP treated ITT population (N=160).
This naïve comparison is summarized in the below figure and text.

Among the CHOP treated patients the median age was 64.
10%, 24%, 26%, and 40% of these patients had low, low-intermediate, intermediate-high, and high IPI respectively.

OS
5-yr OS was 45%, 40%, and 51% for the 61-67 yrs CHOP treated patients, the 55-60 yrs CHOEP treated patients, and the ITT population, respectively (d'Amore et al. 2012).

PFS
5-yr PFS was 34%, 39%, and 44% for the 61-67 yrs CHOP treated patients, the 55-60 yrs CHOEP treated patients, and the ITT population, respectively (d'Amore et al. 2012).

ORR
ORR was 88%, 84%, and 81% for the 61-67 yrs CHOP treated patients, the 55-60 yrs CHOEP treated patients, and the ITT population, respectively (d'Amore et al. 2012).

CR
5-yr PFS was 55%, 50%, and 51% for the 61-67 yrs CHOP treated patients, the 55-60 yrs CHOEP treated patients, and the ITT population, respectively (d'Amore et al. 2012).

None of the above values were subjected to formal statistical analysis; the authors of the publication referred to them as “similar”.

HRQOL
Not Reported

AEs
Not Reported

Table A3l and figure D summarizes these data.

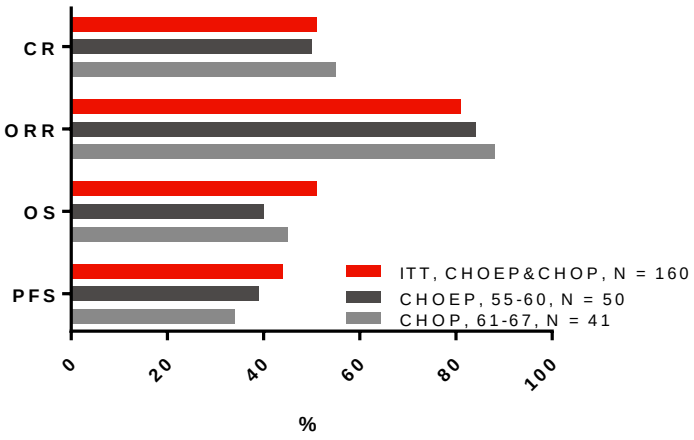


FIGURE D. SUMMARY OF CR, ORR, OS, AND PFS ACCORDING TO PATIENT GROUP (D'AMORE ET AL. 2012).

5.1.3.8 First-line therapy for T cell lymphomas: a retrospective population-based analysis of 906 T cell lymphoma patients

OS

Among 113 CHOP and 68 CHOEP treated PTCL patients, the 5-yrs OS was significantly improved by addition of etoposide (65.6% vs. 47.6%, P = 0.008) (Janikova et al. 2019).
These results were confirmed using multivariable Cox proportional hazard model with IPI-score as a potential confounder (further details of data not reported).

PFS

Among 113 CHOP and 68 CHOEP treated PTCL patients, the 5-yrs PFS was significantly improved by addition of etoposide (59.0% vs. 32.9%, P < 0.001) (Janikova et al. 2019).

HRQOL

Not Reported

AEs

Not Reported

Table A3m summarizes the data.

5.1.3.9 Comparison of gemcitabin, cisplatin, and dexamethasone (GDP), CHOP, and CHOEP in the first-line treatment of peripheral T-cell lymphomas

1-yr OS

For 1yr OS, a statistically significant difference between CHOP, CHOEP, and GDP treated patients (N=40, 42, and 11, respectively) were found (P=0.013) and pairwise comparison was therefore performed. The pairwise analysis showed a statistically significant difference between CHOP and CHOEP treated patients: 65.0% vs. 83.3%, P=0.03 (Jia et al. 2016).

PFS

The study found a statistically insignificant difference in median PFS and 1-yr PFS between CHOP, CHOEP, and GDP (P=0.094 and P=0.078, respectively).

HRQOL

Not Reported

AEs

Not Reported

Table A3n summarizes the data.

5.1.3.10 CHOEP-21 Chemotherapy for Newly Diagnosed Nodal Peripheral T-Cell Lymphomas (PTCLs) in Maharaj Nakorn Chiang Mai Hospital

2- yrs OS
For 2-yr OS, no statistically significant difference between CHOEP and CHOP treated patients (N=24 and 11, respectively) were found (54.4% vs. 51.9%, P=0.65).

2-yrs EFS
No statistically significant difference between CHOEP and CHOP treated patients (N=24 and 11, respectively) were found (37.6% vs. 51.4%, P=0.40).

HRQOL
Not Reported

AEs

Not Reported

Table A3o summarizes the data.

5.1.4 Naïve Comparative analyses of efficacy of CHOP vs. CHOEP

General considerations

The studies presented above are almost all retrospective, observational studies which results in substantial inter-study heterogeneity, inter-study arm heterogeneity, and risk of treatment and selection bias within the individual studies.
Furthermore, the overall level of information that could be extracted from the publications was limited and insufficient to perform statistically valid comparisons, i.e. a general lack of reporting of OS and PFS data at a relative (HR) or Kaplan-Meier curve level. Indeed, information such as patient numbers per study arm, absolute and relative outcomes and confidence intervals were inconsistently reported; frequently conclusions were reported at the level of “no difference was observed” with-out further information. Some publications did not report basic information such as number of patients in the individual subgroup analyses.
Finally, the analysis that addressed issues from the current application (efficacy of CHOP vs. CHOEP) was not performed at the ITT level, but at subgroups of patients from the ITT, who had received CHOP/CHOEP), further downgrading the overall level of evidence.
An attempt to make a formal comparison of CHOP vs. CHOEP using the publications identified was therefore abandoned in favor of a naïve summary (narrative synthesis) of the data presented above.

OS

None of the included studies provide randomized head-to-head comparison of the efficacy of CHOP vs CHOEP in ALCL, or PTCL, patients. The evidence level is thus low.

The six retrospective studies, one prospective single arm trial, and one prospective single-arm trial with historic controls reports 16 analysis of relevance for this application.

These 16 analyses report divergent results for OS. Thus, 10 of the analyses show no difference in OS between CHOP and CHOEP treated patients, 3 analyses show a survival benefit of CHOEP over CHOP, while 3 analyses conversely demonstrate an inferior survival among CHOEP treated patients (as compared to CHOP treated patients), table N.

TABLE N. SUMMARY OF OS DATA FROM STUDIES INCLUDED IN THE INDIRECT EFFICACY COMPARISON OF CHOP AND CHOEP.

Reference	Conclusion	Subgroup N (CHOP vs CHOEP)
(Cederleuf, Bjerregård Pedersen, et al. 2017)	No OS difference	ALK+ ALCL: 18-40 yrs, (17 vs. 23)
	OS benefit of CHOEP	ALK+ ALCL: 41-65 yrs, (16 vs 27)
(d'Amore et al. 2012)	No OS difference	ITT, (N=160) 55-60, CHOEP, (N=50) 61-67, CHOP, (N=41)
(Ellin et al. 2014)	No OS difference	ALK- ALCL, AITL, PTCL-NOS, EATL and TCL U patients (18-70 yrs) (107 vs. 145)
	No OS difference	ALK- ALCL, AITL, PTCL-NOS, EATL and TCL U patients (18-60 yrs) N was not reported)
(Janikova et al. 2019)	OS benefit of CHOEP	PTCL patients (68 vs. 113)
(Jia et al. 2016)	OS benefit of CHOEP	PTCL patients (42 vs. 40)
(Kim et al. 2017)	CHOEP results in inferior OS	ITT (PTCL), National analysis, (646 vs. 609)
	No OS difference	ITT (PTCL), single center, (77 vs 20)
	CHOEP results in inferior OS	PTCL < 45 yrs, (N = 476; unclear how many N in each group)
	No OS difference	PTCL < 45 yrs, (N = 25; unclear how many N in each group)
	CHOEP results in inferior OS	ALCL, National analysis, (N not reported)

	CHOEP results in inferior OS	ALCL, single center analysis (N not reported)
(Schmitz et al. 2010) summarizing 8 studies using variable doses and modifications of CHOP / CHOEP.	No OS difference	18-70 yrs, PTCL Patients (N was not reported)
	No OS difference	18-60 yrs, PTCL Patients with LDH <ULN (41 vs 42)
(Rattarittamrong et al. 2013)	No OS difference	ITT, PTCL patients, Single institution (24 vs. 11)

It is important to note that the above data originates from a heterogenous data background, generally characterized by a low level of evidence.
Indeed, several of the studies report data analyses performed in very small patient populations (e.g. 11 vs. 24 (Rattarittamrong et al. 2013), 41 vs. 42 (Schmitz et al. 2010), 16 vs 27 (Cederleuf, Bjerregård Pedersen, et al. 2017), 40 vs. 42 (Jia et al. 2016) etc). Given these low patient numbers in the analyses and the occasionally very narrow patient populations it is difficult to extend the findings from many of the above studies to a general consensus of the relative efficacy of CHOP/CHOEP within the ALCL/PTCL patient group with certainty. One example of such unclear levels of extendability to the general ALCL/PTCL population, is the finding of a survival benefit of CHOEP (N=27) over CHOP (N=16) specifically in elderly (41-65 yrs) ALK+ ALCL patients (Cederleuf, Bjerregård Pedersen, et al. 2017).

In contrast to the many studies with a relatively low number of study subjects, Kim et al. assessed the efficacy of CHOEP vs. CHOP in populations of 609 and 656 PTCL patients, respectively, and found that CHOEP was less efficacious than CHOP (Kim et al. 2017). This outcome was repeated when Kim et al., did the same analysis specifically in ALCL patients and in PTCL patients < 45 yrs of age (Kim et al. 2017).
On the other hand, Ellin et al., in a cohort of 248 PTCL patients (not including ALK+ ALCL) found no OS difference between CHOEP and CHOP (Ellin et al. 2014).

Given the acknowledged heterogeneity among PTCL entities included in the studies, the inherent risk of treatment bias in retrospective studies, and the above lack of a unified conclusion from the identified studies, it remains impossible to conclude with evidence-based certainty that CHOEP provides an OS-benefit over CHOP for PTCL/ALCL patients.

PFS

None of the included studies provide randomized head-to-head comparison of the efficacy of CHOP vs CHOEP in ALCL, or PTCL, patients. The evidence level is thus low.
The six retrospective studies, one prospective single arm trial, and one prospective single-arm trial with historic controls reports 16 analyses of relevance for this application.
These 16 analyses report divergent results for PFS. Thus, 9 of the analyses show no difference in PFS between CHOP and CHOEP treated patients, 4 analyses show a PFS benefit of CHOEP over CHOP, while 3 analyses conversely demonstrate an inferior PFS among CHOEP treated patients (as compared to CHOP

treated patients), table O.

TABLE O. SUMMARY OF PFS DATA FROM STUDIES INCLUDED IN THE INDIRECT EFFICACY COMPARISON OF CHOP AND CHOEP.

Reference	Conclusion	Subgroup N (CHOP vs CHOEP)
(Cederleuf, Bjerregård Pedersen, et al. 2017)	No PFS benefit of CHOEP	ALK+ ALCL: 18-40 yrs, (17 vs. 23)
	PFS benefit of CHOEP	ALK+ ALCL: 41-65 yrs, (16 vs 27)
(d'Amore et al. 2012)	No PFS benefit of CHOEP	ITT, (N=160) 55-60, CHOEP, (N=50) 61-67, CHOP, (N=41)
(Ellin et al. 2014)	No PFS benefit of CHOEP	ALK- ALCL, AITL, PTCL-NOS, EATL and TCL U patients (18-70 yrs) (107 vs. 145)
	PFS benefit of CHOEP	ALK- ALCL, AITL, PTCL-NOS, EATL and TCL U patients (18-60 yrs) (N was not reported)
(Janikova et al. 2019)	PFS benefit of CHOEP	PTCL patients (68 vs. 113)
(Jia et al. 2016)	No PFS benefit of CHOEP	PTCL patients (42 vs. 40)
(Kim et al. 2017)	CHOEP results in inferior PFS	ITT (PTCL), National analysis, (646 vs. 609)
	No PFS benefit of CHOEP	ITT (PTCL), single center, (77 vs 20)
	CHOEP results in inferior PFS	PTCL < 45 yrs, (N = 476; unclear how many N in each group)
	No PFS benefit of CHOEP	PTCL < 45 yrs, (N = 25; unclear how many N in each group)
	CHOEP results in inferior PFS	ALCL, National analysis, (N not reported)
	No PFS benefit of CHOEP	ALCL, single center analysis (N not reported)
(Schmitz et al. 2010) summarizing 8 studies using variable doses and modifications of CHOP / CHOEP.	No EFs benefit of CHOEP	18-70 yrs, PTCL Patients (N was not reported)
	EFS benefit of CHOEP	18-60 yrs, PTCL Patients with LDH <ULN (41 vs 42)
(Rattarittamrong et al. 2013)	No EFS benefit of CHOEP	ITT – PTCL patients, Single institution

It is important to note that the above data originates from a heterogenous data background, generally characterized by a low level of evidence.

Indeed, several of the studies report data analyses performed in very small patient populations (e.g. 11 vs. 24 (Rattarittamrong et al. 2013), 41 vs. 42 (Schmitz et al. 2010), 16 vs 27 (Cederleuf, Bjerregård Pedersen, et al. 2017), 40 vs. 42 (Jia et al. 2016) etc). Given these low patient numbers in the analyses and the occasional very narrow patient populations it is difficult to extend the findings from many of the above studies to a general consensus of the relative efficacy of CHOP/CHOEP within the ALCL/PTCL patient group with certainty. Two example of such unclear levels of extendability to the general ALCL/PTCL population, is the finding of a survival benefit of CHOEP (N=27) over CHOP (N=16) specifically in elderly (41-65 yrs) ALK+ ALCL patients (Cederleuf, Bjerregård Pedersen, et al. 2017) and the finding of a EFS benefit of CHOEP (N=42) over CHOP (N=41) specifically in younger PTCL patients with LDH < ULN (Schmitz et al. 2010). Similarly, an aged-dependent effect was found by Ellin et al., (Ellin et al. 2014), who among PTCL patients (excl. ALK- ALCL) age 18-70 found no prolongation of PFS with addition of etoposide. However, when the analysis subsequently was narrowed by excluding patients age 61-70, a longer PFS was observed with the addition of etoposide (Ellin et al. 2014).

In contrast to the many studies with a relatively low number of study subjects, Kim et al., assessed the efficacy of CHOEP vs. CHOP in populations of 609 and 656 PTCL patients, respectively, and found that CHOEP was less efficacious than CHOP (Kim et al. 2017). This outcome was repeated when Kim et al., did the same analysis specifically in ALCL patients and in PTCL patients < 45 yrs of age (Kim et al. 2017).

However, outside specific age defined subgroups, the majority of the included studies either did not find a statistically significant difference in PFS between CHOP and CHOEP treated patients (d'Amore et al. 2012; Jia et al. 2016; Rattarittamrong et al. 2013; Schmitz et al. 2010), or found a decrease of efficacy when etoposide was added to CHOP (Kim et al. 2017).

Given the acknowledged heterogeneity among PTCL entities included in the studies, the inherent risk of treatment bias in retrospective studies, and the above lack of a unified conclusion from the identified studies, it remains impossible to conclude with evidence-based certainty that CHOEP provides an PFS benefit over CHOP for PTCL/ALCL patients.

HRQOL

None of the identified studies addressed health related quality of life.

AEs

None of the included studies provide randomized head-to-head comparison of the safety of CHOP vs CHOEP in ALCL, or PTCL, patients. The evidence level is thus low.
One study provided information on the AE-burden of CHOEP vs. CHOP in PTCL patients. This study presented two separate analysis: one large retrospective national registry analysis and one small retrospective single center registry analysis. The large national analysis identified an increased risk of anemia and thrombocytopenia with the addition of etoposide to a CHOP backbone, table P, while the small single center analysis did not, table P

TABLE P. SUMMARY OF AE DATA FROM STUDY INCLUDED IN THE INDIRECT SAFETY COMPARISON OF CHOP AND CHOEP.

Reference	Conclusion	Subgroup N (CHOP vs CHOEP)
(Kim et al. 2017)	CHOEP results in increased risk of transfusion requiring anemia.	ITT (PTCL), National analysis, (646 vs. 609)

	CHOEP results in increased risk of transfusion requiring thrombocytopenia.	ITT (PTCL), National analysis, (646 vs. 609)
	CHOEP did not result in increased risk of transfusion requiring anemia.	PTCL, single center analysis (77 vs. 20)
	CHOEP did not result in increased risk of transfusion requiring thrombocytopenia.	PTCL, single center analysis (77 vs. 20)

This is in accordance with findings from randomized clinical trials of CHOEP vs. CHOP in other lymphoma patient populations, where addition of etoposide is associated with a significant ($p<0.001$) increase of the adverse events anemia and thrombocytopenia (Pfreundschuh, Trümper, Kloess, Schmits, Feller, Rudolph, et al. 2004; Pfreundschuh, Trümper, Kloess, Schmits, Feller, Rübe, et al. 2004).

5.1.4.1 Conclusion

The systematic literature search has not identified a body of literature that consistently demonstrates a statistically significant difference in OS, PFS/EFS or HRQoL among CHOEP or CHOP treated PTCL patients. On the contrary, the majority of the analyses demonstrated no difference in PFS and OS between CHOP and CHOEP (d'Amore et al. 2012; Jia et al. 2016; Rattarittamrong et al. 2013; Schmitz et al. 2010) while other analyses demonstrated conflicting and subgroup specific results (Cederleuf, Bjerregård Pedersen, et al. 2017; Ellin et al. 2014; Kim et al. 2017; Schmitz et al. 2010).

No studies addressed HRQoL differences between CHOP and CHOEP treated patients.

One study and one meta-analysis found an increased risk of anemia and thrombocytopenia among CHOEP treated patients (Deng et al. 2019; Kim et al. 2017). This is in accordance with data from randomized head-to-head phase III trials (Pfreundschuh, Trümper, Kloess, Schmits, Feller, Rudolph, et al. 2004; Pfreundschuh, Trümper, Kloess, Schmits, Feller, Rübe, et al. 2004) that found that addition of etoposide to a backbone of CHOP consistently results in an increased risk of anemia and thrombocytopenia.

Based on the available literature it is not possible to conclude that the addition of etoposide to a backbone of CHOP results in a statistically significant difference in OS, PFS/EFS or HRQOL.

Considering the lack of reproducibility of statistically significant difference in efficacy, the demonstrated efficacy of CHOEP is therefore considered comparable to the demonstrated efficacy of CHOP.

5.1.5 Comparative analyses of A+CHP vs. CHOEP; the Echelon-2 study

Given the lack of evidence-based conclusion of an efficacy difference between CHOP and CHOEP, Takeda will, in accordance with the outline of the protocol, present a comparative analysis of A+CHP vs CHOP, as such data is available from a randomized, double-blind, double-dummy, placebo-controlled head-to-head trial conducted globally (Horwitz et al. 2019).

All data presented below are from analyses performed within the sALCL study population and are summarized in table A3a and table A4a-b.

Data marked in yellow are unpublished and confidential.

OS

With a median follow-up time of 36.3 months, the median OS was not reached for either treatment arm; the estimated 2-yr OS was [redacted] The Kaplan-Meier derived Hazard Ratio for OS was 0.54 (95% CI: 0.34-0.87, p=0.0096) (CHMP 2020b), figure E. It is noteworthy that the two curves separate 2 months after randomization and the prolonged flatness of the A+CHP arm suggest a sustainable effect of A+CHP.

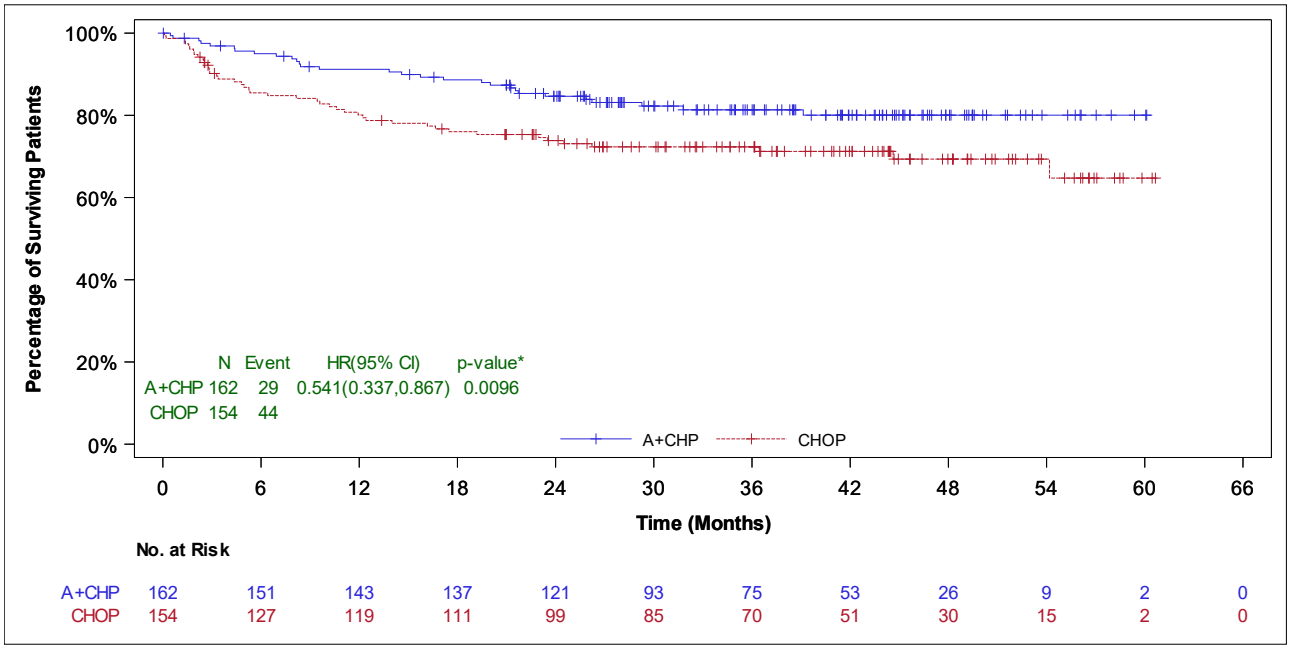


FIGURE E. OVERALL SURVIVAL IN SALCL PATIENTS. MEDIAN FOLLOW-UP: 36.3 MONTHS. FROM (TAKEDA 2019).

PFS

With a median follow-up time of 36.3 months, the median PFS was 55.7 and 54.2 for the A+CHP and CHOP arms respectively.

While the median PFS is numerically similar between the two treatment arms, the Kaplan-Meier curves, figure below, show a markedly different picture of the PFS-events of the sALCL population. The two arms separate very early and stay separated for > 2 yrs.
Thus, the 25% percentile PFS is 15.6 months and 4.6 months for A+CHP and CHOP, respectively (CHMP 2020b) while the (estimated) 2-yrs PFSs were 68.4% (95% CI: 60.4%-75.2%) and 53.9% (95% CI: 45.5%-61.5%), respectively.
However, the flattening of the curves occurs slightly before the median PFS is reached in either arm, figure F, below, and extends to a timepoint (54 months) where only 5 patients remain at risk in either arm. The sudden large drop of both curves at 54 months, is thus an artifact of the low number of patients at risk in either arm at this late timepoint. This sudden drop creates an inconstant course of the curves resulting in numerically similar median PFS despite the clear differences in PFS kinetics between the two arms.
Indeed, the Hazard Ratio for PFS, which takes the course of the entire curves into consideration, was 0.59 (95% CI: 0.42-0.84, p=0.0031), figure F, below, supporting that the PFS of the A+CHP arm is significantly favored over the CHOP arm.

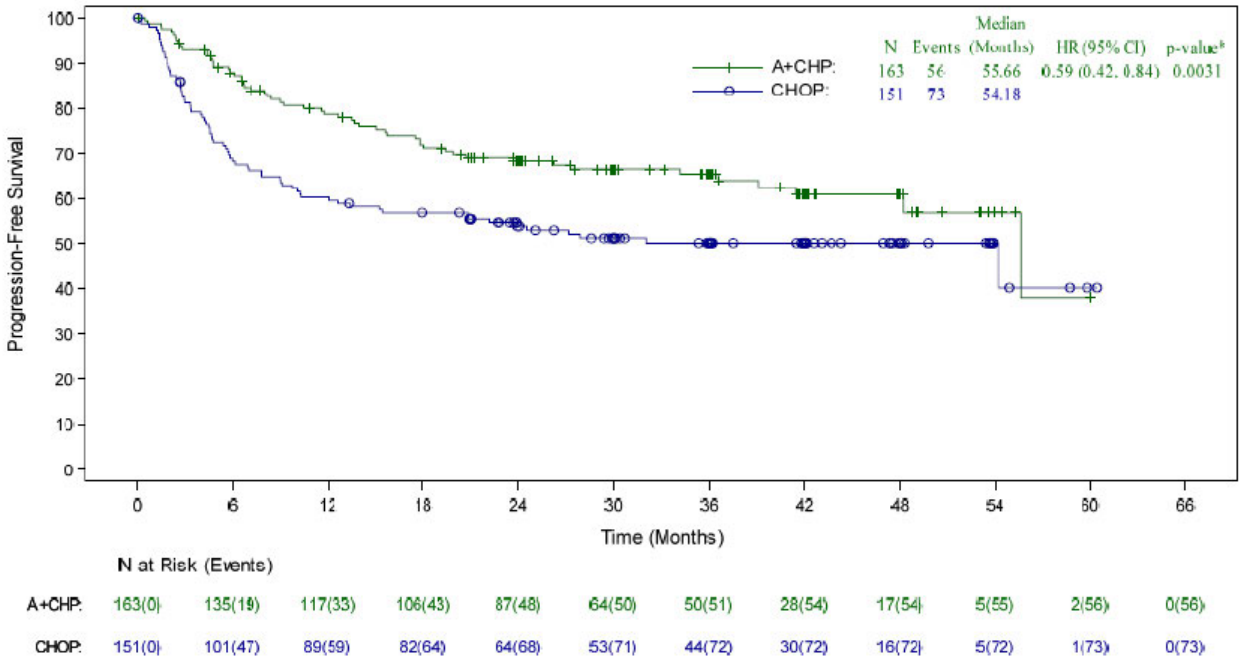


FIGURE F. PROGRESSION FREE SURVIVAL IN THE SALCL PATIENT POPULATION, FROM (CHMP 2020B).

Health Related Quality of Life

[redacted]

Adverse Events

A+CHP substitutes the microtuble disrupting agent Vincristine (O) from CHOP with targeted microtuble disrupting agent: Adcetris (A). The overall Adverse Event profile between A+CHP and CHOP is therefore relatively comparable.

[redacted] Takeda, 2019 #82}.

[redacted] (Takeda 2019).

Two overviews of the specific adverse reactions associated with CHOEP and CHOP, and the frequency of them, are presented below, table Q and R. The overviews are from two large German randomized phase III trials of CHOP and CHOEP in predominantly b-cell lymphoma. While these studies do not address the efficacy of CHOP/CHOEP in T-cell lymphoma, it is reasonable to assume, that the adverse reaction profile is the same across diagnoses.

TABLE Q. SIDE EFFECTS ACCORDING TO TREATMENT AND TREATMENT DENSITY (CHOP/CHOEP) IN LYMPHOMA PATIENTS AGED 18-60 YRS. FROM (PFREUNDSCHUH, TRÜMPER, KLOESS, SCHMITS, FELLER, RUDOLPH, ET AL. 2004).

Side effects according to treatment arms

Effects	CHOP-21, %	CHOP-14, %	CHOEP-21, %	CHOEP-14, %	*P*
Leukocytopenia	34.1	33.6	73.6	72.5	< .001
Thrombocytopenia	2.4	1.2	7.0	22.2	< .001
Anemia	3.6	5.6	8.5	35.4	< .001
Infection	1.8	4.2	4.4	5.2	.390
Mucositis	2.9	3.0	1.6	6.9	.048
Cardiac toxicity	0.6	0.6	2.8	0.6	.232
Neurologic toxicity	3.5	0.6	1.6	3.5	.171
Renal toxicity	0.0	0.0	0.0	1.2	.182
Lung toxicity	0.0	0.6	1.7	1.7	.320
Nausea or vomiting	11.7	6.5	9.4	8.6	.415
Alopecia	63.6	64.8	70.9	67.6	.469

Values in the table represent the percentage of all patients experiencing the respective side effect at least once.

TABLE R. SIDE EFFECTS ACCORDING TO TREATMENT AND TREATMENT DENSITY (CHOP/CHOEP) IN LYMPHOMA PATIENTS AGED 61-75 YRS. FROM (PFREUNDSCHUH, TRÜMPER, KLOESS, SCHMITS, FELLER, RÜBE, ET AL. 2004).

	CHOP-21, %	CHOP-14, %	CHOEP-21, %	CHOEP-14, %	*P*
Leukocytopenia	72.1	70.1	94.4	92.4	< .001
Thrombocytopenia	4.7	15.1	28.4	50.8	< .001
Anemia	12.5	19.5	28.7	45.1	< .001
Infection	8.0	10.6	13.2	24.1	< .001
Mucositis	0.0	7.1	4.9	14.3	< .001
Cardiac toxicity	3.4	4.7	3.7	5.0	.871
Neurologic toxicity	3.4	3.6	6.1	4.3	.617
Renal toxicity	1.1	0.0	0.6	0.6	.756
Lung toxicity	4.0	4.7	3.0	6.2	.560
Nausea or vomiting	8.0	13.5	9.7	15.4	.126
Alopecia	62.5	58.3	58.2	52.7	.328

A direct qualitative comparison of the most common (> 20%) adverse events of A+CHP vs. CHOP is presented in table S below. Data are from the Safety Population from Echelon-2 (Horwitz et al. 2019).

TABLE S. MOST COMMON (> 20%) ADVERSE EVENTS OF A+CHP AND CHOP (HORWITZ ET AL. 2019).

	A+CHP – N=223		CHOP N= 226	
	Any Grade, %	Grade > 3, %	Any Grade, %	Grade > 3, %
Nausea	46	2	38	2
Peripheral sensory Neuropathy	45	4	41	3
Neutropenia	38	35	38	34
Diarrhoea	38	6	20	1

Constipation	29	1	30	1
Alopecia	26	0	25	1
Pyrexia	26	2	19	0
Vomiting	26	1	17	2
Fatigue	24	1	20	2
Anaemia	21	13	16	10

A direct qualitative comparison of common (> 10%) adverse events of brentuximab vedotin and vincristine is presented in table below. Data are from the Safety Population from Echelon-2 (CHMP 2020b).

TABLE T. COMMON (>10%) ADVERSE EVENTS OF A+CHP AND CHOP (CHMP 2020B).

Preferred Term	A+CHP (N=223) n (%)	CHOP (N=226) n (%)
Any event	201 (90)	193 (85)
Peripheral sensory neuropathy	98 (44)	87 (38)
Neutropenia	75 (34)	68 (30)
Nausea	71 (32)	61 (27)
Constipation	47 (21)	50 (22)
Alopecia	38 (17)	30 (13)
Diarrhea	36 (16)	16 (7)
Fatigue	36 (16)	36 (16)
Febrile neutropenia	35 (16)	28 (12)
Vomiting	32 (14)	25 (11)
Anemia	30 (13)	23 (10)
Decreased appetite	26 (12)	16 (7)
Pyrexia	22 (10)	14 (6)

A qualitative and quantitative summary of the adverse reactions associated with brentuximab vedotin monotherapy is presented in Table U, below – from (CHMP 2020a).

Tables A4a-b summarizes the comparative analysis presented in this section.

TABLE U. ADVERSE REACTIONS FOR BRENTUXIMAB VEDOTIN ARE LISTED BY MEDDRA SYSTEM ORGAN CLASS AND PREFERRED TERM. WITHIN EACH SYSTEM ORGAN CLASS, ADVERSE REACTIONS ARE LISTED UNDER FREQUENCY CATEGORIES OF: VERY COMMON (≥ 1/10); COMMON (≥ 1/100 TO < 1/10); UNCOMMON (≥ 1/1,000 TO < 1/100); RARE (≥ 1/10,000 TO < 1/1,000); VERY RARE (< 1/10,000); NOT KNOWN (CANNOT BE ESTIMATED FROM THE AVAILABLE DATA). WITHIN EACH FREQUENCY GROUPING, ADVERSE REACTIONS ARE PRESENTED IN THE ORDER OF DECREASING SERIOUSNESS. FROM (CHMP 2020A).

System organ class	**Adverse reactions (monotherapy)**
Infections and infestations	
Very common:	Infection, upper respiratory tract infection
Common:	Herpes zoster, pneumonia, herpes simplex, oral candidiasis
Uncommon:	Pneumocystis jiroveci pneumonia, staphylococcal bacteraemia, cytomegalovirus infection or reactivation, sepsis/septic shock
Frequency not known:	Progressive multifocal leukoencephalopathy
Blood and lymphatic system disorders	
Very common:	Neutropenia
Common:	Anaemia, thrombocytopenia
Uncommon:	Febrile neutropenia
Immune system disorders	
Uncommon:	Anaphylactic reaction
Metabolism and nutrition disorders	
Very common:	
Common:	Hyperglycaemia
Uncommon:	Tumour lysis syndrome
Psychiatric disorders	
Very common:	
Nervous system disorders	
Very common:	Peripheral sensory neuropathy, peripheral motor neuropathy
Common:	Dizziness
Uncommon:	Demyelinating polyneuropathy
Respiratory, thoracic and mediastinal disorders	
Very common:	Cough, dyspnoea
Gastrointestinal disorders	
Very common:	Nausea, diarrhoea, vomiting, constipation, abdominal pain
Uncommon:	Pancreatitis acute
Hepatobiliary disorders	
Common:	Alanine aminotransferase/aspartate aminotransferase (ALT/AST) increased

5.2 What is the clinical value of brentuximab vedotin in combination with cyclophosphamide, doxorubicin and prednisolone (CHP) compared with cyclophosphamide, doxorubicin, vincristine, and prednisolone (CHOP) for previously untreated patients with sALCL who are not candidates for HDT and ASCT?

5.2.1 General considerations

As the data supporting clinical question 2 is the same data supporting clinical question 1, references to the relevant sections from clinical question 1 will be made below.

5.2.2 Presentation of relevant studies

The Echelon-2 study did not enroll ALK+ sALCL patients with IPI 0-1, and none of the prior studies of A+CHP as 1. Line treatment has included ALK+ sALCL patients with IPI 0-1. The data therefore does not address this specific patient population. However, there is no mechanistic reason to believe that the relative benefit of A+CHP vs. CHOP would not extend to ALK+ sALCL patients with IPI 0-1.

See section 5.1.1.1

5.2.3 Results per study

See section 5.1.2.1 and table A3a.

5.2.4 Comparative analyses

No patients with ALK+ sALCL IPI 0-1 have been included in the analyses, as Takeda do not have data for this specific patient population.

See section 5.1.4

Table A4b summarizes the comparative analysis specifically for this section.

6 Additional data requests

6.1 General considerations

Takeda understands the wish to assess data in the most complete manner possible and therefore seek to provide the requested data whenever possible. However, it is essential that it is understood and accepted that the requested data consists of post-hoc analyses in very small patient groups and that no statistical validity therefore can be inferred from these analyses.

As such, the OS and PFS analyses can only function to support the overall robustness of the efficacy conclusions made within the ITT population and the prespecified sALCL population.

Confidentiality

All additional analyses presented in section 6.3 through 6.5 have been made on the request of the Medicines Council, and are therefore unpublished. Takeda request that the data remain confidential.

HDT and SCT

In accordance with global SOC, stem-cell transplant was not a requirement in the Echelon-2 study and was therefore left to the investigator's discretion.

In keeping with the marked geographic differences in use of HDT, Savage et al. found significant geographic heterogeneity in the use of HDT and SCT in the Echelon-2 study (Savage et al. 2019).

Given the lack of requirement for HDT and SCT, the stratified data presented below must be interpreted cautiously. It is likely that the decision to transplant is biased towards patients with baseline poor prognostics, such as high IPI-score.

Indeed, the largest difference, by far, in the number of transplanted patients between the two treatment arms is found within the patients with IPI 4-5 (73.1% vs. 13.6%, P<0.0001). This finding of most transplants performed in patients with tje worst prognosis, supports the view that intent to transplant was not uniformly distributed across IPI scores, resulting in a plausible risk of treatment bias vis-à-vis transplant.

Given this plausible treatment bias, the fraction of patients who underwent HDT and SCT is therefore not necessarily a reflection of the efficacy of A+CHP and CHOP within the individual sub-populations.

6.2 Impact of adaptation of A+CHP in first line treatment on later lines treatment

Current Danish Guideline for the treatment of relapsed ALCL instructs remission inducing treatment with ICE or DHAP, alternatively single-agent usage of Adcetris/brentuximab vedotin (A). Re-use of Adcetris following use in first line treatments is therefore a potential treatment strategy for relapsed patients.

There is ample evidence for the efficacy of re-use of Adcetris. Thus, objective response to BV retreatment for 23 retreated patients from the A+CHP arm in Echelon-2 was 57% (13/23), of which 43% (10/23) reached CR and 13% (3/23) reached PR (Takeda 2019). In a similar study of retreatment of RR Hodgkin Lymphoma and RR ALCL patients who previously responded to Adcetris monotherapy, the objective response rates for RR HL and RR ALCL patients were 60% and 88%, respectively (Bartlett et al. 2014).

Thus, re-treatment with Adcetris among patients who previously responded is associated with a high degree of disease control. As such, retreatment with Adcetris in RR ALCL patients will remain a reasonable clinical choice left to the physician.
The median length of retreatment was reported to be 7 cycles (Bartlett et al. 2014).

6.3 Subgroup data for OS and PFS stratified according to ALK-status

6.3.1 OS/PFS data for ALK- sALCL patients

FIGURE G KM CURVES OF OS FOR ALK- SALCL PATIENTS. COMPUTED FROM LOG-RANK TEST USING STRATIFICATION FACTORS (ALK-POSITIVE SALCL: YES/NO AND IPI SCORE: 0-1/2-3/4-5) AT RANDOMIZATION (TAKEDA 2019).

FIGURE H. KM CURVES OF PFS FOR ALK- SALCL PATIENTS. COMPUTED FROM LOG-RANK TEST USING STRATIFICATION FACTORS (ALK-POSITIVE SALCL: YES/NO AND IPI SCORE: 0-1/2-3/4-5) AT RANDOMIZATION (TAKEDA 2019).

TABLE V. EFFICACY ESTIMATES OF A+CHP AND CHOP FOR ALK- ALCL PATIENTS. OS/PFS RATE IS ESTIMATED USING KAPLAN-MEIER METHODS AND 95% C.I. IS CALCULATED USING THE COMPLEMENTARY LOG-LOG TRANSFORMATION METHOD. B: FROM STRATIFIED LOG-RANK TEST WITH STRATIFICATION FACTORS (ALK-POSITIVE SALCL: YES/NO AND IPI SCORE: 0-1/2-3/4-5) AT RANDOMIZATION. C: CHI-SQUARE TEST (TAKEDA 2019).

6.3.2 OS/PFS data for ALK+ sALCL patients

FIGURE I. KM CURVES OF OS FOR ALK+ SALCL PATIENTS. COMPUTED FROM LOG-RANK TEST USING STRATIFICATION FACTORS (ALK-POSITIVE SALCL: YES/NO AND IPI SCORE: 0-1/2-3/4-5) AT RANDOMIZATION (TAKEDA 2019).

FIGURE J. KM CURVES OF PFS FOR ALK+ SALCL PATIENTS. COMPUTED FROM LOG-RANK TEST USING STRATIFICATION FACTORS (ALK-POSITIVE SALCL: YES/NO AND IPI SCORE: 0-1/2-3/4-5) AT RANDOMIZATION (TAKEDA 2019).

TABLE W. EFFICACY ESTIMATES OF A+CHP AND CHOP FOR ALK+ ALCL PATIENTS. OS/PFS RATE IS ESTIMATED USING KAPLAN-MEIER METHODS AND 95% C.I. IS CALCULATED USING THE COMPLEMENTARY LOG-LOG TRANSFORMATION METHOD. B: FROM STRATIFIED LOG-RANK TEST WITH STRATIFICATION FACTORS (ALK-POSITIVE SALCL: YES/NO AND IPI SCORE: 0-1/2-3/4-5) AT RANDOMIZATION. C: CHI-SQUARE TEST (TAKEDA 2019).

6.3.3 Baseline Characteristics for ALK+/- ALCL patients

See Appendix 5.

6.4 Subgroup data for OS and PFS stratified according to IPI score

6.4.1 OS/PFS data for ALCL patients with IPI 0-1

FIGURE K. KM CURVES OF OS FOR SALCL PATIENTS WITH IPI SCORE 0-1 (TAKEDA 2019).

FIGURE L. KM CURVES OF PFS FOR SALCL PATIENTS WITH IPI SCORE 0-1 (TAKEDA 2019).

TABLE X. EFFICACY ESTIMATES OF A+CHP AND CHOP FOR ALCL PATIENTS WITH IPI 0-1. A: OS/PFS RATE IS ESTIMATED USING KAPLAN-MEIER METHODS AND 95% C.I. IS CALCULATED USING THE COMPLEMENTARY LOG-LOG TRANSFORMATION METHOD. B: FROM STRATIFIED LOG-RANK TEST WITH STRATIFICATION FACTORS (ALK-POSITIVE SALCL: YES/NO AND IPI SCORE: 0-1/2-3/4-5) AT RANDOMIZATION. C: CHI-SQUARE TEST (TAKEDA 2019).

6.4.2 OS/PFS data for ALCL patients with IPI 2-3

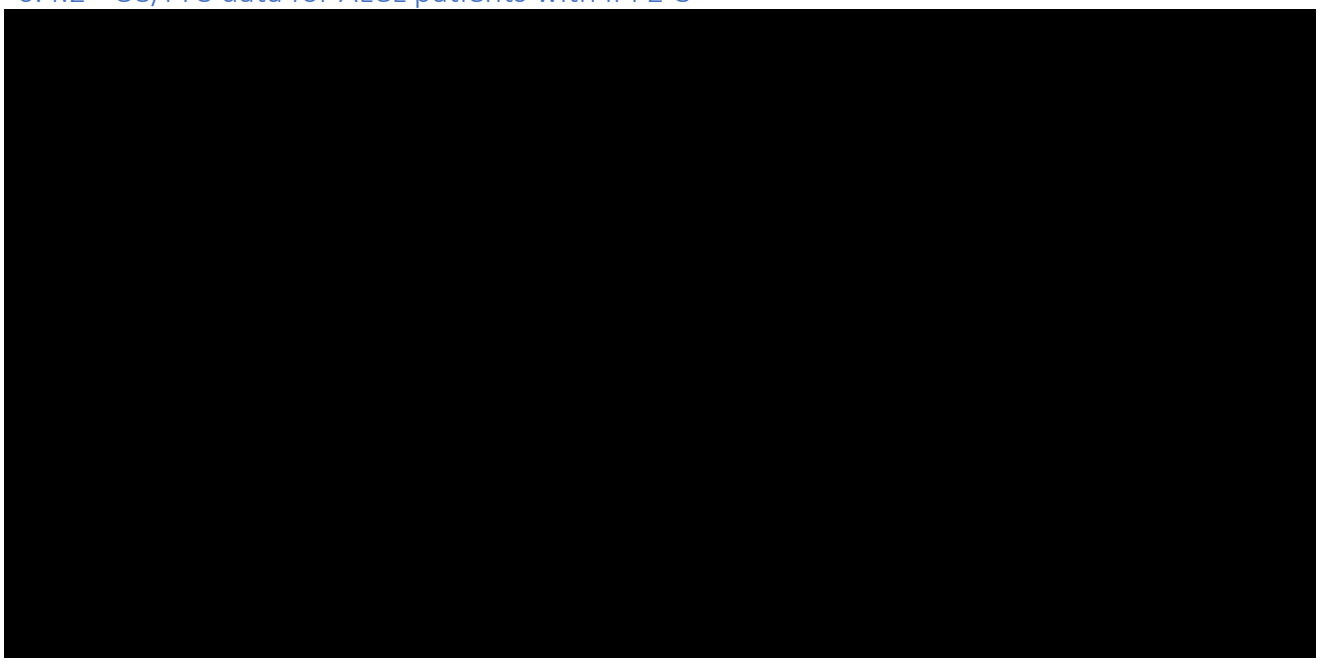


FIGURE M. KM CURVES OF OS FOR SALCL PATIENTS, IPI 2-3 (TAKEDA 2019).

FIGURE N. KM CURVES OF PFS FOR SALCL PATIENTS, IPI 2-3 (TAKEDA 2019).

TABLE Y. EFFICACY ESTIMATES OF A+CHP AND CHOP FOR ALCL PATIENTS WITH IPI 2-3. A: OS/PFS RATE IS ESTIMATED USING KAPLAN-MEIER METHODS AND 95% C.I. IS CALCULATED USING THE COMPLEMENTARY LOG-LOG TRANSFORMATION METHOD. B: FROM STRATIFIED LOG-RANK TEST WITH STRATIFICATION FACTORS (ALK-POSITIVE SALCL: YES/NO AND IPI SCORE: 0-1/2-3/4-5) AT RANDOMIZATION. C: CHI-SQUARE TEST (TAKEDA 2019).

6.4.3 OS/PFS data for ALCL patients with IPI 4-5

FIGURE O. KM CURVES OF OS FOR SALCL PATIENTS, IPI 4-5 (TAKEDA 2019).

FIGURE P. KM CURVES OF PFS FOR SALCL PATIENTS, IPI 4-5 (TAKEDA 2019).

TABLE Z. EFFICACY ESTIMATES OF A+CHP AND CHOP FOR ALCL PATIENTS WITH IPI 4-5. A: OS/PFS RATE IS ESTIMATED USING KAPLAN-MEIER METHODS AND 95% C.I. IS CALCULATED USING THE COMPLEMENTARY LOG-LOG TRANSFORMATION METHOD. B: FROM STRATIFIED LOG-RANK TEST WITH STRATIFICATION FACTORS (ALK-POSITIVE SALCL: YES/NO AND IPI SCORE: 0-1/2-3/4-5) AT RANDOMIZATION. C: CHI-SQUARE (TAKEDA 2019).

6.4.4 Baseline Characteristics for ALCL patients summarized by IPI-score

See Appendix 5.

6.5 Subgroup data for OS and PFS stratified according to age

6.5.1 OS/PFS data for sALCL patients, < 60 yrs

FIGURE Q. KM CURVES OF OS FOR SALCL PATIENTS < 60 YRS (TAKEDA 2019).

FIGURE R. KM CURVES OF PFS FOR SALCL PATIENTS < 60 YRS (TAKEDA 2019).

[redacted]

TABLE AA. EFFICACY ESTIMATES OF A+CHP AND CHOP FOR ALCL PATIENTS < 60 YRS. A: OS/PFS RATE IS ESTIMATED USING KAPLAN-MEIER METHODS AND 95% C.I. IS CALCULATED USING THE COMPLEMENTARY LOG-LOG TRANSFORMATION METHOD. B: FROM STRATIFIED LOG-RANK TEST WITH STRATIFICATION FACTORS (ALK-POSITIVE SALCL: YES/NO AND IPI SCORE: 0-1/2-3/4-5) AT RANDOMIZATION. C: CHI-SQUARE TEST (TAKEDA 2019).

6.5.2 OS/PFS data for ALCL patients ⩾ 60 yrs

FIGURE S. KM CURVES OF OS FOR SALCL PATIENTS ≥ 60 YRS. COMPUTED FROM LOG-RANK TEST USING STRATIFICATION FACTORS (ALK-POSITIVE SALCL: YES/NO AND IPI SCORE: 0-1/2-3/4-5) AT RANDOMIZATION (TAKEDA 2019).

FIGURE T. KM CURVES OF PFS FOR SALCL PATIENTS ≥ 60 YRS. COMPUTED FROM LOG-RANK TEST USING STRATIFICATION FACTORS (ALK-POSITIVE SALCL: YES/NO AND IPI SCORE: 0-1/2-3/4-5) AT RANDOMIZATION (TAKEDA 2019).

TABLE BB. EFFICACY ESTIMATES OF A+CHP AND CHOP FOR ALCL PATIENTS ≥ 60 YRS. A: OS/PFS RATE IS ESTIMATED USING KAPLAN-MEIER METHODS AND 95% C.I. IS CALCULATED USING THE COMPLEMENTARY LOG-LOG TRANSFORMATION METHOD. B: FROM STRATIFIED LOG-RANK TEST WITH STRATIFICATION FACTORS (ALK-POSITIVE SALCL: YES/NO AND IPI SCORE: 0-1/2-3/4-5) AT RANDOMIZATION. C: CHI-SQUARE TEST (TAKEDA 2019).

6.6 Subgroup data for OS stratified according to ALK status and IPI score

6.6.1 OS data for ALK- sALCL patients, IPI 0-1, 2-3, and 4-5

FIGURE U. KM CURVES OF OS FOR ALK- SALCL PATIENTS IPI SCORE 0-1. COMPUTED FROM LOG-RANK TEST USING STRATIFICATION FACTORS (ALK-POSITIVE SALCL: YES/NO AND IPI SCORE: 0-1/2-3/4-5) AT RANDOMIZATION (TAKEDA 2019).

FIGURE V. KM CURVES OF OS FOR ALK- SALCL PATIENTS IPI SCORE 2-3. COMPUTED FROM LOG-RANK TEST USING STRATIFICATION FACTORS (ALK-POSITIVE SALCL: YES/NO AND IPI SCORE: 0-1/2-3/4-5) AT RANDOMIZATION (TAKEDA 2019).

FIGURE W. KM CURVES OF OS FOR ALK- SALCL PATIENTS IPI SCORE 4-5. COMPUTED FROM LOG-RANK TEST USING STRATIFICATION FACTORS (ALK-POSITIVE SALCL: YES/NO AND IPI SCORE: 0-1/2-3/4-5) AT RANDOMIZATION (TAKEDA 2019).

TABLE CC: EFFICACY ESTIMATES OF A+CHP AND CHOP FOR ALK- ALCL PATIENTS, IPI SCORES 0-1, 2-3, AND 4-5. A: OS RATE IS ESTIMATED USING KAPLAN-MEIER METHODS AND 95% C.I. IS CALCULATED USING THE COMPLEMENTARY LOG-LOG TRANSFORMATION METHOD. B: FROM STRATIFIED LOG-RANK TEST WITH STRATIFICATION FACTORS (ALK-POSITIVE SALCL: YES/NO AND IPI SCORE: 0-1/2-3/4-5) AT RANDOMIZATION (TAKEDA 2019).

6.6.2 OS data for ALK+ sALCL patients, IPI 0-1, 2-3, and 4-5

FIGURE X. KM CURVES OF OS FOR ALK+ SALCL PATIENTS IPI SCORE 2-3. COMPUTED FROM LOG-RANK TEST USING STRATIFICATION FACTORS (ALK-POSITIVE SALCL: YES/NO AND IPI SCORE: 0-1/2-3/4-5) AT RANDOMIZATION (TAKEDA 2019). NO DATA IS DEPICTED; ALK+ SALCL WITH IPI 0-1 WAS NOT ALLOWED IN THE STUDY.

FIGURE Y. KM CURVES OF OS FOR ALK+ SALCL PATIENTS IPI SCORE 2-3. COMPUTED FROM LOG-RANK TEST USING STRATIFICATION FACTORS (ALK-POSITIVE SALCL: YES/NO AND IPI SCORE: 0-1/2-3/4-5) AT RANDOMIZATION (TAKEDA 2019).

FIGURE Z. KM CURVES OF OS FOR ALK+ SALCL PATIENTS IPI SCORE 4-5. COMPUTED FROM LOG-RANK TEST USING STRATIFICATION FACTORS (ALK-POSITIVE SALCL: YES/NO AND IPI SCORE: 0-1/2-3/4-5) AT RANDOMIZATION (TAKEDA 2019).

TABLE DD. EFFICACY ESTIMATES OF A+CHP AND CHOP FOR ALK- ALCL PATIENTS, IPI SCORES O-1, 2-3, AND 4-5. A: ALK+ SALCL WITH IPI 0-1 WAS NOT ALLOWED IN THE STUDY. B:OS RATE IS ESTIMATED USING KAPLAN-MEIER METHODS AND 95% C.I. IS CALCULATED USING THE COMPLEMENTARY LOG-LOG TRANSFORMATION METHOD. C: FROM STRATIFIED LOG-RANK TEST WITH STRATIFICATION FACTORS (ALK-POSITIVE SALCL: YES/NO AND IPI SCORE: 0-1/2-3/4-5) AT RANDOMIZATION (TAKEDA 2019).

References

Bartlett, N. L., R. Chen, M. A. Fanale, P. , A. Gopal, S. E. Smith, R. Advani, J. V. Matous, R. Ramchandren, J. D. Rosenblatt, D. Huebner, P. Levine, L. Grove, and A. Forero-Torres. 2014. 'Retreatment with brentuximab vedotin in patients with CD30-positive hematologic malignancies', *J Hematol Oncol*, 7: 24.

Cederleuf, H., M. Bjerregård Pedersen, M. Jerkeman, T. Relander, F. d'Amore, and F. Ellin. 2017. 'The addition of etoposide to CHOP is associated with improved outcome in ALK+ adult anaplastic large cell lymphoma: A Nordic Lymphoma Group study', *Br J Haematol*, 178: 739-46.

Cederleuf, H., L. Hjort Jakobsen, F. Ellin, P. de Nully Brown, T. Stauffer Larsen, M. Bøgsted, T. Relander, M. Jerkeman, and T. C. El-Galaly. 2017. 'Outcome of peripheral T-cell lymphoma in first complete remission: a Danish-Swedish population-based study', *Leuk Lymphoma*, 58: 2815-23.

CHMP. 2020a. "Adcetris Summary of Product Characteristics (SPC)." In.

———. 2020b. "Assessment Report Adcetris (EPAR)." In.

d'Amore, Francesco, Thomas Relander, Grete F. Lauritzsen, Esa Jantunen, Hans Hagberg, Harald Anderson, Harald Holte, Anders Österborg, Mats Merup, Peter Brown, Outi Kuittinen, Martin Erlanson, Bjørn Østenstad, Unn-Merete Fagerli, Ole V. Gadeberg, Christer Sundström, Jan Delabie, Elisabeth Ralfkiaer, Martine Vornanen, and Helle E. Toldbod. 2012. 'Up-Front Autologous Stem-Cell Transplantation in Peripheral T-Cell Lymphoma: NLG-T-01', *Journal of Clinical Oncology*, 30: 3093-99.

Deng, S., S. Lin, J. Shen, and Y. Zeng. 2019. 'Comparison of CHOP vs CHOPE for treatment of peripheral T-cell lymphoma: a meta-analysis', *Onco Targets Ther*, 12: 2335-42.

Ellin, Fredrik, Jenny Landström, Mats Jerkeman, and Thomas Relander. 2014. 'Real-world data on prognostic factors and treatment in peripheral T-cell lymphomas: a study from the Swedish Lymphoma Registry', *Blood*, 124: 1570-77.

Horwitz, Steven, Owen A. O'Connor, Barbara Pro, Tim Illidge, Michelle Fanale, Ranjana Advani, Nancy L. Bartlett, Jacob Haaber Christensen, Franck Morschhauser, Eva Domingo-Domenech, Giuseppe Rossi, Won Seog Kim, Tatyana Feldman, Anne Lennard, David Belada, Árpád Illés, Kensei Tobinai, Kunihiro Tsukasaki, Su-Peng Yeh, Andrei Shustov, Andreas Hüttmann, Kerry J. Savage, Sam Yuen, Swaminathan Iyer, Pier Luigi Zinzani, Zhaowei Hua, Meredith Little, Shangbang Rao, Joseph Woolery, Thomas Manley, Lorenz Trümper, David Aboulafia, Ranjana Advani, Onder Alpdogan, Kiyoshi Ando, Luca Arcaini, Luca Baldini, Naresh Bellam, Nancy Bartlett, David Belada, Dina Ben Yehuda, Fabio Benedetti, Peter Borchman, Dominique Bordessoule, Pauline Brice, Javier Briones, Dolores Caballero, Angelo Michele Carella, Hung Chang, June Weon Cheong, Seok-Goo Cho, Ilseung Choi, Sylvain Choquet, Andrei Colita, Angela Giovanna Congui, Francesco D'Amore, Nam Dang, Kelly Davison, Sophie de Guibert, Peter de Nully Brown, Vincent Delwail, Judit Demeter, Francesco di Raimondo, Young Rok Do, Eva Domingo, Michael Douvas, Martin Dreyling, Thomas Ernst, Michelle Fanale, Keith Fay, Tatyana Feldman, Silvia Fernandez Ferrero, Ian Winchester Flinn, Andres Forero-Torres, Christopher Fox, Jonathan Friedberg, Noriko Fukuhara, Jose Garcia-Marco, Jorge Gayoso Cruz, Jose Gomez Codina, Remy Gressin, Andrew Grigg, Ronit Gurion, Jacob Haaber Christensen, Corinne Haioun, Roman Hajek, Mathias Hanel, Kiyohiko Hatake, Robert Hensen, Netanel Horowitz, Steven Horwitz, Andreas Huttmann, Arpad Illes, Tim Illidge, Kenichi Ishizawa, Miguel Islas-Ohlmayer, Eric Jacobsen, Murali Janakiram, Wojciech Jurczak, Mark Kaminski, Koji Kato, Won Seog Kim, Ilya Kirgner, Swaminathan Iyer, Ching-Yuan Kuo, Mihaela Cornelia Lazaroiu, Katell Le Du, Jong-Seok Lee, Steven LeGouill, Anne Lennard, Paul LaRosee, Itai Levi, Brian Link, Herve Maisonneuve, Dai Maruyama, Jiri Mayer, John McCarty, Pam McKay, Yosuke Minami, Heidi Mocikova, Enrica Morra, Franck Morschhauser, Javier Munoz, Hirokazu Nagai, Owen O'Connor, Stephen Opat, Ruth Pettengell, Antonio Pezzutto, Michael Pfreundschuh, Andrzej Pluta, PierLuigi Porcu, Barbara Pro, Hang Quach, Alessandro Rambaldi, William Renwick, Ruben Reyes, Antonia Rodriguez Izquierdo,

Giuseppe Rossi, Jia Ruan, Chiara Rusconi, Gilles Salles, Armando Santoro, Jose Sarriera, Kerry Savage, Hirohiko Shibayama, Andrei Shustov, Cheolwon Suh, Anna Sureda, Mitsune Tanimoto, Masafumi Taniwaki, Herve Tilly, Kensei Tobinai, Marek Trneny, Lorenz Trumper, Norifumi Tsukamoto, Kunihiro Tsukasaki, Umberto Vitolo, Jan Walewski, Eckhart Weidmann, Martin Wilhelm, Mathias Witzens-Harig, Abdulraheem Yacoub, Kazuhito Yamamoto, Su-Peng Yeh, Sung-Soo Yoon, Sam Yuen, Hwan Jung Yun, Jasmine Zain, and Pier Luigi Zinzani. 2019. 'Brentuximab vedotin with chemotherapy for CD30-positive peripheral T-cell lymphoma (ECHELON-2): a global, double-blind, randomised, phase 3 trial', *The Lancet*, 393: 229-40.

Janikova, A., R. Chloupkova, V. Campr, P. Klener, J. Hamouzova, D. Belada, V. Prochazka, R. Pytlik, J. Pirnos, J. Duras, H. Mocikova, Z. Bortlicek, N. Kopalova, J. Mayer, and M. Trneny. 2019. 'First-line therapy for T cell lymphomas: a retrospective population-based analysis of 906 T cell lymphoma patients', *Ann Hematol*, 98: 1961-72.

Jia, Bo, Shaoxuan Hu, Jianliang Yang, Shengyu Zhou, Peng Liu, Yan Qin, Lin Gui, Sheng Yang, Hua Lin, Changgong Zhang, Puyuan Xing, Lin Wang, Mei Dong, Liqiang Zhou, Yan Sun, Xiaohui He, and Yuankai Shi. 2016. 'Comparison of gemcitabin, cisplatin, and dexamethasone (GDP), CHOP, and CHOPE in the first-line treatment of peripheral T-cell lymphomas', *Hematology*, 21: 536-41.

Kim, Y. A., J. M. Byun, K. Park, G. H. Bae, D. Lee, D. S. Kim, S. S. Yoon, and Y. Koh. 2017. 'Redefining the role of etoposide in first-line treatment of peripheral T-cell lymphoma', *Blood Adv*, 1: 2138-46.

Liu, X., M. Yang, M. Wu, W. Zheng, Y. Xie, J. Zhu, Y. Song, and W. Liu. 2019. 'A retrospective study of the CHOP, CHOPE, and CHOPE/G regimens as the first-line treatment of peripheral T-cell lymphomas', *Cancer Chemother Pharmacol*, 83: 443-49.

Morel, Alexandre, Josette Brière, Laurence Lamant, Michaël Loschi, Corinne Haioun, Richard Delarue, Olivier Tournilhac, Emmanuel Bachy, Anne Sonet, Sandy Amorim, Camille Laurent, Philippe Gaulard, Hervé Tilly, and David Sibon. 2017. 'Long-term outcomes of adults with first-relapsed/refractory systemic anaplastic large-cell lymphoma in the pre-brentuximab vedotin era: A LYSA/SFGM-TC study', *European Journal of Cancer*, 83: 146-53.

Pfreundschuh, Michael, Lorenz Trümper, Marita Kloess, Rudolf Schmits, Alfred C. Feller, Christian Rudolph, Marcel Reiser, Dieter K. Hossfeld, Bernd Metzner, Dirk Hasenclever, Norbert Schmitz, Bertram Glass, Christian Rübe, Markus Loeffler, and the German High-Grade Non-Hodgkin's Lymphoma Study Group. 2004. 'Two-weekly or 3-weekly CHOP chemotherapy with or without etoposide for the treatment of young patients with good-prognosis (normal LDH) aggressive lymphomas: results of the NHL-B1 trial of the DSHNHL', *Blood*, 104: 626-33.

Pfreundschuh, Michael, Lorenz Trümper, Marita Kloess, Rudolf Schmits, Alfred C. Feller, Christian Rübe, Christian Rudolph, Marcel Reiser, Dieter K. Hossfeld, Hartmut Eimermacher, Dirk Hasenclever, Norbert Schmitz, Markus Loeffler, and the German High-Grade Non-Hodgkin's Lymphoma Study Group. 2004. 'Two-weekly or 3-weekly CHOP chemotherapy with or without etoposide for the treatment of elderly patients with aggressive lymphomas: results of the NHL-B2 trial of the DSHNHL', *Blood*, 104: 634-41.

Pro, B., R. Advani, P. Brice, N. L. Bartlett, J. D. Rosenblatt, T. Illidge, J. Matous, R. Ramchandren, M. Fanale, J. M. Connors, K. Fenton, D. Huebner, J. M. Pinelli, D. A. Kennedy, and A. Shustov. 2017. 'Five-year results of brentuximab vedotin in patients with relapsed or refractory systemic anaplastic large cell lymphoma', *Blood*, 130: 2709-17.

Rattarittamrong, E., L. Norasetthada, A. Tantiworawit, C. Chai-Adisaksopha, and W. Nawarawong. 2013. 'CHOEP-21 chemotherapy for newly diagnosed nodal peripheral T-cell lymphomas (PTCLs) in Maharaj Nakorn Chiang Mai Hospital', *J Med Assoc Thai*, 96: 1416-22.

Savage, Kerry J, Steven M. Horwitz, Ranjana H Advani, Jacob H. Christensen, Eva Domingo-Domenech, Giuseppe Rossi, Franck Morschhauser, Onder Alpdogan, Cheolwon Suh, Kensei Tobinai, Andrei R Shustov, Marek Trneny, Sam Yuen, Pier Luigi Zinzani, Lorenz Truemper, Timothy Illidge, Owen O'Connor, Barbara Pro, Meredith Little, Veronica Bunn, Keenan Fenton, Thomas Manley, and Swaminathan P. Iyer. 2019. 'An Exploratory Analysis of Brentuximab Vedotin Plus CHP (A+CHP) in

the Frontline Treatment of Patients with CD30+ Peripheral T-Cell Lymphomas (ECHELON-2): Impact of Consolidative Stem Cell Transplant', *Blood*, 134: 464-64.

Schmitz, Norbert, Lorenz Trümper, Marita Ziepert, Maike Nickelsen, Anthony D. Ho, Bernd Metzner, Norma Peter, Markus Loeffler, Andreas Rosenwald, and Michael Pfreundschuh. 2010. 'Treatment and prognosis of mature T-cell and NK-cell lymphoma: an analysis of patients with T-cell lymphoma treated in studies of the German High-Grade Non-Hodgkin Lymphoma Study Group', *Blood*, 116: 3418-25.

Takeda. 2019. "Unpublished Data on File." In.

7 Appendices

Literature search

The literature search was done according to the protocol – see section 8.1.1 and 8.1.2

7.1.1 PubMed

Search Strategy:

#	Søgetermer	Kommentar
#1	Lymphoma, Large-Cell, Anaplastic[mh] OR Lymphoma, T-Cell, Peripheral[mh]	Søgetermer for indikationen (P)
#2	(Lymphom*[tiab] AND (Anaplastic[tiab] OR (Peripheral[tiab] AND T-Cell[tiab]))) OR PTCL[tiab] OR ALCL[tiab]	
#3	#1 OR #2	
#4	Brentuximab Vedotin[mh] OR brentuximab[tiab] OR adcetris*[tiab] OR SGN-35[tiab] OR cAC10-vcMMAE[tiab] OR A+CHP[tiab]	Intervention (I)
#5	CHOEP protocol[nm] OR EPOCH protocol[nm] OR CHOEP[tiab] OR CHOPE[tiab] OR CHOP-E[tiab] OR VACPE[tiab] OR EPOCH[tiab] OR CAVPE[tiab] OR DA-EPOCH[tiab]	Komparator (C)
#6	Cyclophosphamide[mh] OR B-518[tiab] OR Cyclophospha*[tiab] OR Cytophosphan*[tiab] OR Cytoxan[tiab] OR Endoxan[tiab] OR NSC-26271[tiab] OR Neosar[tiab] OR Procytox[tiab] OR Sendoxan[tiab]	
#7	Doxorubicin[mh] OR Doxorubicin[tiab] OR Adriablastin*[tiab] OR Adriamycin[tiab] OR Adriblastin*[tiab] OR DOXO-cell[tiab] OR Doxorubicin*[tiab] OR Myocet[tiab] OR Rubex[tiab] OR Urokit Doxo-cell[tiab]	
#8	Etoposide[mh] OR Etopos*[tiab] OR Celltop[tiab] OR Eposid*[tiab] OR Lastet[tiab] OR NSC-141540[tiab] OR Toposar[tiab] OR VP-16*[tiab] OR Vepesid*[tiab]	
#9	Prednisone[mh] OR Prednisolone[mh] OR Predni*[tiab] OR Pronison*[tiab] OR Dacorti*[tiab] OR Cortan*[tiab] OR Dehydrocortison*[tiab] OR Encorto*[tiab] OR Deltasone[tiab] OR Liquid Pred[tiab] OR Meticorten[tiab] OR Orasone[tiab] OR Panafcort[tiab] OR Panasol[tiab] OR Rectodelt[tiab] OR Sterapred[tiab] OR Ultracorten[tiab] OR Winpred[tiab] OR delta-Cortisone[tiab]	
#10	Vincristine[mh] OR Vincris*[tiab] OR Citomid[tiab] OR Farmistin[tiab] OR Oncovin*[tiab] OR Onkocristin[tiab] OR Vintec[tiab]	
#11	#5 OR (#6 AND #7 AND #8 AND #9 AND #10)	
#12	#3 AND (#4 OR #11)	Kombination af P, I og C
#13	Case Reports[pt] OR Comment[pt] OR Editorial[pt] OR Letter[pt] OR Review[pt] OR Systematic Review[pt]	Eksklusion af specifikke publikationstyper
#14	#12 NOT #13	Linje #14 = endelig søgning

TABLE EE. SEARCH STRATEGY FOR PUBMED.

7.1.2 CENTRAL Search Strategy

#	Søgetermer	Kommentar
#1	[mh "Lymphoma, Large-Cell, Anaplastic"] OR [mh "Lymphoma, T-Cell, Peripheral"]	Søgetermer for indikationen (P)
#2	((Lymphom* AND (Anaplastic OR (Peripheral AND T-Cell))) OR PTCL OR ALCL):ti,ab,kw	
#3	#1 OR #2	
#4	[mh "Brentuximab Vedotin"]	Intervention (I)
#5	(brentuximab* OR adcetris* OR SGN-35):ti,ab,kw	Komparator (C)
#6	#4 OR #5	
#7	(CHOEP OR CHOPE OR CHOP-E OR VACPE OR EPOCH OR CAVPE OR DA-EPOCH):ti,ab,kw	
#8	[mh "Cyclophosphamide"]	
#9	(B-518 OR Cyclophospha* OR Cytophosphan* OR Cytoxan OR Endoxan OR NSC-26271 OR Neosar OR Procytox OR Sendoxan):ti,ab,kw	
#10	#8 OR #9	
#11	[mh "Doxorubicin"]	
#12	(Doxorubicin OR Adriablastin* OR Adriamycin OR Adriblastin* OR DOXO-cell OR Doxorubicin* OR Myocet OR Rubex OR Urokit Doxo-cell):ti,ab,kw	
#13	#11 OR #12	
#14	[mh "Etoposide"]	
#15	(Etopos* OR Celltop OR Eposid* OR Lastet OR NSC-141540 OR Toposar OR VP-16* OR Vepesid*):ti,ab,kw	
#16	#14 OR #15	
#17	[mh "Prednisone"] OR [mh "Prednisolone"]	
#18	(Predni* OR Pronison* OR Dacorti* OR Cortan* OR Dehydrocortison* OR Encorto* OR Deltasone OR Liquid Pred OR Meticorten OR Orasone OR Panafcort OR Panasol OR Rectodelt OR Sterapred OR Ultracorten OR Winpred OR delta-Cortisone):ti,ab,kw	
#19	#17 OR #18	
#20	[mh "Vincristine"]	
#21	(Vincris* OR Citomid OR Farmistin OR Oncovin* OR Onkocristin OR Vintec):ti,ab,kw	
#22	#20 OR #21	
#23	#7 OR (#10 AND #13 AND #16 AND #19 AND #22)	
#24	#3 AND (#6 OR #23)	Kombination af P, I og C
#25	(clinicaltrials.gov or trialsearch):so	Eksklusion af specifikke publikationstyper
#26	"conference abstract":pt	
#27	#25 or #26	
#28	#24 NOT #27	Linje #28 = endelig søgning

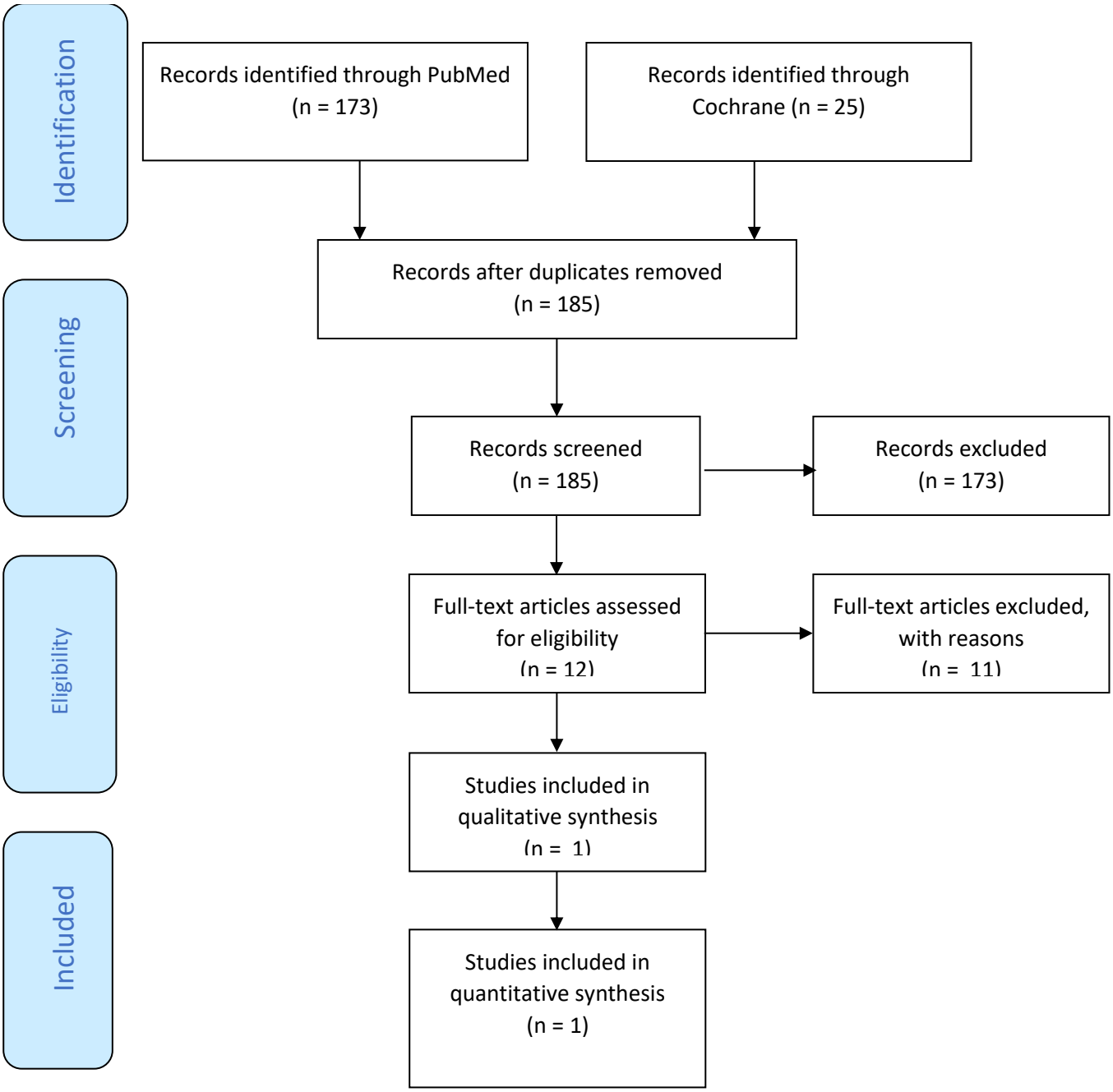
TABLE FF: SEARCH STRATEGY FOR CENTRAL.

Table A1 Inclusion and exclusion criteria

Inclusion criteria	Population: Intervention(s): Comparator(s): Outcomes: Settings (if applicable): Study design: Language restrictions: Other search limits or restrictions applied:
Exclusion criteria	Population: Intervention(s): Comparator(s): Outcomes: Settings (if applicable): Study design: Language restrictions: Other search limits or restrictions applied:

7.1.3 Prisma Flow Diagram of article selection for Clinical Question 1

FIGURE AA. *PRISMA FLOW DIAGRAM OF ARTICLE SELECTION FOR CLINICAL QUESTION 1*



7.1.4 Main characteristics of included studies

7.1.4.1 Study characteristics

Table A2 Main study characteristics
(Complete this table for each included study.)

TABLE A2. MAIN STUDY CHARACTERISTICS.

Trial name	Echelon-2
NCT number	NCT01777152
Objective	Superiority study of brentuximab vedotin + CHP vs. CHOP in the 1. Line treatment of CD30-positive mature T-cell lymphoma.
Publications – title, author, journal, year	Brentuximab vedotin with chemotherapy for CD30-positive peripheral T-cell lymphoma (ECHELON-2): a global, double-blind, randomised, phase 3 trial. Horwitz S, O'Connor OA, Pro B, Illidge T, Fanale M, Advani R, et al. The Lancet, 2019 (10168):229-40.
Study type and design	Randomized, double-blinded, double-dummy controlled, placebo-controlled phase 3 study. Patients were randomly assigned 1:1 using a central interactive web response system (IWRS) that assigned a unique subject randomization number but did not specify the actual treatment assignment. Randomization numbers and their corresponding treatment assignments were assigned to subjects per the randomization list by sequential ascending block number, and by sequential ascending randomization numbers within the appropriate strata. Stratification was performed according to 1) ALK+ sALCL versus all other histological types, and 2) IPI scpore (0-1, 2-3, 4-5). Cross-over was not possible, but unmasking of the treatment was permitted in the case of PD via a formal unblinding procedure.
Follow-up time	Median follow-up time was 36.2 months (3-yrs)
Population (inclusion and exclusion criteria)	**Inclusion Criteria**: Patients with newly diagnosed, CD30-positive mature T-cell lymphomas Fluorodeoxyglucose (FDG)-avid disease by PET and measurable disease of at least 1.5 cm by CT Eastern Cooperative Oncology Group (ECOG) performance status less than or equal to 2. **Exclusion Criteria:** History of another primary invasive malignancy that has not been in remission for at least 3 years Current diagnosis of primary cutaneous CD30-positive T-cell lymphoproliferative disorders and lymphomas or mycosis fungoides History of progressive multifocal leukoencephalopathy (PML) Cerebral/meningeal disease related to the underlying malignancy

<table>
<tr><td>Intervention</td><td>Experimental; A+CHOP, N=226 (sALCL=162)
brentuximab vedotin, cyclophosphamide, doxorubicin, and prednisone

Drug: brentuximab vedotin
1.8 mg/kg every 3 weeks by IV infusion for 6-8 cycles

Drug: doxorubicin
50 mg/m2 every 3 weeks by IV infusion for 6-8 cycles

Drug: prednisone
100 mg on Days 1 to 5 of each 3-week cycle, orally for 6-8 cycles

Drug: cyclophosphamide
750 mg/m2 every 3 weeks by IV infusion for 6-8 cycles

Active Comparator, N=226 (sALCL=154)
cyclophosphamide, doxorubicin, vincristine, and prednisone

Drug: doxorubicin
50 mg/m2 every 3 weeks by IV infusion for 6-8 cycles

Drug: prednisone
100 mg on Days 1 to 5 of each 3-week cycle, orally for 6-8 cycles

Drug: vincristine
1.4 mg/m2 (maximum 2 mg) every 3 weeks by IV infusion for 6-8 cycles

Drug: cyclophosphamide
750 mg/m2 every 3 weeks by IV infusion for 6-8 cycles</td></tr>
<tr><td>Baseline characteristics</td><td>
<table>
<tr><th colspan="3"><u>sALCL Population</u></th></tr>
<tr><th>Patient characteristics</th><th>A + CHP
n=162</th><th>CHOP
n=154</th></tr>
<tr><td>Median age (range)</td><td>55.0 (18-85)</td><td>54.0 (18-83)</td></tr>
<tr><td>Patients ≥ 65 years old (%)</td><td>38 (23)</td><td>36 (23)</td></tr>
<tr><td>Male sex, n (%)</td><td>95 (59)</td><td>110 (71)</td></tr>
<tr><td>ECOG status, n (%)</td><td></td><td></td></tr>
<tr><td>0</td><td>58 (36)</td><td>53 (34)</td></tr>
<tr><td>1</td><td>62 (38)</td><td>61 (40)</td></tr>
<tr><td>2</td><td>41 (25)</td><td>40 (26)</td></tr>
<tr><td colspan="3">Disease Characteristics</td></tr>
<tr><td>Diagnosis, per local assessment, n (%)[a]</td><td></td><td></td></tr>
<tr><td>sALCL</td><td>162 (100)</td><td>154 (100)</td></tr>
<tr><td>ALK-positive</td><td>49 (30)</td><td>49 (32)</td></tr>
<tr><td>ALK-negative</td><td>113 (70)</td><td>105 (68)</td></tr>
<tr><td>Median time from diagnosis to first dose, months (range)</td><td>0.8 (0, 19)</td><td>0.9 (0, 10)</td></tr>
</table>
</td></tr>
</table>

Disease stage at initial diagnosis of PTCL, n (%)			
Stage I		12 (7)	7 (5)
Stage II		22 (14)	27 (18)
Stage III		29 (18)	46 (30)
Stage IV		99 (61)	74 (48)
IPI score			
0		7 (4)	14 (9)
1		34 (21)	18 (12)
2		58 (36)	60 (39)
3		37 (23)	40 (26)
4		22 (14)	16 (10)
5		4 (2)	6 (4)
Extranodal involvement at time of diagnosis, n (%)			
≤ 1 site		94 (58)	95 (62)
>1 site		68 (42)	59 (38)
Baseline bone marrow biopsy-lymphoma involvement, n (%)			
Yes		15 (9)	13 (8)
No		147 (91)	141 (92)

From (CHMP 2020a).

Primary and secondary endpoints	Primary Endpoint • PFS per IRF PFS was defined as the time from randomization to death, disease progression or use of subsequent anticancer chemotherapy, which ever came first. Key Secondary Endpoints • PFS per IRF for subjects with sALCL • CR rate per IRF following the completion of study treatment • OS • ORR per IRF following the completion of study treatment Additional Endpoints • Incidence of ATA (Antitherapeutic Antibody) to brentuximab vedotin • Medical Resource Utilization based on the number of medical care encounters • Quality of life measured by EORTC QLQ-C30, FACT/GOG-NTX subscale, and EQ-5D-3L
Method of analysis	The Intent-to-Treat (ITT) analysis set included all randomized subjects. The efficacy analysis were done in the ITT set. The Safety Analysis Set included all subjects who received any amount of brentuximab vedotin or any component of CHOP; subjects who received any dose of brentuximab vedotin were analysed in the A+CHP arm; subjects who did not receive brentuximab vedotin but received any dose of any component of CHOP were analysed in the CHOP arm.

	PFS Kaplan-Meier methods were used to assess PFS. The stratified log-rank test without adjustments for covariates was used in the primary evaluation of PFS using the ITT analysis set and was tested at an overall one-sided, α=0.025 level. Cox regression of PFS was used to estimate the hazard ratio of the A+CHP arm to the CHOP arm **OS** OS was defined as the time from randomization to death due to any cause (OS=date of death – date of randomization + 1). Any subject for whom death was not already known was censored for OS on the date the subject was last known to be alive (i.e., date of last contact), or data cut-off date. Subjects lacking data beyond the day of randomization were censored on the date of randomization (i.e., OS duration of 1 day).The stratified log-rank test without adjustments for covariates was used in the evaluation of OS between treatment arms. OS was analysed using Kaplan Meier methodology. The two-sided 95% CIs for the median were calculated using the complementary log-log transformation method (Collett 1994). **HRQoL** Quality of life was measured using 3 different PRO instruments: the EORTC QLQC30, FACT/GOG-NTX, and EQ-5D-3L. PRO instrument total/subscale scores and change from baseline were summarized by treatment group and visit using descriptive statistics. In addition, the change from baseline was analysed using linear mixed models. Sensitivity analyses for missing data were conducted using imputation and pattern mixture models. PRO scores were also summarized by PFS status. PRO were measured at C1,D1, C2&3, D1, EOT and at long term follow up. **Key secondary endpoints**: A fixed sequence testing procedure (Westfall 2001) were used to ensure type I error control for key secondary endpoints at an overall one-sided alpha level of 0.025. **PFS per IRF in Subjects with sALC**L Endpoint was analysed in the same manner as the primary analysis of PFS per IRF. Subjects needed to have a central confirmation of the sALCL diagnosis
Subgroup analyses	PFS (prespecified) and OS (post-hoc) analysis were done in the sALCL population. **PFS and OS** Endpoint was analysed in the same manner as the primary analysis of PFS per IRF. Subjects needed to have a central confirmation of the sALCL diagnosis PFS in sALCL patients was a prespecified analysis that was fully powered. As such the analysis is valid. The application contains numerous post-hoc analysis requested by the scientific committee of the Medicines Council. These analysis are, from a

	statistical stand-point, invalid, insofar they are post-hoc and do not contain sufficient numbers of patients or events to be powered.

7.1.5 Results per study

Table A3a Results of study Echelon-2 – sALCL patients

Trial name:	Echelon-2									
NCT number:	NCT01777152									
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Hazard/Odds/ Risk ratio	95% CI	*P* value		
Median overall survival for sALCL patients	A+CHP	162	NR	NE	NE	NE	HR: 0.54	0.337–0.867	0.0096	OS and PFS rates were estimated using Kaplan-Meier methods and 95% C.I. was calculated using the complementary log-log transformation method (Collett, 1994). P-value was calculated using stratified log-rank test with stratification factors (i.e. ALK-positive sALCL: Yes/No and IPI score: 0-1/2-3/4-5) at randomization.	*(Takeda 2019)*
	CHOP	154	NR								
2-year survival for sALCL patients	A+CHP	162	[redacted]	[redacted]							*(Takeda 2019)*
	CHOP	154	[redacted]								
Median PFS for sALCL patients	A+CHP	162	55.66 (48.20-NR)	1.48			HR: 0.59	0.42–0.84	0.0031		*(Takeda 2019)*
	CHOP	154	54.18 (13.44-NR)								
2-year PFS for sALCL patients	A+CHP	163	68.4 (60.4%-75.2%)	14.5%							*(Takeda 2019)*
	CHOP	151	53.9% (45.5%-61.5%)								
HRQoL Mean Change from Baseline to EOT For sALCL patients	A+CHP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]					*(Takeda 2019)*
	CHOP	[redacted]	[redacted]								

HRQoL Mean Change from Baseline to EOFU For sALCL patients	A+CHP	[redacted]	[redacted]	[redacted]	The Overall analysis uses least squares means for change from baseline, differences in LS means in change from baseline, 95% CIs and p-values. All results were obtained using mixed effects models. Baseline is defined as the last observed measurement on or before the date of initial dose of any study drug.	(Takeda 2019)
	CHOP	[redacted]	[redacted]	[redacted]		
Discontinuation due to AE sALCL	A+CHP	160	[redacted]	[redacted]	Relative Risk and CMH chi-square p-value were calculated using a Cochran-Mantel-Haenszel chi-square test with stratification factors (ALK-positive sALCL: Yes/No and IPI score: 0-1/2-3/4-5) at randomization. Differences (%) and 95% CI were calculated using an unstratified model.	(Takeda 2019)
	CHOP	154	[redacted]	[redacted]7		
AEs Grade 3-4 sALCL	A+CHP	160	[redacted]	[redacted]		
	CHOP	154	[redacted]	[redacted]		

Table A3b Results of study *Treatment and prognosis of mature T-cell and NK-cell lymphoma: an analysis of patients with T-cell lymphoma treated in studies of the German High-Grade Non-Hodgkin Lymphoma Study Group* – ***Combined data from ALK+/-, AITL, PTCLU patients aged < 60 yrs with LDH < ULN***

Trial name:	Treatment and prognosis of mature T-cell and NK-cell lymphoma: an analysis of patients with T-cell lymphoma treated in studies of the German High-Grade Non-Hodgkin Lymphoma Study Group – **Combined data from ALK+/-, AITL, PTCLU patients aged < 60 yrs with LDH < ULN**										
NCT number:											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Hazard/Odds/ Risk ratio	95% CI	*P* value		
3-yrs Overall survival	CHOP	41	NR	**"Not Significant"**		**0.176**	NR	NR	NR	Event-free survival (EFS) defined as time from randomization or start of therapy to disease progression, start of salvage therapy, further (unplanned) treatment (excluding first-line chemo- and radiotherapy), relapse, or death from any cause, and overall survival (OS) defined as time from randomization or start of therapy to death from any cause, were analyzed by the Kaplan-Meier method.	*(Schmitz et al. 2010)*
	CHOEP	42	NR								
3-yrs EFS	CHOP	41	74.5% (68.9–80.2)	**10.7**	NR	**0.003**	NR	NR	NR		
	CHOEP	42	63.8% (57.6–70.0)								
HRQoL	CHOP	NR		NR							
	CHOEP	NR									
AEs	CHOP	NR									
	CHOEP	NR									

NR: Not Reported

Table A3c Results of study *The addition of etoposide to CHOP is associated with improved outcome in ALK+ adult anaplastic large cell lymphoma: A Nordic Lymphoma Group study.*

Trial name:	*The addition of etoposide to CHOP is associated with improved outcome in ALK+ adult anaplastic large cell lymphoma: A Nordic Lymphoma Group study.* ***Subanalysis of ALK+ ALCL patients 41-65 yrs old***										
NCT number:											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Hazard/Odds/ Risk ratio	95% CI	*P* value		
Overall survival	CHOP	16	NR	**NR**		**NR**	0.38	0.14-0.99	0.047	Survival curves were estimated with the Kaplan–Meier method, groups were compared using the log-rank test, and risk factor analysis was performed using Cox proportional hazards ratio regression. Factors with P ≤ 0_1 according to univariate analysis were adjusted for in multivariate models. All p values were 2-sided, and differences were regarded as statistically significant when P < 0_05.	*(Cederleuf, Bjerregård Pedersen, et al. 2017)*
	CHOEP	27	NR								
PFS	CHOP	16	NR	**NR**	NR	**NR**	0.45	0.18-1.15	0.096		
	CHOEP	27	NR								
*Overall survival Adjusted**	CHOP	16	NR				0.25	0.09-0.76	0.014		
	CHOEP	27	NR								
*PFS Adjusted**	CHOP	16	NR				0.32	0.11-0.92	0.034		
	CHOEP	27	NR								

*: adjusted for IPI-score. Similar results were obtained when the data was adjusted for gender and LDH
NR: Not Reported

Table A3d Results of study *The addition of etoposide to CHOP is associated with improved outcome in ALK+ adult anaplastic large cell lymphoma: A Nordic Lymphoma Group study*

Trial name:	Table A3c Results of study *The addition of etoposide to CHOP is associated with improved outcome in ALK+ adult anaplastic large cell lymphoma: A Nordic Lymphoma Group study.* ***Subanalysis of ALK+ ALCL patients aged 18-40 yrs***										
NCT number:	*Insert NCT number*										
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Hazard/Odds/ Risk ratio	95% CI	*P* value		
Overall survival	CHOP	17	NR			Not Significant			Not significnt	Survival curves were estimated with the Kaplan–Meier method, groups were compared using the log-rank test, and risk factor analysis was performed using Cox proportional hazards ratio regression. Factors with P ≤ 0_1 according to univariate analysis were adjusted for in multivariate models. All p values were 2-sided, and differences were regarded as statistically significant when P < 0_05.	*(Cederleuf, Bjerregård Pedersen, et al. 2017)*
	CHOEP	23	NR								
PFS	CHOP	17	NR			Not Significant			Not Significant		
	CHOEP	23	NR								
HRQoL	CHOP										
	CHOEP										
AEs	CHOP										
	CHOEP										

NR: Not Reported.

Table A3e Results of study *Redefining the role of etoposide in first-line treatment of peripheral T-cell lymphoma*

Trial name:	Redefining the role of etoposide in first-line treatment of peripheral T-cell lymphoma. *PTCL patients from Single Center University Hospital*										
NCT number:											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Hazard/Odds/ Risk ratio	95% CI	*P* value		
Overall survival	CHOP CHOEP	77 20		**NR**	NR	**0.654**	NR	NR	NR	OS and PFS were estimated using Kaplan-Meier methods. Univariate and multivariate proportional hazards regression models were used to identify independent risk factors of survival by Cox proportional hazards models. Predictors achieving P < 0.1 in univariate analysis were sequentially preceded to multivariable models. Differences between groups were assessed using the Student t-test or 1 way analysis of variance for continuous variables and Pearson Chi-square test for categorical variables. All analysis were performed using SAS.	*(Kim et al. 2017)*
PFS	CHOP CHOEP	77 NR 20 NR		**NR**	NR	**0.383**	NR	NR	NR		
HRQOL	CHOP CHOEP										
AEs	CHOP CHOEP										

NR: Not Reported.

Table A3f Results of study *Redefining the role of etoposide in first-line treatment of peripheral T-cell lymphoma.*

Trial name:	Redefining the role of etoposide in first-line treatment of peripheral T-cell lymphoma. ***PTCL patients from South Korean National Registry***										
NCT number:											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Hazard/Odds/ Risk ratio	95% CI	*P* value		
Overall survival	CHOP CHOEP	646 609	NR NR	**NR**	NR	**> 0.001**	HR: 0.746	0.59-0.95	0.016	OS and PFS were estimated using Kaplan-Meier methods. Univariate and multivariate proportional hazards regression models were used to identify independent risk factors of survival by Cox proportional hazards models. Predictors achieving P < 0.1 in univariate analysis were sequentially preceded to multivariable models. Differences between groups were assessed using the Student t-test or 1 way analysis of variance for continuous variables and Pearson Chi-square test for categorical variables. All analysis were performed using SAS.	*(Kim et al. 2017)*
PFS	CHOP CHOEP	646 609	NR NR	**NR**	NR	**> 0.001**	0.474	0.25-0.88	0.019		
AEs anemia requiring transfusion	CHOP CHOEP	646 609	11.3% 19.0%	7.7		**> 0.001**					
AEs thrombocytopenia requiring transfusion	CHOP CHOEP	646 609	13.6% 21.0%	7.4		**> 0.001**					

NR: Not Reported.

Table A3g Results of study Redefining the role of etoposide in first-line treatment of peripheral T-cell lymphoma

Trial name:	Redefining the role of etoposide in first-line treatment of peripheral T-cell lymphoma. ***ALCL patients from Single Center University Hospital***										
NCT number:											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Hazard/Odds/ Risk ratio	95% CI	*P* value		
Overall survival	CHOP CHOEP	NR NR		**NR**	NR	**0.240**	NR	NR	NR	OS and PFS were estimated using Kaplan-Meier methods. Univariate and multivariate proportional hazards regression models were used to identify independent risk factors of survival by Cox proportional hazards models. Predictors achieving P < 0.1 in univariate analysis were sequentially preceded to multivariable models. Differences between groups were assessed using the Student t-test or 1 way analysis of variance for continuous variables and Pearson Chi-square test for categorical variables. All analysis were performed using SAS.	*(Kim et al. 2017)*
PFS	CHOP CHOEP	NR NR	NR NR	**NR**	NR	**0.944**	NR	NR	NR		
HRQOL	CHOP CHOEP										
AEs anemia requiring transfusion	CHOP CHOEP	77 20	13.0 30.0	17.0	NR	0.091					
AEs thrombocytopenia requiring transfusion	CHOP CHOEP	77 20	11.7 15.0	3.3	NR	0.708					

NR: Not Reported.

Table A3h Results of study Redefining the role of etoposide in first-line treatment of peripheral T-cell lymphoma.
ALCL patients from South Korean National Registry

Trial name:	Redefining the role of etoposide in first-line treatment of peripheral T-cell lymphoma. ***ALCL patients from South Korean National Registry***										
NCT number:											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Hazard/Odds/ Risk ratio	95% CI	*P* value		
Overall survival	CHOP	NR	NR	**NR**	NR	**0.03 In Favor of CHOP**	NR	NR	NR	OS and PFS were estimated using Kaplan-Meier methods. Univariate and multivariate proportional hazards regression models were used to identify independent risk factors of survival by Cox proportional hazards models. Predictors achieving P < 0.1 in univariate analysis were sequentially preceded to multivariable models. Differences between groups were assessed using the Student t-test or 1 way analysis of variance for continuous variables and Pearson Chi-square test for categorical variables. All analysis were performed using SAS.	*(Kim et al. 2017)*
	CHOEP	NR	NR								
PFS	CHOP	NR	NR	**NR**	NR	**0.041 in favor of CHOP**	NR	NR	NR		
	CHOEP	NR	NR								
HRQOL	CHOP										
	CHOEP										
AEs	CHOP										
	CHOEP										

NR: Not Reported.

Table A3i Results of study Redefining the role of etoposide in first-line treatment of peripheral T-cell lymphoma.
PTCL patients from South Korean National Registry aged < 45 yrs

Trial name:	Redefining the role of etoposide first-line treatment of peripheral T-cell lymphoma. ***PTCL patients from South Korean National Registry aged < 45 yrs***											
NCT number:												
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	**N 476 in total**	Result (CI)	Difference	95% CI	*P* value	Hazard/Odds/ Risk ratio	95% CI	*P* value		
Overall survival	CHOP	NR	NR	**NR**	NR	**0.003 In Favor of CHOP**	NR	NR	NR	OS and PFS were estimated using Kaplan-Meier methods. Univariate and multivariate proportional hazards regression models were used to identify independent risk factors of survival by Cox proportional hazards models. Predictors achieving P < 0.1 in univariate analysis were sequentially preceded to multivariable models. Differences between groups were assessed using the Student t-test or 1 way analysis of variance for continuous variables and Pearson Chi-square test for categorical variables. All analysis were performed using SAS.	*(Kim et al. 2017)*
	CHOEP	NR	NR								
PFS	CHOP	NR	NR	**NR**	NR	**< 0.001 in favor of CHOP**	NR	NR	NR		
	CHOEP	NR	NR								
HRQOL	CHOP										
	CHOEP										
AEs	CHOP										
	CHOEP										

NR: Not Reported.

Table A3j Results of study *Real-world data on prognostic factors and treatment in peripheral T-cell lymphomas: a study from the Swedish Lymphoma Registry*

Trial name:	Real-world data on prognostic factors and treatment in peripheral T-cell lymphomas: a study from the Swedish Lymphoma Registry ***Analysis of ALK- ALCL, AITL, TCL U, and EATL patients with an upper age limit of 70***											
NCT number:												
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Hazard Ratio	95% CI	*P* value		
5-yr Overall survival	CHOP CHOEP	145 107	30% 47%	**NR**	NR	**NR**	0.78	NR	P=0.288		*(Ellin et al. 2014)*
5-yr PFS	CHOP CHOEP	145 107	23% 40%	**NR**	NR	**NR**	0.84	NR	P=0.424		
HRQOL	CHOP CHOEP										
AEs	CHOP CHOEP										

NR: Not Reported.

Table A3k Results of study *Real-world data on prognostic factors and treatment in peripheral T-cell lymphomas: a study from the Swedish Lymphoma Registry*

Trial name:	Real-world data on prognostic factors and treatment in peripheral T-cell lymphomas: a study from the Swedish Lymphoma Registry ***Analysis of ALK- ALCL, AITL, TCL U, and EATL patients with an upper age limit of 60***										
NCT number:											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Hazard Ratio	95% CI	*P* value		
5-yr Overall survival	CHOP CHOEP	NR NR	NR NR	**NR**	NR	**NR**	0.58	0.33-1.01	P=0.052	Survival curves were estimated with the Kaplan-Meier method, groups were compared using the log-rank test, and risk factor analysis was made by Cox regression. Factors were analyzed in univariable analysis, and all factors with P # .1 were retained in the multivariable model.	*(Ellin et al. 2014)*
5-yr PFS	CHOP CHOEP	NR NR	NR NR	**NR**	NR	**NR**	0.49	0.29-0.83	P=0.008		
HRQOL	CHOP CHOEP										
AEs	CHOP CHOEP										

NR: Not Reported.

Table A3l Results of study *Up-front autologous stem-cell transplantation in peripheral T-cell lymphoma: NLG-T-01.*

Trial name:	Up-front autologous stem-cell transplantation in peripheral T-cell lymphoma: NLG-T-01.										
NCT number:											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Hazard Ratio	95% CI	*P* value		
5-yr Overall survival	CHOP	42	45%	**5%**	NR	**"similar"***				Survival curves were estimated with the Kaplan-Meier method, groups were compared using the log-rank test, and risk factor analysis was made by Cox regression. Factors were analyzed in univariable analysis, and all factors with P # .1 were retained in the multivariable model.	*(d'Amore et al. 2012)*
	CHOEP	50	40%								
5-yr PFS	CHOP	42	34%	**-5%**	NR	**"similar"***					
	CHOEP	50	39%								
ORR	CHOP	42	88%	4%	NR	**"similar"***					
	CHOEP	50	84%								
CR	CHOP	42	55%	5%	NR	**"similar"***					
	CHOEP	50	50%								

NR: Not Reported.

*: the authors did not report a formal statistical analysis, but reported that the data were "similar" (d'Amore et al. 2012)

Table A3m Results of study *First-line therapy for T cell lymphomas: a retrospective population-based analysis of 906 T cell lymphoma patients*

Trial name:	*First-line therapy for T cell lymphomas: a retrospective population-based analysis of 906 T cell lymphoma patients*											
NCT number:												
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Hazard Ratio	95% CI	*P* value		
5-yr Overall survival	CHOP	113	47.6%	**18.0**	NR	**0.008**	NR	NR	NR	Progression-free survival (PFS) and overall survival (OS) were estimated using the Kaplan-Meier method. The comparison of OS and PFS between different subgroups (type of T cell lymphoma; CHOP vs. CHOEP; intention-to-treat auto-SCT vs. nonauto-SCT) was carried out by means of the logrank test.	*(Janikova et al. 2019)*
	CHOEP	68	65.6%								
5-yr PFS	CHOP	113	32.9%	**26.1**	NR	**< 0.001**	NR	NR	NR		
	CHOEP	68	59.0%								
HRQOL	CHOP			NR	NR	NR	NR	NR	NR		
	CHOEP										
AEs	CHOP			NR	NR	NR	NR	NR	NR		
	CHOEP										

NR: Not Reported.

7.1.5.1 Table A3n Results of study Comparison of gemcitabin, cisplatin, and dexamethasone (GDP), CHOP, and CHOPE in the first-line treatment of peripheral T-cell lymphomas (Jia et al. 2016).

Trial name:	Comparison of gemcitabin, cisplatin, and dexamethasone (GDP), CHOP, and CHOPE in the first-line treatment of peripheral T-cell lymphomas											
NCT number:												
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Hazard Ratio	95% CI	*P* value		
1-yr Overall survival	CHOP	40	65.0%	**18.3**	NR	**0.030**	NR	NR	NR	Survival analysis was estimated by the Kaplan–Meier method, and differences between curves were analyzed using the log-rank test. The Cox proportional hazards model was used for multivariate analysis.	*(Jia et al. 2016)*
	CHOEP	42	83.3%								
median PFS	CHOP	40	6.0 months	**9.6**	NR	**0.094**	NR	NR	NR		
	CHOEP	42	15.6 months								
HRQOL	CHOP			NR	NR	NR	NR	NR	NR		
	CHOEP										
AEs	CHOP			NR	NR	NR	NR	NR	NR		
	CHOEP										

NR: Not Reported.

7.1.5.2 *Table A3o Results of study CHOEP-21 Chemotherapy for Newly diagnosed Nodal Peripherial T-Cell Lymphomas (PTCLs) in Maharaj Nakorn Chiang Mai Hospital.*

Trial name:	CHOEP-21 Chemotherapy for Newly diagnosed Nodal Peripherial T-Cell Lymphomas (PTCLs) in Maharaj Nakorn Chiang Mai Hospital.											
NCT number:												
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Hazard Ratio	95% CI	*P* value		
2-yr Overall survival	CHOP	11	51.9%	**2.5%**	NR	**0.65**	NR	NR	NR	Survival analysis was estimated by the Kaplan–Meier method, and EFS and OS were compared according to the Kaplan-Meier method.	(Rattarittamrong et al. 2013)
	CHOEP	24	54.4%								
2-yr PFS	CHOP	11	51.4%	**- 13.8%**	NR	**0.40**	NR	NR	NR		
	CHOEP	24	37.6%								
HRQOL	CHOP			NR	NR	NR	NR	NR	NR		
	CHOEP										
AEs	CHOP			NR	NR	NR	NR	NR	NR		
	CHOEP										

NR: Not Reported.

Results per PICO: *What is the clinical value of brentuximab vedotin in combination with cyclophosphamide, doxorubincine and prednisolone (CHP) compared with cyclophosphamide, doxorubincine, vincristine, etoposide, and prednisolone (CHOEP) or cyclophosphamide, doxorubincine, vincristine, and prednisolone (CHOP) for previously untreated patients with sALCL who are candidates for HDT and ASCT?*

Table A4a Results referring to *What is the clinical value of brentuximab vedotin in combination with cyclophosphamide, doxorubincine and prednisolone (CHP) compared with cyclophosphamide, doxorubincine, vincristine, etoposide, and prednisolone (CHOEP) or cyclophosphamide, doxorubincine, vincristine, and prednisolone (CHOP) for previously untreated patients with sALCL who are candidates for HDT and ASCT?*

Results per outcome	*Attach forest plots and statistical results as a separate file.* *Results from the comparative analysis should be given in the table below, if possible.*							
		Absolute difference in effect			Relative difference in effect			Methods used for quantitative synthesis
	Studies included in the analysis	Difference	CI	*P* value	Hazard/Odds/Risk ratio	CI	*P* value	
Median overall survival	Echelon-2	NE	NA	NA	HR: 0.54	0.34–0.87	0.0096	OS and PFS rates were estimated using Kaplan-Meier methods and 95% C.I. was calculated using the complementary log-log transformation method (Collett, 1994). P-value was calculated using stratified log-rank test with stratification factors (i.e. ALK-positive sALCL: Yes/No and IPI score: 0-1/2-3/4-5) at randomization.
2-year survival	Echelon-2	[redacted]	NA	NA	NA	NA	NA	
Median PFS	Echelon-2	1.48	NA	NA	HR: 0.59	0.42 – 0.84	0.0031	
2-yrs PFS	Echelon-2	14.5%	NA	NA	NA	NA	NA	
HRQoL Mean Change from Baseline to EOT	Echelon-2	-0.22	-7.89, 7.44	0.9545	NA	NA	NA	The Overall analysis uses least squares means for change from baseline, differences in LS means in change from baseline, 95% CIs and p-values. All results were obtained using mixed effects models. Baseline is defined as the last observed measurement on or before the date of initial dose of any study drug.
HRQoL Mean Change from Baseline to EOFU	Echelon-2	-3.47	-12.64-5.71	0.4563	NA	NA	NA	
Discontinuation due to AE, %	Echelon-2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Relative Risk and CMH chi-square p-value were calculated using a Cochran-Mantel-Haenszel chi-square test with stratification factors (ALK-positive sALCL: Yes/No and IPI score: 0-1/2-3/4-5) at randomization. Differences (%) and 95% CI were calculated using an unstratified model.
AEs Grade 3-4, %	Echelon-2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

Results per PICO: What is the clinical value of brentuximab vedotin in combination with cyclophosphamide, doxorubincine and prednisolone (CHP) compared with cyclophosphamide, doxorubincine, vincristine, and prednisolone (CHOP) for previously untreated patients with sALCL who are not candidates for HDT and ASCT?

Table A4b Results referring to *What is the clinical value of brentuximab vedotin in combination with cyclophosphamide, doxorubincine and prednisolone (CHP) compared with cyclophosphamide, doxorubincine, vincristine, and prednisolone (CHOP) for previously untreated patients with sALCL who are not candidates for HDT and ASCT?*

Results per outcome	*Attach forest plots and statistical results as a separate file.* *Results from the comparative analysis should be given in the table below, if possible.*							
		Absolute difference in effect			Relative difference in effect			Methods used for quantitative synthesis
	Studies included in the analysis	Difference	CI	*P* value	Hazard/Odds/Risk ratio	CI	*P* value	
Median overall survival	Echelon-2	NE	NA	NA	HR: 0.54	0.34–0.87	0.0096	OS and PFS rates were estimated using Kaplan-Meier methods and 95% C.I. was calculated using the complementary log-log transformation method (Collett, 1994). P-value was calculated using stratified log-rank test with stratification factors (i.e. ALK-positive sALCL: Yes/No and IPI score: 0-1/2-3/4-5) at randomization.
2-year survival	Echelon-2	[redacted]	NA	NA	NA	NA	NA	
Median PFS	Echelon-2	1.48			HR: 0.59	0.42 – 0.84	0.0031	
2-yrs PFS	Echelon-2	14.5%	NA	NA	NA	NA	NA	
HRQoL Mean Change from Baseline to EOT	Echelon-2	[redacted]	[redacted]	[redacted]	NA	NA	NA	The Overall analysis uses least squares means for change from baseline, differences in LS means in change from baseline, 95% CIs and p-values. All results were obtained using mixed effects models. Baseline is defined as the last observed measurement on or before the date of initial dose of any study drug.
HRQoL Mean Change from Baseline to EOFU	Echelon-2	[redacted]	[redacted]	[redacted]	NA	NA	NA	
Discontinuation due to AE, %	Echelon-2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Relative Risk and CMH chi-square p-value were calculated using a Cochran-Mantel-Haenszel chi-square test with stratification factors (ALK-positive sALCL: Yes/No and IPI score: 0-1/2-3/4-5) at randomization. Differences (%) and 95% CI were calculated using an unstratified model.
AEs Grade 3-4, %	Echelon-2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

Appendix 5.

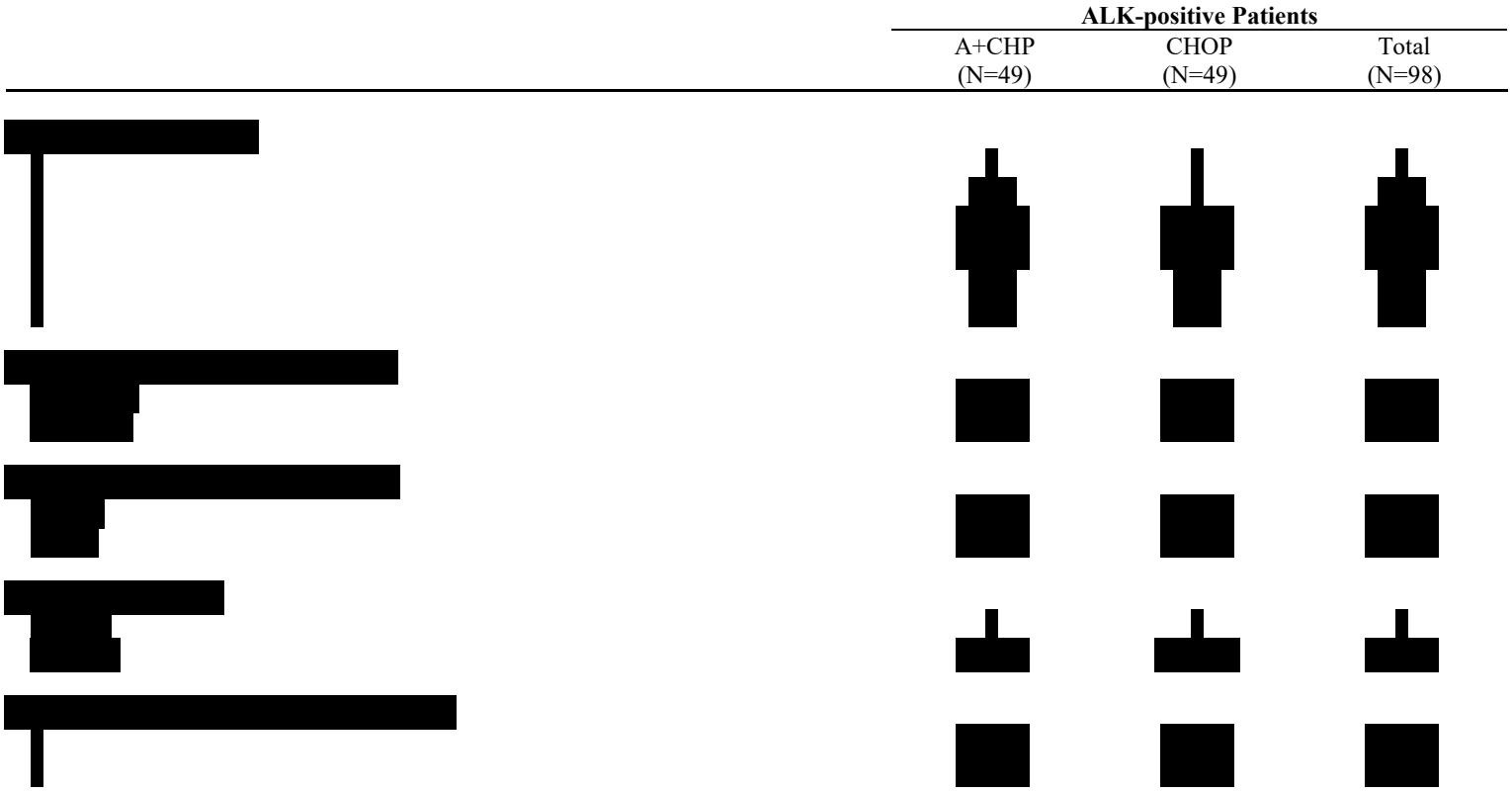
Baseline Characteristics of subgroup analysis requested by the Medicines Council.

Table 95.7.2.2.1
Summary of Baseline Disease Characteristics
ITT Analysis Set - sALCL

	ALK-positive Patients		
	A+CHP (N=49)	CHOP (N=49)	Total (N=98)
[redacted]			

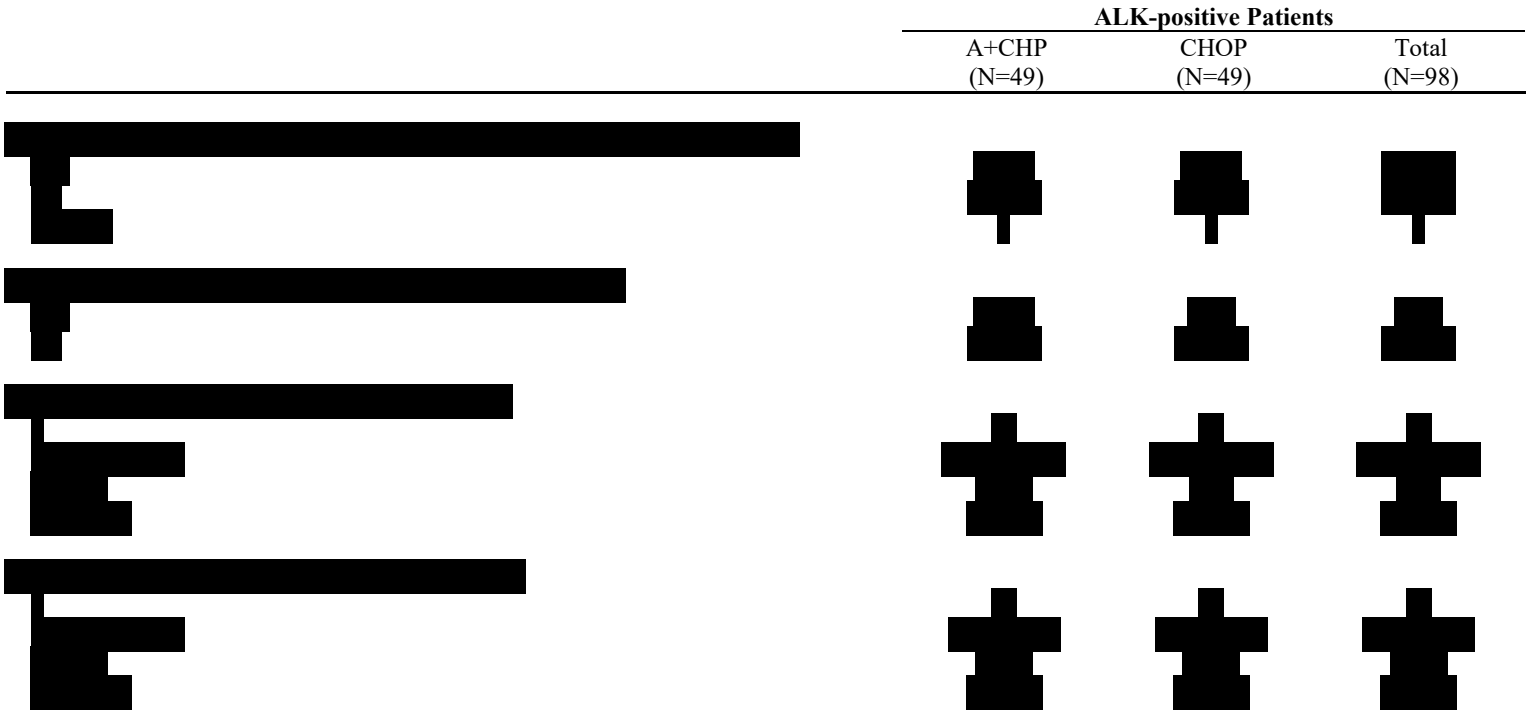
a. Two patients had local CD30 percentage values reported by the site to be >= 10%, but exact percentage values were not reported.

Table 95.7.2.2.1
Summary of Baseline Disease Characteristics
ITT Analysis Set - sALCL



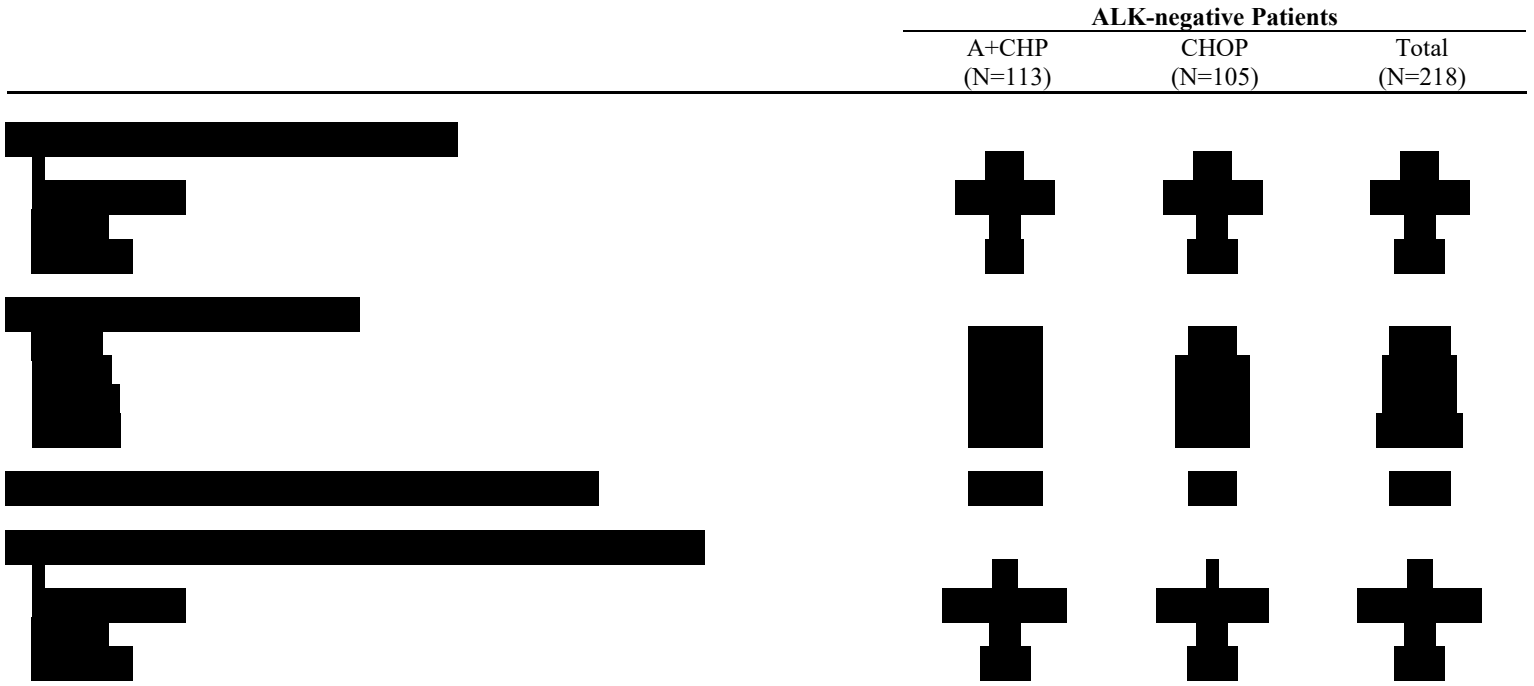
a. Two patients had local CD30 percentage values reported by the site to be >= 10%, but exact percentage values were not reported.

Table 95.7.2.2.1
Summary of Baseline Disease Characteristics
ITT Analysis Set - sALCL



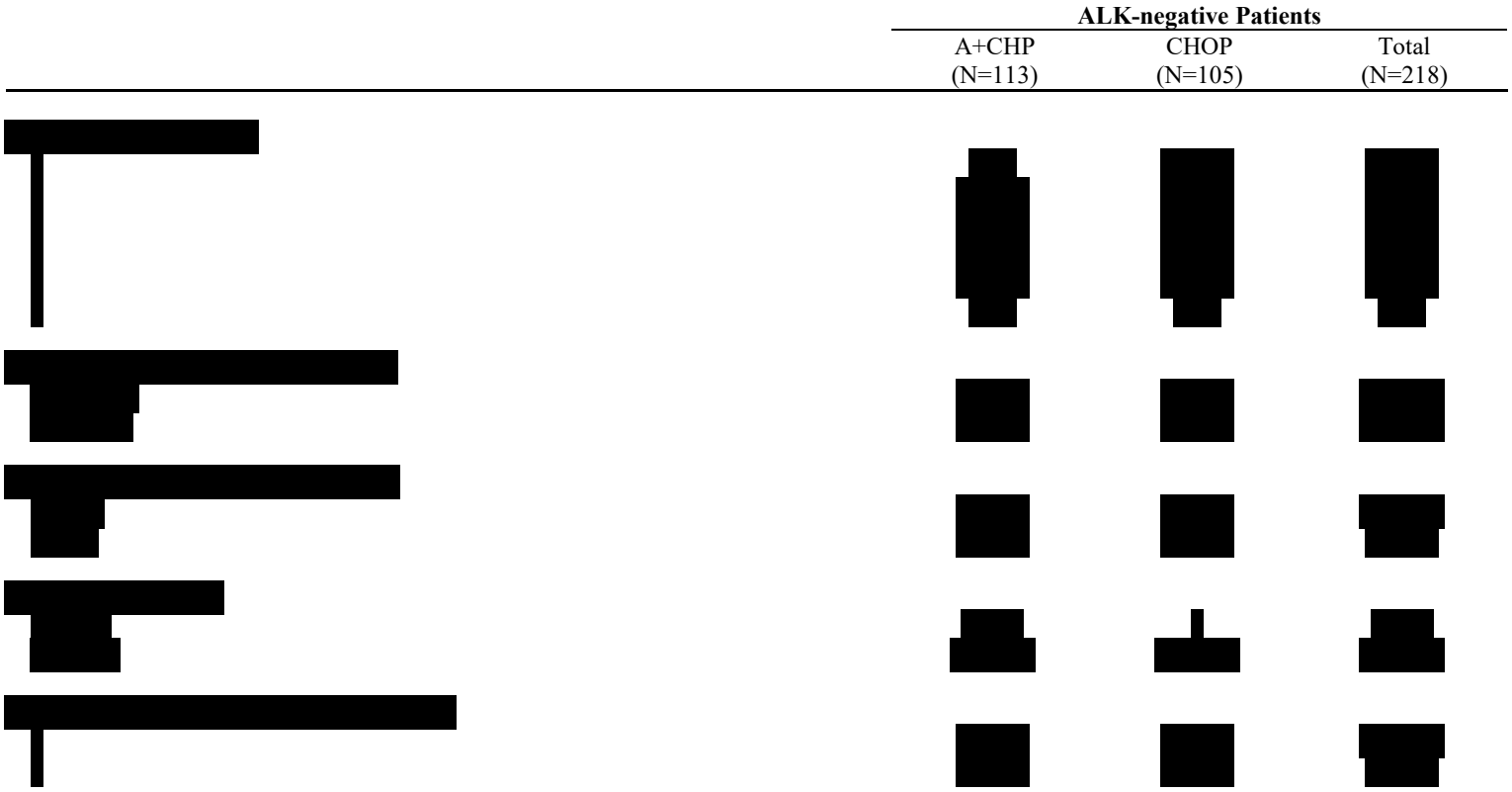
a. Two patients had local CD30 percentage values reported by the site to be >= 10%, but exact percentage values were not reported.

Table 95.7.2.2.1
Summary of Baseline Disease Characteristics
ITT Analysis Set - sALCL



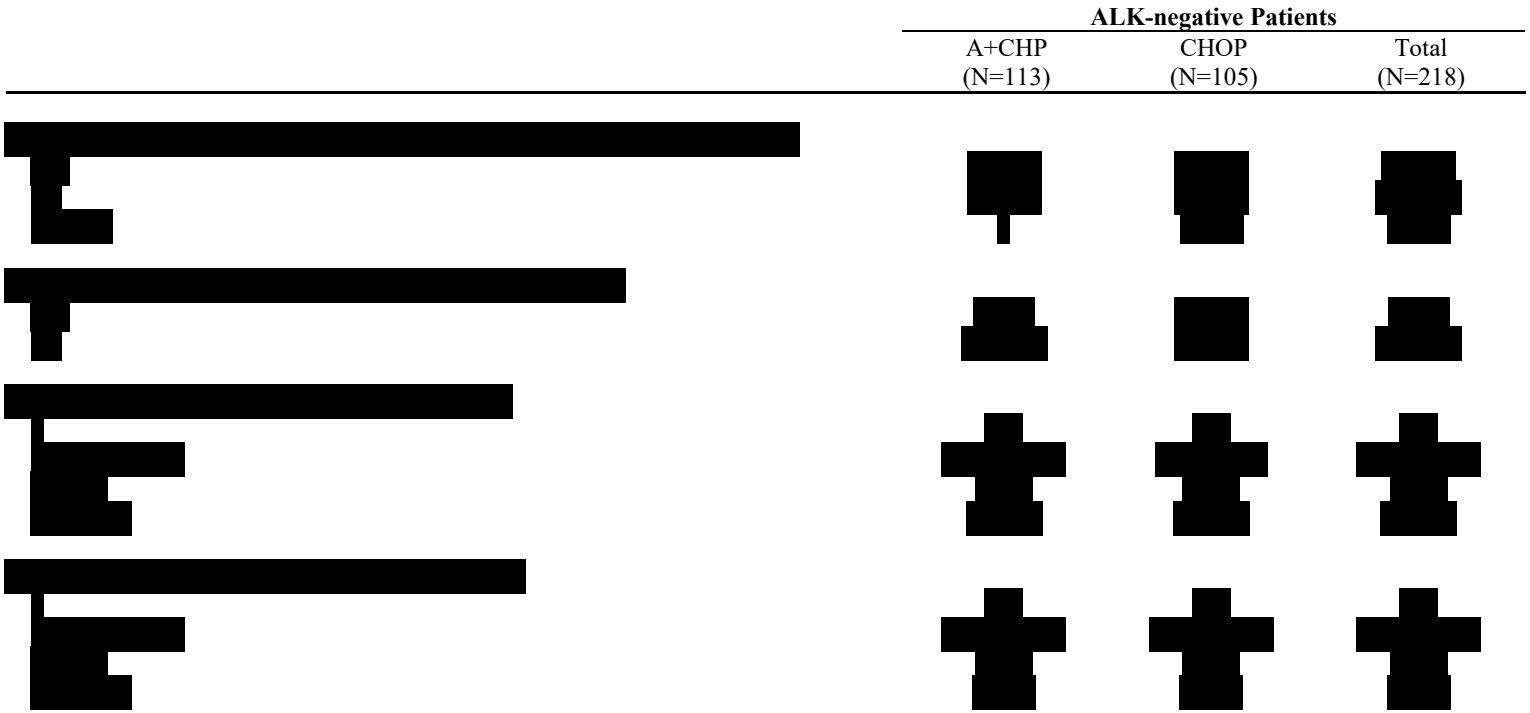
a. Two patients had local CD30 percentage values reported by the site to be >= 10%, but exact percentage values were not reported.

Table 95.7.2.2.1
Summary of Baseline Disease Characteristics
ITT Analysis Set - sALCL



a. Two patients had local CD30 percentage values reported by the site to be >= 10%, but exact percentage values were not reported.

Table 95.7.2.2.1
Summary of Baseline Disease Characteristics
ITT Analysis Set - sALCL



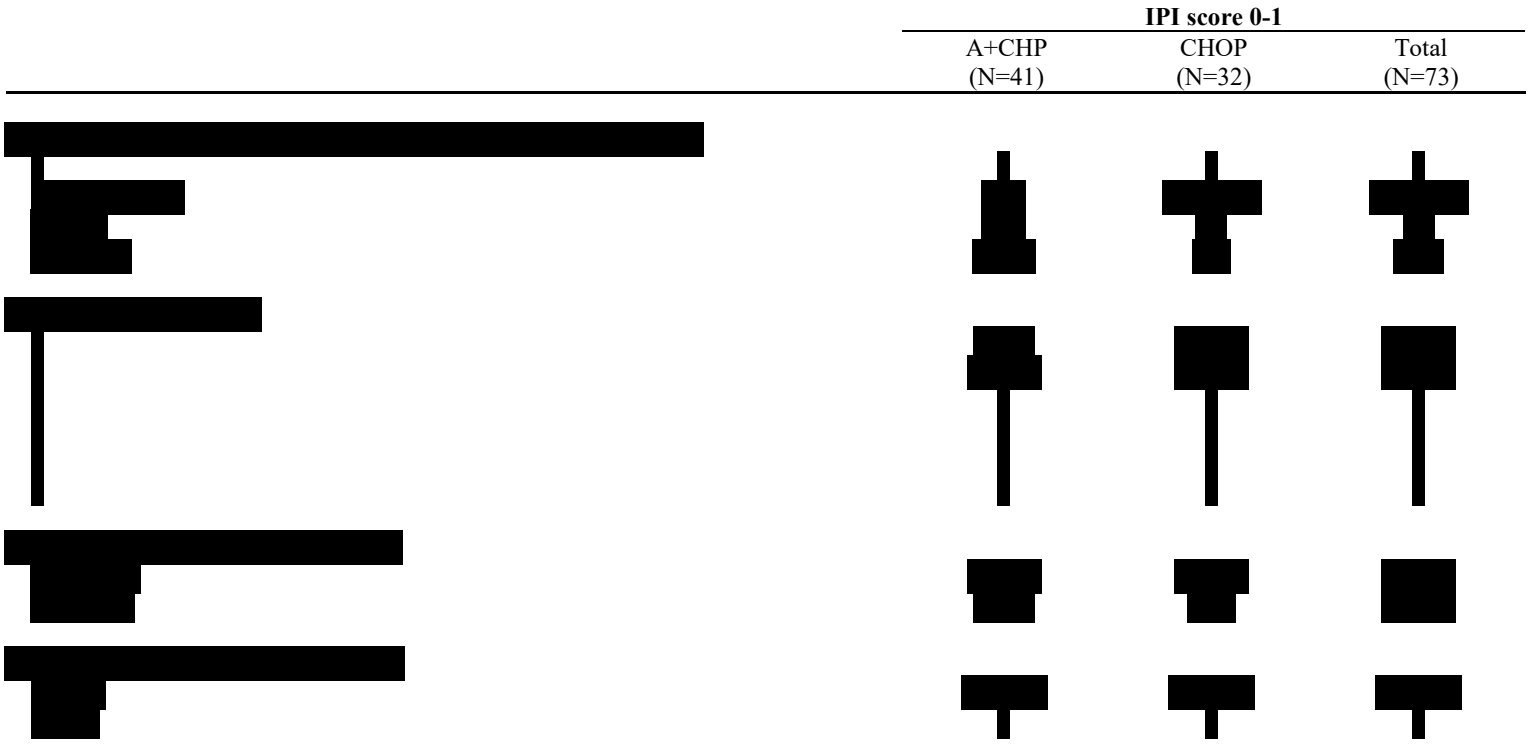
a. Two patients had local CD30 percentage values reported by the site to be >= 10%, but exact percentage values were not reported.

Table 95.7.2.2.2
Summary of Baseline Disease Characteristics
ITT Analysis Set - sALCL

	IPI score 0-1		
	A+CHP (N=41)	CHOP (N=32)	Total (N=73)
[redacted]			

a. Two patients had local CD30 percentage values reported by the site to be >= 10%, but exact percentage values were not reported.

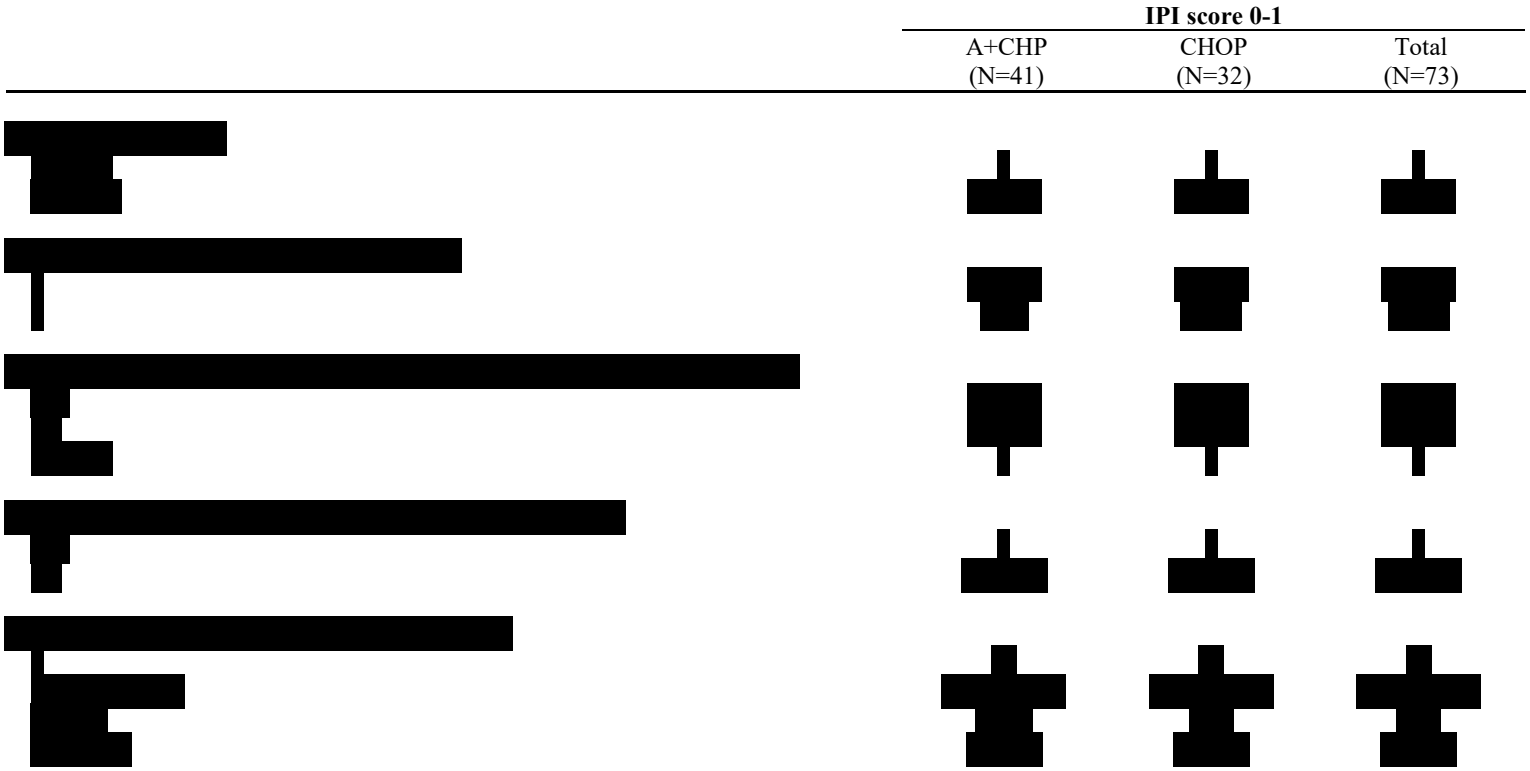
Table 95.7.2.2.2
Summary of Baseline Disease Characteristics
ITT Analysis Set - sALCL



	IPI score 0-1		
	A+CHP (N=41)	CHOP (N=32)	Total (N=73)

a. Two patients had local CD30 percentage values reported by the site to be >= 10%, but exact percentage values were not reported.

Table 95.7.2.2.2
Summary of Baseline Disease Characteristics
ITT Analysis Set - sALCL



a. Two patients had local CD30 percentage values reported by the site to be >= 10%, but exact percentage values were not reported.

Table 95.7.2.2.2
Summary of Baseline Disease Characteristics
ITT Analysis Set - sALCL

	IPI score 0-1		
	A+CHP (N=41)	CHOP (N=32)	Total (N=73)
[redacted]	[redacted]	[redacted]	[redacted]

a. Two patients had local CD30 percentage values reported by the site to be >= 10%, but exact percentage values were not reported.

Table 95.7.2.2.2
Summary of Baseline Disease Characteristics
ITT Analysis Set - sALCL

	IPI score 2-3		
	A+CHP (N=95)	CHOP (N=100)	Total (N=195)
[redacted]			

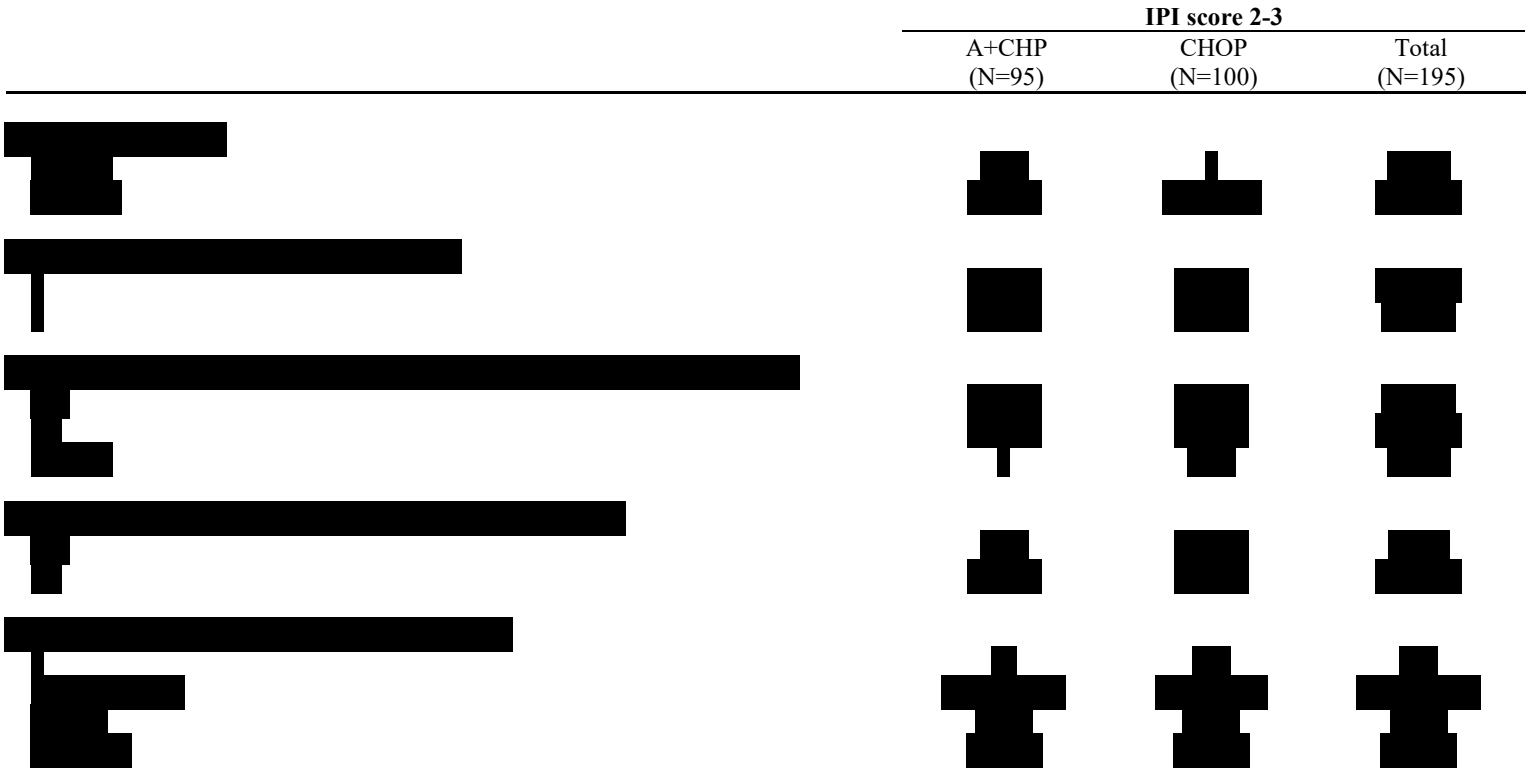
a. Two patients had local CD30 percentage values reported by the site to be >= 10%, but exact percentage values were not reported.

Table 95.7.2.2.2
Summary of Baseline Disease Characteristics
ITT Analysis Set - sALCL

	IPI score 2-3		
	A+CHP (N=95)	CHOP (N=100)	Total (N=195)
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

a. Two patients had local CD30 percentage values reported by the site to be >= 10%, but exact percentage values were not reported.

Table 95.7.2.2.2
Summary of Baseline Disease Characteristics
ITT Analysis Set - sALCL



a. Two patients had local CD30 percentage values reported by the site to be >= 10%, but exact percentage values were not reported.

Table 95.7.2.2.2
Summary of Baseline Disease Characteristics
ITT Analysis Set - sALCL

	IPI score 2-3		
	A+CHP (N=95)	CHOP (N=100)	Total (N=195)
[redacted]	[redacted]	[redacted]	[redacted]

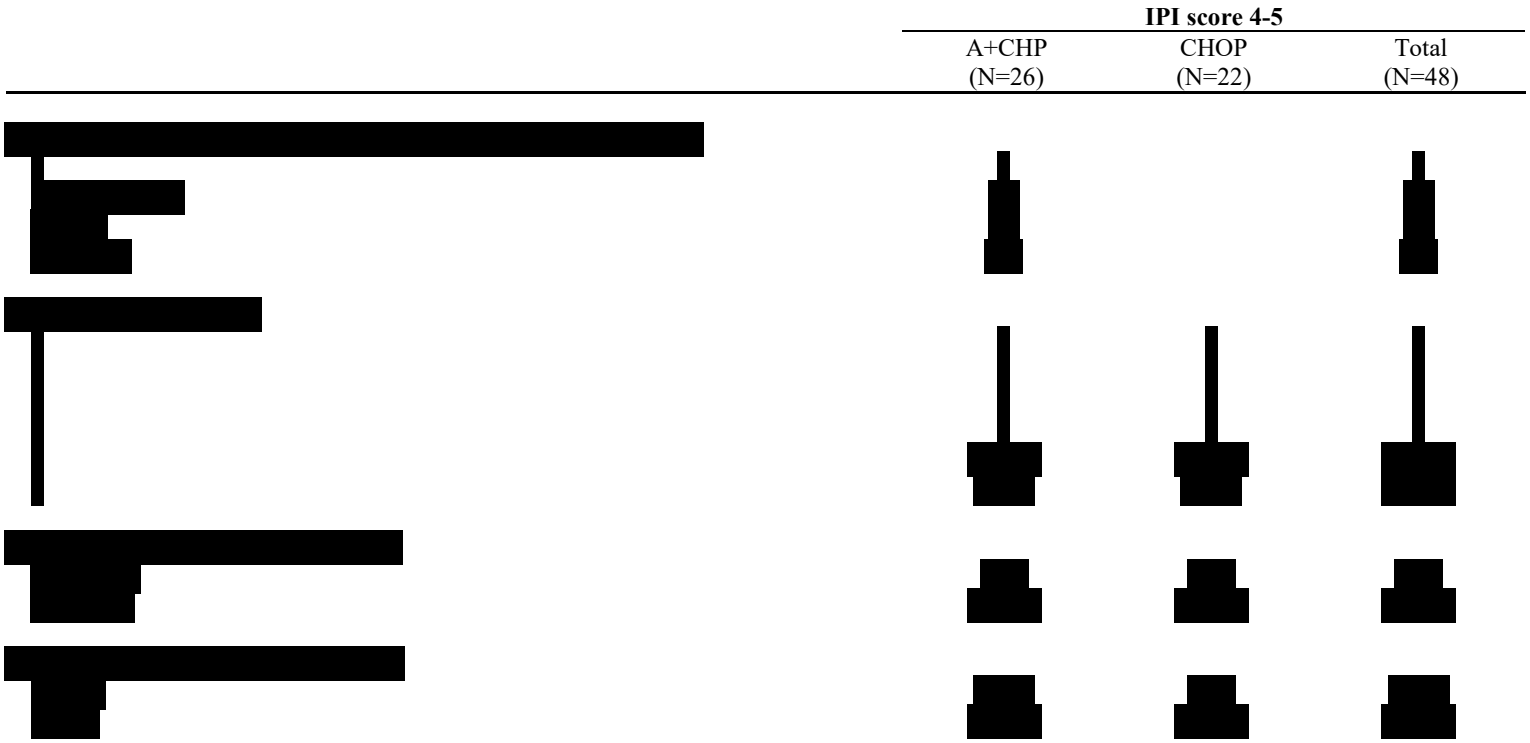
a. Two patients had local CD30 percentage values reported by the site to be >= 10%, but exact percentage values were not reported.

Table 95.7.2.2.2
Summary of Baseline Disease Characteristics
ITT Analysis Set - sALCL

	IPI score 4-5		
	A+CHP (N=26)	CHOP (N=22)	Total (N=48)
[redacted]			

a. Two patients had local CD30 percentage values reported by the site to be >= 10%, but exact percentage values were not reported.

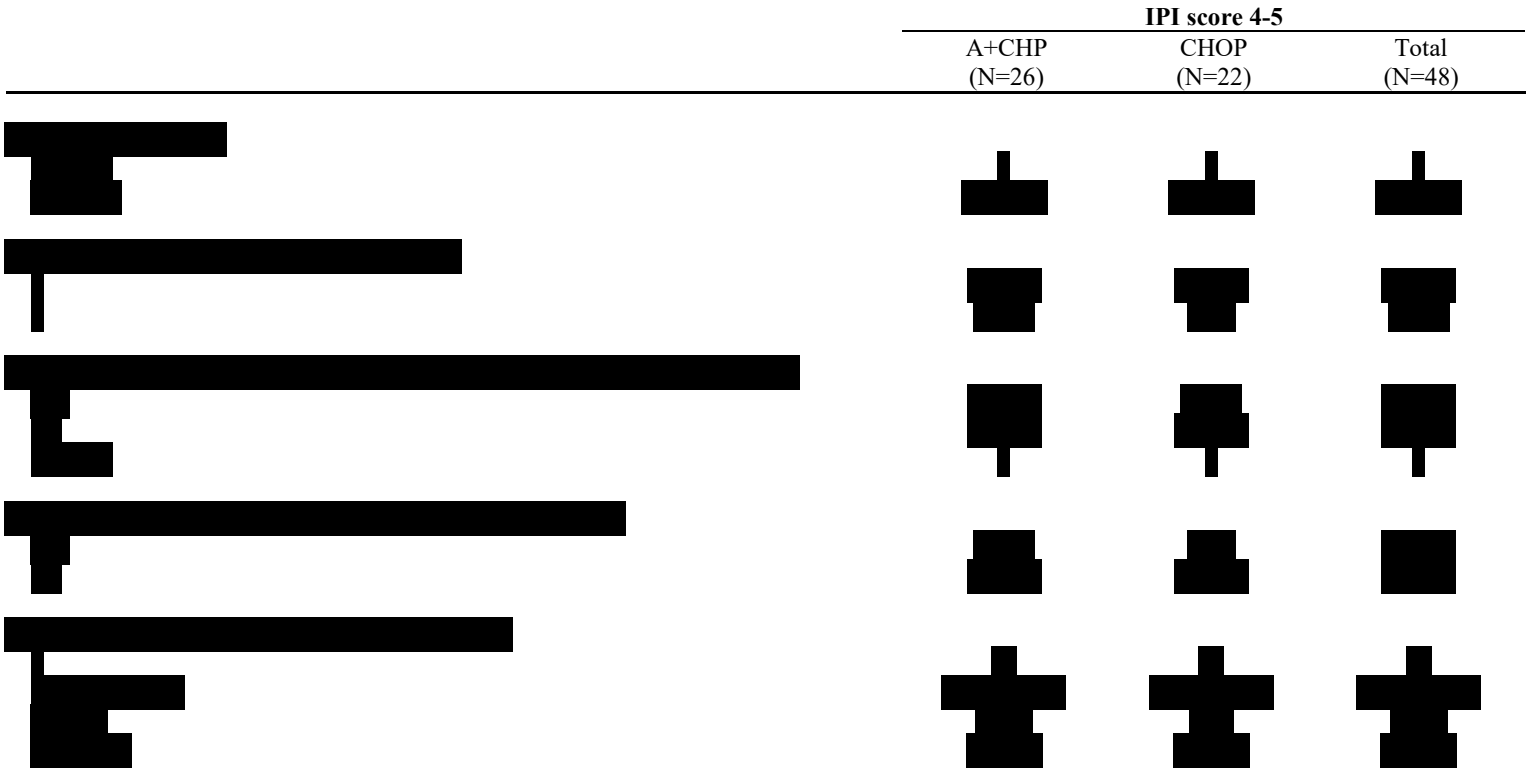
Table 95.7.2.2.2
Summary of Baseline Disease Characteristics
ITT Analysis Set - sALCL



	IPI score 4-5		
	A+CHP (N=26)	CHOP (N=22)	Total (N=48)

a. Two patients had local CD30 percentage values reported by the site to be >= 10%, but exact percentage values were not reported.

Table 95.7.2.2.2
Summary of Baseline Disease Characteristics
ITT Analysis Set - sALCL



a. Two patients had local CD30 percentage values reported by the site to be >= 10%, but exact percentage values were not reported.

Table 95.7.2.2.2
Summary of Baseline Disease Characteristics
ITT Analysis Set - sALCL

	IPI score 4-5		
	A+CHP (N=26)	CHOP (N=22)	Total (N=48)
[redacted]	[redacted]	[redacted]	[redacted]

a. Two patients had local CD30 percentage values reported by the site to be >= 10%, but exact percentage values were not reported.

Subgroup data for OS & PFS stratified according to ALK status and IPI score

Unpublished and confidential

OS data for ALK- sALCL patients, IPI 0-1, 2-3, and 4-5

Figure A. KM curves of OS for ALK- sALCL patients IPI score 0-1. Computed from log-rank test using stratification factors (ALK-positive sALCL: Yes/No and IPI score: 0-1/2-3/4-5) at randomization (Takeda 2019).

Figure B. KM curves of OS for ALK- sALCL patients IPI score 2-3. Computed from log-rank test using stratification factors (ALK-positive sALCL: Yes/No and IPI score: 0-1/2-3/4-5) at randomization (Takeda 2019).

Figure C. KM curves of OS for ALK- sALCL patients IPI score 4-5. Computed from log-rank test using stratification factors (ALK-positive sALCL: Yes/No and IPI score: 0-1/2-3/4-5) at randomization (Takeda 2019).

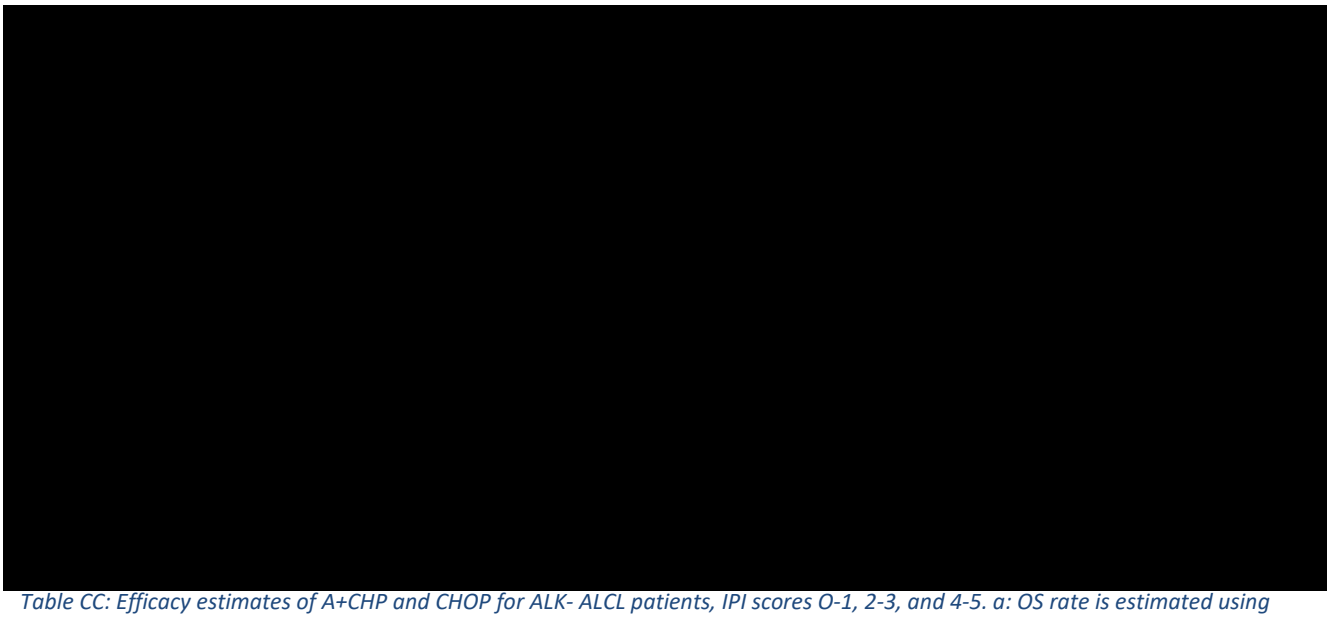


Table CC: Efficacy estimates of A+CHP and CHOP for ALK- ALCL patients, IPI scores O-1, 2-3, and 4-5. a: OS rate is estimated using Kaplan-Meier methods and 95% C.I. is calculated using the complementary log-log transformation method. b: From stratified log-rank test with stratification factors (ALK-positive sALCL: Yes/No and IPI score: 0-1/2-3/4-5) at randomization (Takeda 2019).

OS data for ALK+ sALCL patients, IPI 0-1, 2-3, and 4-5

Figure D. KM curves of OS for ALK+ sALCL patients IPI score 0-1. Computed from log-rank test using stratification factors (ALK-positive sALCL: Yes/No and IPI score: 0-1/2-3/4-5) at randomization (Takeda 2019). No data is depicted; ALK+ sALCL with IPI 0-1 was not allowed in the study.

Figure E. KM curves of OS for ALK+ sALCL patients IPI score 2-3. Computed from log-rank test using stratification factors (ALK-positive sALCL: Yes/No and IPI score: 0-1/2-3/4-5) at randomization (Takeda 2019).

Figure F. KM curves of OS for ALK+ sALCL patients IPI score 4-5. Computed from log-rank test using stratification factors (ALK-positive sALCL: Yes/No and IPI score: 0-1/2-3/4-5) at randomization (Takeda 2019).

Table DD. Efficacy estimates of A+CHP and CHOP for ALK- ALCL patients, IPI scores O-1, 2-3, and 4-5. a: ALK+ sALCL with IPI 0-1 was not allowed in the study. b:OS rate is estimated using Kaplan-Meier methods and 95% C.I. is calculated using the complementary log-log transformation method. c: From stratified log-rank test with stratification factors (ALK-positive sALCL: Yes/No and IPI score: 0-1/2-3/4-5) at randomization (Takeda 2019).

PFS data for ALK- sALCL patients, IPI 0-1, 2-3, and 4-5

Figure AA. KM curves of PFS for ALK- sALCL patients IPI score 0-1. Computed from log-rank test using stratification factors (ALK-positive sALCL: Yes/No and IPI score: 0-1/2-3/4-5) at randomization (Takeda 2019).

Figure BB. KM curves of PFS for ALK- sALCL patients IPI score 2-3. Computed from log-rank test using stratification factors (ALK-positive sALCL: Yes/No and IPI score: 0-1/2-3/4-5) at randomization (Takeda 2019).

Figure CC. KM curves of PFS for ALK- sALCL patients IPI score 4-5. Computed from log-rank test using stratification factors (ALK-positive sALCL: Yes/No and IPI score: 0-1/2-3/4-5) at randomization (Takeda 2019).

Table EE: Efficacy estimates of A+CHP and CHOP for ALK- ALCL patients, IPI scores O-1, 2-3, and 4-5. a: OS rate is estimated using Kaplan-Meier methods and 95% C.I. is calculated using the complementary log-log transformation method. b: From stratified log-rank test with stratification factors (ALK-positive sALCL: Yes/No and IPI score: 0-1/2-3/4-5) at randomization (Takeda 2019).

PFS data for ALK+ sALCL patients, IPI 0-1, 2-3, and 4-5

Figure DD. KM curves of PFS for ALK+ sALCL patients IPI score 0-1. Computed from log-rank test using stratification factors (ALK-positive sALCL: Yes/No and IPI score: 0-1/2-3/4-5) at randomization (Takeda 2019). No data is depicted; ALK+ sALCL with IPI 0-1 was not allowed in the study.

Figure EE. KM curves of PFS for ALK+ sALCL patients IPI score 2-3. Computed from log-rank test using stratification factors (ALK-positive sALCL: Yes/No and IPI score: 0-1/2-3/4-5) at randomization (Takeda 2019).

Figure FF. KM curves of PFS for ALK+ sALCL patients IPI score 4-5. Computed from log-rank t3st using stratification factors (ALK-positive sALCL: Yes/No and IPI score: 0-1/2-3/4-5) at randomization (Takeda 2019).

allowed in the study. b:PFS rate is estimated using Kaplan-Meier methods and 95% C.I. is calculated using the complementary log-log transformation method. c: From stratified log-rank test with stratification factors (ALK-positive sALCL: Yes/No and IPI score: 0-1/2-3/4-5) at randomization (Takeda 2019).

Data Cuts From the Echelon-2 Study In The Public Domain

Prepared by

Anders Dydensborg, M. Sc., Ph. D., *Medical Advisor Onco-Hematology, Denmark*
Cassie Dong, Ph. D., *Scientific Fellow Oncology Biostats*
Meredith Little, MPH., *Associate Scientific Director Clinical Science*
Fabrizio Trinchese, MD, *Medical Director Onco-Hematology, Europe and Canada*
Raphael Yugi, MD, M. Sc., MBA, *Global Value and Access Lead Adcetris*

Data Cuts for Overall Survival Analysis in the Public Domain

*The primary analysis is supported by a proactive **OS Sweep***

Summary

The primary data cut from 2018 is the pertinent data to use for the assessment of clinical benefit of Adcetris in sALCL

- The **primary data cut from 2018 was the only data cut to formally evaluate OS;** the remaining data cuts were exploratory
- The subsequent **2019 analysis** was at the request of EMA, **mainly to understand differences between sALCL and the non-sALCL** populations and **was not pre-planned**. This data, and any further analysis, **has not undergone a *survival sweep* and was not "cleaned up" with the same rigor as the planned analysis**
- **OS was a non-powered secondary endpoint in E-2**; the **CIs are therefore expected to be wide** due to lack of power. E-2 is still the only study to show (unprecedented) OS benefit in this rare patient population
- **OS in sALCL was neither powered nor a prespecified endpoint** and the CIs will remain wide in course of the study. The **benefit in sALCL is consistent with the ITT results and clinically robust**
- **There is significant cross-over from patients in the CHOP arm to the BV arm**. This is a possible confounder in the OS results which will increase at later data cuts
- Based on the **unprecedented PFS and OS data** in E-2, t**here has been rapid uptake by HTA bodies** globally, including Europe

Introduction

This document is an addendum to the clinical part of the ongoing application for reimbursement of BV for first line treatment of sALCL patients in Denmark and addresses the data quality supporting OS analyses of the sALCL subgroup of patients from the Echelon-2 trial at two different timepoints: the prespecified primary analysis performed in 2018 and an auxiliary *ad hoc* analysis performed in 2019 on the request of EMA.

The 2018 data cut was pre-specified and took place following a rigorous *survival sweep* and formal database lock, which permits a more robust assessment of clinical benefit, including OS. This is compared to the ad hoc and unplanned data cut in 2019, which was not subjected to a *survival sweep* or a formal database lock. More rationales are provided below.

The data from Echelon-2 are practice changing

All HTA bodies who have finalized their assessment of the value of brentuximab vedotin (BV) for first line treatment of systemic Anaplastic Large Cell Lymphoma (sALCL) have approved BV for this indication.

Globally, the list of countries includes: Canada, USA, Israel, and Japan; in Europe the list includes United Kingdom, Germany, France, the Netherlands, the Czech Republic, and Austria.

In the Nordics, Sweden and Finland have approved reimbursement of BV for sALCL.

The primary data cut was the only data cut to formally evaluate OS; the remaining data cuts were exploratory

The primary data cut from 2018 was preplanned to support the primary analyses. Consequently, every effort was made to collect the most up-to-date survival status of patients through a *Survival Sweep* and thus more accurate deaths information were captured across the treatment arms. In addition, the entire clinical data set underwent a stringent data cleaning process prior to database lock.

The data cut from 2019 was not preplanned, but conducted at the request of EMA/CHMP as part of an ad hoc analysis request aimed at describing differences between the sALCL population and the non-sALCL population in the Echelon-2 study.

Consequently, the data did not include a survival sweep and was not formally locked.
The data may therefore not have fully captured all the death information.

In accordance with general study principles, and potential differences in data quality, the prespecified 2018 data cut is much more robust for clinical conclusions and statistical inference, whereas the 2019 data cut is part of an ad hoc analysis and should not be considered inferential but is rather descriptive.

These principles were adhered to by EMA/CHMP, who in the summary of efficacy, and basis for approval, cited the 2018 PFS and OS rates and did not address the 2019 analysis.

OS was a non-powered secondary endpoint in E-2; the CIs are therefore expected to be wide due to lack of power throughout the study

The Echelon-2 study sample size of ~450 was designed to achieve 80% power to detect difference in the primary endpoint PFS per IRF in the ITT population. The study was not designed to detect OS differences in the sALCL subgroup population.
The OS analyses are thus underpowered and confidence interval of the Hazard Ratio (HR) is expected to be wide, even when the HR is low at 0.54 to 0.63.
Currently 78 death events have occurred; to have 80% power for a true HR of 0.63 a total of 148 deaths are needed.
Internal analysis from Takeda estimates a study duration of more than 10 years to achieve 80% power with 450 sample size with a true HR of 0.63.
In line with this, the Clinical Expert Committee (*Fagudvalget*) in the protocol for the assessment estimated that a median OS would not be reached without a considerable follow-up.

Overall Survival difference is Robust and Maintained through-out follow-up

Figure A and B depicts the KM curves for OS derived from the 2018 (figure A) and 2019 (figure B) data cuts.

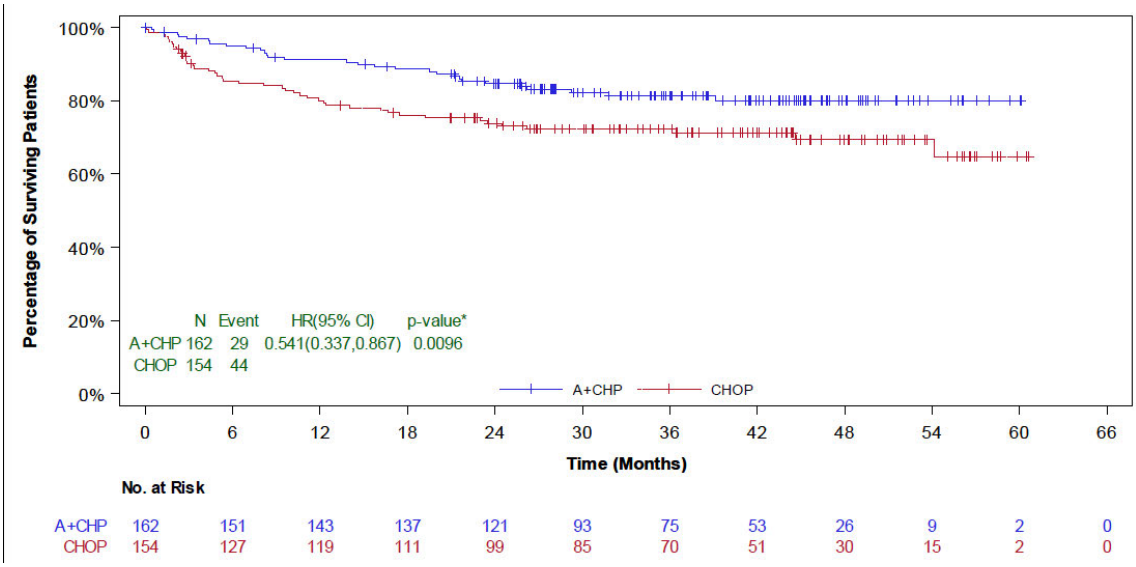


Figure A: KM curves of Overall Survival of the sALCL subgroup of patients from Echelon-2 performed with the prespecified primary data cut in August 2018.

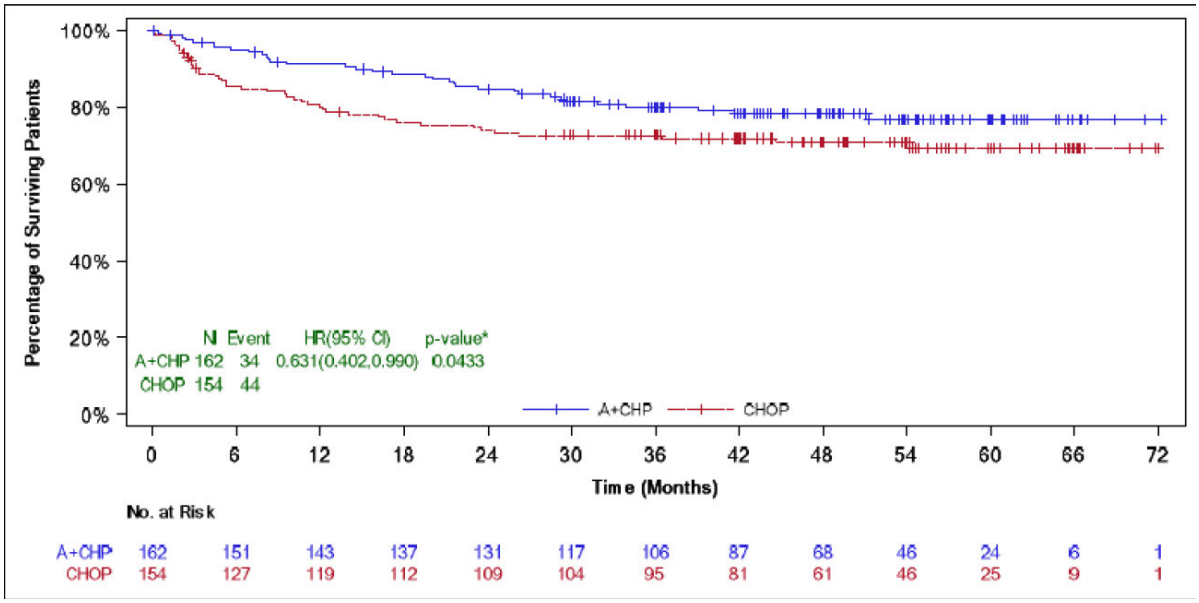


Figure B: KM curves of Overall Survival of the sALCL subgroup of patients from Echelon-2 performed with the ad hoc descriptive data cut in September 2019.

Both results are clinically meaningful with HR estimates of 0.54 (95% CI: 0.34; 0.87, P=0.0096) (CHMP 2020) and 0.63 (95% CI: 0.40; 0.99, P=0.0433) (CHMP 2020) which are consistent with the OS results found in the *Intention To Treat* (ITT) population (HR: 0.66, 95% CI: 0.46; 0.95, P=0.0244) (Horwitz et al. 2019).

Furthermore, both KM curves **separate early** and **remain separated** throughout the follow-up time, while the upper bound of the 95% confidence interval (CI) remains below 1.00.

The Clinical Expert Committee (Fagudvalget) additionally requested OS-rates after 2-yrs as this timepoint was considered relevant to evaluate the efficacy from a **clinical perspective** (lymfomer 2020). These rates demonstrated a 2-yr OS difference of 10.7%; more than double the prespecified clinical relevant difference of 5% (lymfomer 2020).

Cross-Over and Imbalanced use of subsequent therapies may dilute the OS effect
The above demonstrated difference in OS effect is seen despite a large imbalanced use of subsequent therapies between the study arms, potentially diluting the OS effect.
More specifically, 37% of the patients in the CHOP arm received systemic therapy for residual or progressive disease as compared to 20 % of the subjects in the A+CHP arm.
As for subsequent BV therapy 25% of the CHOP patients received BV containing regiments while 10% of the patients in the A+CHP arm received BV containing regiments.

Progression occurs early in the diseases course – late stage assessment of OS measures the efficacy of subsequent therapy
The majority of sALCL patients who relapse, relapse rapidly after treatment irrespective of ALK-status (Mak et al. 2013). This highlights the relevance of the OS benefit at the primary data cut. Overall Survival measured at a late stage is, on the other hand, confounded by the subsequent treatment; in essence the survival is an effect of the subsequent therapy.
Such a confounding factor will be more and more pronounced the longer the follow-up is.
This is of particular relevance in a situation where the subsequent therapy is imbalanced and favors the control arm over the A+CHP arm (see above).

Conclusion

- The Overall Survival benefit of A+CHP vs CHOP is considerable and practice changing as recognized by all HTA bodies so far.
- The Kaplan-Meier curves of OS show consistent separation with a HR ranging from 0.54 to 0.63 and 95% CI below 1.00.
- OS rates show a consistent survival benefit around 10% over time; double the defined minimal clinically relevant value of 5%.
- This effect is seen despite
    - the study not being powered for an OS analysis; the wide confidence interval of the HR is expected due to the lack of power.
    - Likely dilution of the OS effect of A+CHP due to considerable imbalanced use of subsequent therapy favoring the CHOP arm: 25% BV use in the CHOP arm vs. 10% BV use in the A+CHP arm.

Finally, **it is the position of Takeda that the prespecified 2018 primary analysis provides the reliable estimate of the survival benefit** as:

- This data cut is more robust since it was prespecified; the data set contain proactive collected and verified data, while the 2019 data cut was ad hoc, without a proactive survival sweep, and the stringent processes associated with a formal data base lock.
    - As a consequence, the 2019 data cut may not accurately capture all the deaths in both arms. Considering the small sample size, this may disproportionally impact the numerical results of the confidence interval.
- General study principles suggest that unplanned ad-hoc analysis based on data that have not undergone the stringent process of a Survival Sweep, or the processes associated with a formal data base lock, should not be inferential, but should only be considered descriptive
    - These principles were adhered to by EMA
- Longer Follow-Up is likely to lead to increased confounding by subsequent therapy

References

CHMP. 2020. "Assessment Report Adcetris Procedure No. EMEA/H/C/002455/II/0070." In.

Horwitz, S., O. A. O'Connor, B. Pro, T. Illidge, M. Fanale, R. Advani, N. L. Bartlett, J. H. Christensen, F. Morschhauser, E. Domingo-Domenech, G. Rossi, W. S. Kim, T. Feldman, A. Lennard, D. Belada, Á Illés, K. Tobinai, K. Tsukasaki, S. P. Yeh, A. Shustov, A. Hüttmann, K. J. Savage, S. Yuen, S. Iyer, P. L. Zinzani, Z. Hua, M. Little, S. Rao, J. Woolery, T. Manley, and L. Trümper. 2019. 'Brentuximab vedotin with chemotherapy for CD30-positive peripheral T-cell lymphoma (ECHELON-2): a global, double-blind, randomised, phase 3 trial', *Lancet*, 393: 229-40.

lymfomer, Medicinrådets Fagudvalg vedr. 2020. 'Medicinrådets protokol for vurdering af brentuximab vedotin i kombination med cyclophosphamid, doxorubicin og prednisolon til behandling af tidligere ubehandlet systemisk anaplastisk storcellet T- cellelymfom'.

Mak, V., J. Hamm, M. Chhanabhai, T. Shenkier, R. Klasa, L. H. Sehn, D. Villa, R. D. Gascoyne, J. M. Connors, and K. J. Savage. 2013. 'Survival of patients with peripheral T-cell lymphoma after first relapse or progression: spectrum of disease and rare long-term survivors', *J Clin Oncol*, 31: 1970-6.

Data Cuts for Overall Survival Analysis in the Public Domain

*The primary analysis is supported by a proactive **OS Sweep***

Appendix 1

*Rationale for, and the impact of, an **Overall Survival Sweep***

An *Overall Survival Sweep* is an effort by the study team to collect patient status (alive/dead) for all patients, regardless of visit scheduling, within a compressed timeline before data cutoff.

Typically an OS sweep will have verified the status of all patients 1-2 months prior to the Data Cut Off.

Below is an example of why this is done:

Assuming that the below patients are in long term follow up, visits are every 6 months, and the data cutoff is December 31, 2020:

Patient	Date of last visit	Estimated date of next visit	Date of Data Cut Off	Date of Death
1	June 15, 2020	December 15, 2020	December 31, 2020	October 1, 2020
2	Sep 15, 2020	March 15, 2021	December 31, 2020	October 1, 2020

Both of these patients had the same date of death (October 1st, 2020) but only patient #1 would have been collected in a standard process.
The patient would not have been able to make the visit on December 15th because the patient died. However, having the visit on the books would 1) prompt the site to schedule the visit and 2) when realizing the patient was deceased, record the date of death.
Because the date of death as well as the estimated next visit precede the Data Cut Off date of Dec 31st 2020, the patient's death would be captured in a normal "unclean" "unlocked" database.

Patient number 2 is the type of patient that may be missing from a Data Cut Off without an OS sweep.
Here, the patient was seen in Sep 2020 and were alive. The next visit isn't until March of the following year. This patient also died on Oct 1st but the death *may* not have been recognized by the site because the next scheduled contact wouldn't be until well after the data cutoff date.

These are the types of deaths that are missed if an OS sweep is not conducted and all patients' status confirmed within 1-2 months of the data cutoff date.

In summary, an OS sweep ensures the most accurate death count at a given (pre planned) data cutoff, which is most important when evaluating OS. When evaluating an OS output from an unplanned data cutoff, it is possible that some deaths have occurred but haven't been captured.

In addition, there is no way to ensure the missing deaths were balanced between the treatment arms – when looking at very small number of additional deaths, missing even 1-3 deaths on a particular treatment arm can have a large impact on confidence intervals.

5-year Follow-Up data from Echelon-2

Echelon-2 5-yr follow-up

The aim of the current data submission is provide the Medicines Council data with the longest possible follow-up. The data constitutes PFS and OS data for the ITT study population and the sALCL subpopulation from the Echelon-2 trial with 5-yrs follow-up.
The PFS analyses and OS analysis in the ITT population were preplanned, while the OS analysis in the sALCL population was ad hoc; all analyses were done on the basis of proactive data collection (survival sweep).
The data herein was presented at ASH, 2020.
After 5 yrs follow up

- The Echelon-2 data remain practice changing through its combination of increased efficacy with a similar AE burden

Thus,

- PFS and OS in the ITT population as well as PFS remain statistically significant.
- The PFS analysis in the sALCL subgroup show a statistically significant Hazard Ratio of 0.55.
- The unpowered ad hoc analysis of OS in the sALCL subgroup of patients show a Hazard Ratio of 0.66 with wide Confidence Intervals due to
    - lack of power for this analysis.
    - Imbalanced use of subsequent therapy

Updated Data

PFS	A+CHP, N=226	CHOP, N=226	Difference	Hazard Ratio
Events, N(%)	94 (41.5)	125 (55.3)		
Median PFS Months[a,] (CI)	62.26 (NR)	23.75(NR)	38.51	0.70 (0.53; 0.91) P=0.0077
OS	A+CHP, N=226	CHOP, N=226	Difference	Hazard Ratio
Number of Death, N(%)	68 (30.1)	89 (39.3)		
Median OS Months[a,] (CI)	NR (-, -)	NR (-, -)	NE	0.72 (0.53; 0.99) P=0.0424

Table A: PFS and OS of the ITT population with 5-yr follow-up [1]. NR: not reported in the poster presented at ASH. NE: not estimable.

PFS	A+CHP, N=162	CHOP, N=154	Difference	Hazard Ratio
Events, N(%)	53 (32.7)	77 (50)		
Median PFS Months[a,] (CI)	NR (-, -)	54.18 (-, -)	NE	0.55 (0.39; 0.79) P=0.0009
OS	A+CHP, N=162	CHOP, N=154	Difference	Hazard Ratio
Number of Death, N(%)	NR	NR		
Median OS Months[a,] (CI)	NR (-, -)	NR (-, -)	NE	0.66 (0.43; 1.01) P=NR

Table B: PFS and OS of sALCL patients with 5-yr follow-up [1]. NR: not reported in the poster presented at ASH. NE: not estimable.

Context to Updated Data

The trial was a first line PTCL trial powered for PFS in the ITT population
The Echelon-2 trial was a first line trial that was powered for PFS in the PTCL (ITT) population. OS in the ITT and PFS in the sALCL subgroup of patients were predefined analyses. However, the study was not powered for OS in the ITT group or PFS in the sALCL subgroup of patients. Similarly, the study was not powered for the ad hoc analysis of OS in the sALCL subgroup of patients.
This lack of power for OS in the ITT population, let alone the sALCL subgroup, is not unusual for first line cancer trials where PFS is widely accepted as a surrogate for OS since it allows for accelerated approval [2, 3]. Indeed, both patient population and timeframe would be unsustainably inflated if first line trials are to be powered for OS. Accordingly, both EMA and FDA accepted the trial design prior to study start.

Due to the lack of formal statistical power for OS in the ITT population, **an analysis of OS in a subgroup of patients is expected to result in wide 95% Confidence Intervals (CI), even when the HR is low at 0.66**.
Due to confounding by subsequent therapy (see below), these underpowered Confidence Intervals are expected to widen further with longer follow-up.

Overall Survival and PFS differences are robust and maintained through-out follow-up
At 5-years follow-up the OS and PFS differences in the ITT population remain statistically and clinically significant at 0.70 (95% CI: 0.53; 0.91, P=0.0077) and 0.72 (95% CI: 0.53; 0.99, P=0.0424) [1]. Indeed, the PFS advantage in the ITT population, for which the trial was powered, demonstrated a **3-year** (38 months) **improvement of median PFS.**

The corresponding Hazard Ratio values for the unpowered sALCL subpopulation are consistent with the ITT population at 0.55 (0.39; 0.79, P=0.00009) and 0.66 (0.43; 1.01) for PFS and OS, respectively [1].

Regardless of the slight increase in the point estimate of the HR with time, the **overall survival benefit remains robust** as demonstrated by the continued 10% increase in survival in the A+CHP arm vs. the CHOP arm across time (table C).

Time, Months	6	12	24	36	48
OS Rate, A+CHP (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OS Rate, CHOP (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Difference, %	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table C: OS rates over time. From the 3-year analysis.

Similarly, and as demonstrated in communications with the Medicines Council [4], the Kaplan-Meier curves from the 3 and 4-year analyses show **early** and **consistent separation** of OS curves.

Cross-Over and Imbalanced use of subsequent therapies may dilute the OS effect
The above demonstrated difference in OS effect is seen despite a large imbalanced use of subsequent therapies between the study arms, potentially diluting the OS effect.
More specifically, 37% of the patients in the CHOP arm received systemic therapy for residual or progressive disease as compared to 20 % of the subjects in the A+CHP arm.
As for subsequent BV therapy 25% of the CHOP patients received BV containing regiments while 10% of the patients in the A+CHP arm were retreated with BV containing regiments.

Progression occurs early in the disease course – late stage assessment of OS measures the efficacy of subsequent therapy
The majority of sALCL patients who relapse do so rapidly after treatment irrespective of ALK-status [5]. This highlights the relevance of the OS benefit at the primary data cut. Overall Survival measured at a late stage is, on

the other hand, confounded by the subsequent treatment; in essence the survival is an effect of the subsequent therapy.
Such a confounding factor will be more and more pronounced the longer the follow-up is.
This is of particular relevance in a situation where the subsequent therapy is imbalanced and favors the control arm over the A+CHP arm (see above).

The robust PFS and OS results are obtained and maintained without increased AE burden
The above demonstrated difference in OS effect is seen with-out an increase of AEs as compared to CHOP.
Indeed, the rates of grade ≥ 3 AEs was 58.75% and 63.63% in the A+CHP and CHOP arms, respectively (absolute reduction of 4.88, RR 0.925 (95% CI: 0.78; 1.10, P=0.3832).
Importantly, in the sALCL population the rate of discontinuation due to AEs was 3.75% and 9.1% in the A+CHP and CHOP arms, respectively (absolute reduction: 5.3%, RR: 0.397 (95% CI: 0.15; 1.05, P=0.05).

The Echelon-2 trial remains practice changing
As previously communicated the treatment tested in the Echelon-2 trial has been rapidly adopted by every single HTA body so far, as well as the NCCN [4].

Conclusion

- PFS shows a consistent clinically significant effect with a Hazard Ratio of 0.55 (95% CI: 0.39; 0.79, P=0.00009) and median PFS still not reached in A+CHP treated patients at five years follow-up
- OS rates show a consistent survival benefit around 10% over time; double the defined minimal clinically relevant value of 5%, as well as a Hazard Ratio at 0.66 (95% CI: 0.43; 1.01)
    - This effect is seen despite:
        - The study not being powered for analyses in the sALCL subgroup.
        - Likely dilution of the OS effect of A+CHP due to considerable imbalanced use of subsequent therapy favoring the CHOP arm.
        - Longer follow-up is likely to lead to increased OS confounding by subsequent therapy.
        - **The wide confidence interval of the HR of OS is expected due to the lack of power and the confounding effect of subsequent treatments, the effect of which only will be more pronounced with longer follow-up.**
- Additionally, the practice changing efficacy data are obtained with **no added toxicity** as compared to CHOP; a regiment widely considered less toxic than CHOEP.

References

1 Steven M. Horwitz OAOC, Barbara Pro, Tim Illidge, Swami P. Iyer, Ranjana Advani, Nancy L. Bartlett, Jacob Haaber Christensen, Franck Morschhauser, Eva Domingo-Domenech, Giuseppe Rossi, Won Seog Kim, PhD, Tatyana A. Feldman, Tobias Menne, MD, David Belada, Árpád Illés, Kensei Tobinai, Kunihiro Tsukasaki, Su-Peng Yeh, Andrei R Shustov, Andreas Hüttmann, Kerry J. Savage, Sam Yuen, Pier Luigi Zinzani, Harry Miao, Veronica Bunn, Keenan Fenton, Michelle A. Fanale, Markus Puhlmann, Lorenz Truemper. The Echelon-2 Trial: 5-Year Results of a Randomized, Double-Blind, Phase 3 Study of Brentuximab Vedotin and CHP (A+CHP) Versus CHOP in Frontline Treatment of Patients with CD30-Positive Peripheral T-Cell Lymphoma. *ASH*: Virtual, 2020.

2 Guideline on the evaluation of anticancer medicinal products in man. In: EMA/CHMP (ed). EMA, 2017.

3 Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics Guidance for Industry. In: U.S. Department of Health and Human Services FaDA, Oncology Center of Excellence (ed). FDA, 2018.

4 Dydensborg A, Dong C, Little M, Trinchese F, Yugi R. Data Cuts From the Echelon-2 Study In The Public Domain. In: Council M (ed), 2020.

5 Mak V, Hamm J, Chhanabhai M, Shenkier T, Klasa R, Sehn LH *et al*. Survival of patients with peripheral T-cell lymphoma after first relapse or progression: spectrum of disease and rare long-term survivors. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2013; 31: 1970-1976.

Brentuximab vedotin (Adcetris) for the treatment of systematic anaplastic large-cell lymphoma

Cost Analysis and Budget Impact Report

ABBREVIATIONS

CHP:	cyclophosphamide, doxorubicin, and prednisone
PPP:	Pharmacy Purchase Price
ALK:	Anaplastic Lymphoma Kinase
ATC:	Anatomical Therapeutic Chemical classification system
BIM:	Budget Impact Model
EMA:	European Medicines Agency
EPAR:	European Publish Assessment Report
HTA:	Health Technology Assessment
NICE:	National Institute for Health & Care Excellence
SOC:	Standard of care
TEAE:	(Treatment-Emergent) Adverse Event
CHOP:	Cyclophosphamide, doxorubicin, vincristine, and prednisone
TLV:	Tandvårds- och Läkemedelsförmånsverke
CHOEP:	Cyclophosphamide, doxorubicin, vincristine, etoposide, and prednisone
SCT:	Stem cell transplantation
AutoSCT:	Autologous stem cell transplantation
AlloSCT:	Allogeneic stem cell transplantation
PR:	Partial response
CR:	Compleate response
A:	Adcetris
DLG:	Danish Lymphoma Group

1 SUMMARY

Introduction: sALCL is a subtype of PTCL, a rare and heterogeneous group of lymphoid malignancies, and is represented as the third most frequent group of non-cutaneous T-cell lymphomas (1). In Denmark, sALCL is estimated to have an incidence of approximately 21 patients per year and a median age of diagnosis of 34 years (1,2). Common symptoms are classic B-symptoms (night sweats, fever, weight loss) as well as more diffuse symptoms such as rash, swollen liver/spleen. Dissemination sites include bone marrow, liver, spleen, skin, and lung. The sALCL population can be placed into subpopulations based on so-called ALK-status, comorbidities, age, and IPI-status, which determines treatment choice for specific patient populations. Younger patients who are ALK-positive are often recommended treatment with either CHOP or CHOEP, while ALK-negative patients primarily are suggested treatment with CHOEP. These patients are usually assessed as candidates for stem cell transplantation (SCT). Older patients with comorbidities are normally assessed not candidates for high-dose treatments and SCT and are therefore treated with CHOP independent of their ALK-status (3).

Recently, EMA recommended Brentuximab vedotin (Adcetris) as first-line treatment for sALCL. The efficacy and safety of Adcetris in previously untreated patients with sALCL have been evaluated in the global ECHELON-2 trial, where the primary endpoint, progression-free survival, was met. Among sALCL, treatment with A+CHP demonstrated a significant and clinically meaningful extension in PFS compared to treatment with CHOP (p=0.0031) (4).

Objective: This analysis aims to evaluate incremental cost pr. patient and total budget impact associated with current treatment of sALCL with introduction of brentuximab vedotin as a standard of care treatment option for adult patients previously untreated for sALCL. The analysis will evaluate the lifetime incremental costs per patient (30 years), as well as budget impact for the period of 2021-2026 including accumulated 5-year costs.

Method: The budget impact model is a simple model focusing on cost comparison of drug acquisition costs as well as relevant hospital costs associated with treatment with intervention and comparator. The model estimates incremental cost between the technologies from a marginal perspective, i.e. costs assumed to be equal for both brentuximab vedotin and CHOP/CHOEP are excluded from the budget impact analysis. For the cost analysis, standard parametric curves has been fitted to the PFS and OS data to extrapolate the outcomes observed in the ECHELON-2 trial and estimate the long-term costs of each technology.

Results: The total eligible patient population for the A+CHP treatment over a five-year time horizon is estimated to [redacted] patients based on assumed market shares, leaving [redacted] patients to be treated with CHOP/CHOEP. By year four, the model predicts that all patients will be treated with A+CHP. The budget impact of recommending A+CHP as first-line treatment for patients previously untreated for sALCL is estimated to be [redacted] kr. The lifetime cost per patients in the A+CHP arm for the base case scenario is estimated to be [redacted] kr.

Conclusion: The results are driven largely by increased acquisition costs associated with Adcetris. However, the analysis also estimated substantial cost savings associated with reduced administration costs of first- and second-line treatments, including Adcetris. Results were most sensitive to parameters which determined the size of the eligible population and use of subsequent A+CHP treatment.

Sigurd Hilborg
Health Economist & Market Access Manager

Takeda Pharma a/s
Delta Park 45
2665 Vallensbæk Strand
Denmark

Phone: (0045) 60 944922
Email: Sigurd.hilborg@takeda.com

Contents

DRG codes used in this assessment:

Procedure	Unit cost	DRG2020
Anaemia	4.732 kr.	16PR02
Diarrhoea	5.297 kr.	06MA11
Febrile neutropenia	58.620 kr.	01MA03
Leukopenia	6.114 kr.	16PR01
Neutropenia	27.036 kr.	01MA04
Pneumonia	37.050 kr.	04MA13
Thrombocytopenia	37.603 kr.	16MA03
CT scan	2.032 kr.	30PR06
PET scan (3+ areas)	2.470 kr.	36PR07
Consultation	1.512 kr.	23MA04
Full blood count/clinical bio-chemistry/Urea and electrolytes	28.271 kr.	17MA03
Bone marrow biopsy	14.935 kr.	17PR01
Liver function test	28.271 kr.	17MA03
Autologues SCT	171.378 kr.	26MP24
Alogenues SCT	688.233 kr.	26MP22
Radiotherapy	4.426 kr.	27MP07

Reference: (5)

2 BACKGROUND

2.1 Introduction

On 26 March 2020, the European Medicines Agency approved brentuximab vedotin (BV) in combination with cyclophosphamide, doxorubicin, and prednisone (CHP) for adult patients with previously untreated sALCL (6). The European Medicine Agency (EMA) qualified BV as an orphan drug based on following criteria (7):

- Indicated for a disease affecting ≤5 people per 10,000 (0.05% of the population)
- Intended for a life-threatening or chronically debilitating disease
- Must be of significant benefit to those affected by the disease
- It is unlikely that marketing the drug will create sufficient return-on-investment within the lifetime of the patients, however, the drug is still launched due to the high unmet need

Takeda Pharma submitted the preliminary application to the Danish Medicines Council on 28 February 2020, and the final reimbursement dossier for the Danish Medicines Council on 1 September 2020 (8). The product has been registered and visible in the Danish Medicines Agency via www.medicinpriser.dk since 28 April 2014 (9).

The approval of BV was granted by EMA based on the Phase III ECHELON-2 trial which was conducted in order to compare efficacy and safety of BV in combination with CHP (A+CHP) with standard cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) for the treatment of previously untreated patients with CD30+ peripheral T-cell lymphoma (PTCL). ECHELON-2 was a randomized, double-blind, double-dummy, placebo-controlled, active-comparator study conducted at 132 sites in 17 countries across North America, Europe, Asia Pacific, and the Middle East. The trial was powered for the intention-to-treat (ITT) population, as well as for sALCL PFS per independent review facility (4).

2.2 Systemic Anaplastic Large Cell Lymphoma

sALCL represents a subgroup of the broader disease classification called PTCL. Applicable for all subgroups of PTCL is that they classify as rare heterogeneous diseases of hematological tumors originating from mature T cells. Subtypes are classified according to origin (nodal/extranodal/leukemic) and putative cell of origin (3).

sALCL is the third most common group of non-cutaneous T-cell lymphomas and has two subgroups separated by the presence of "anaplastic lymphoma kinase" (ALK) in malignant cells. The subgroups are ALK-positive and ALK-negative. ALK-positive affects younger patients (median 34 years), while ALK-negative affects older patients (median 54-61 years). There are no known predisposing factors (3).

Approximately 1.400 new lymphoma cases are registered each year in Denmark, and approximately 90 percent of them are categorized as non-Hodgkin lymphoma, while the remaining 10 percent is defined as

Hodkins lymphoma (3,10). Based on data derived from the Danish Lymphoma Database, it is assessed that approximately 21 patients are diagnosed with sALCL per year (2).

2.3 Diagnosis

sALCL diagnosis is based on a compilation of different clinical tests and scans performed at the hospital. The approaches taken are the following:

- histopathological assessment of bioptic material from lymph nodes, tonsils, spleen, bone marrow, or other affected organs
- Immunohistochemical analyzes for establishing the diagnosis. These consists of 'primary' and 'secondary' markers, such as CD30, CD45, and PAX5
- Molecular analyzes within PTCL diagnosis include clonality assay, fluorescence in situ hybridization (FISH) and non-fluorescence, non-isotopic in situ hybridization (ISH)
- Diagnostic imaging. Currently, there is no definitive evidence for which imaging technic to use in T cell lymphomas. Imaging is typically applied three times during time from diagnosis to end of treatment. At time of diagnosis, imaging is used to map out disease staging. Second time imaging is applied is during interim scan to assess the effect of treatment. And the third and final scan is used to assess final response evaluation (1,3).

Biochemical tests are performed to evaluate hematological quantities, liver values, kidney values, coagulation numbers, virus parameters, and specific proteins (1,3).

2.4 Treatment options

2.4.1 First-line treatment

Treatment of sALCL patients is divided into categories based on patient's age, comorbidity, and whether the lymphoma is ALK-positive or ALK-negative. The primary treatment option for younger patients without severe comorbidities who are ALK-positive and candidates for high dose treatment (HDT) is CHOEP given in 6 series every 14 days. As an alternative, patients can be given CHOP of 6 to 8 series every 14 days. Younger patients who are ALK-negative and HDT candidates are given CHOEP of 6 series every 14 days. If the patient experiences partial response or complete response, a stem cell transplantation is used as a consolidative treatment (1).

Patients who are older than 65 years and/or have comorbidities who aren't candidates for HDT are treated in 6 series every 14 or 21 days with CHOP. Treatment choice for elderly patients is independent of ALK-status (1).

2.4.2 Treatment with A+CHP

Brentuximab vedotin is an antibody-drug conjugate (ADC) composed of a CD30-directed monoclonal antibody that is covalently linked to the antimicrotubule agent monomethyl auristatin E (MMAE). Targeted delivery of MMAE to CD30-expressing tumor cells is the primary mechanism of action of brentuximab vedotin. However, the direct cytotoxicity associated with brentuximab vedotin may be augmented by

secondary effects (11). The mode of action of brentuximab vedotin ensures it predominantly targets tumour cells. A+CHP is recommended for all CD30+ patients regardless of ALK-status as first-line treatment.

2.4.3 Administration of first-line treatments

CHOP, CHOEP, and BV are all administered as intravenous infusions. BV is administered over 30 minutes, with the recommended dose in combination with chemotherapy for previously untreated sALCL being 1.8 mg/kg up to a maximum of 180 mg every 3 weeks for 6 to 8 cycles. In the ECHELON-2 trial average BSA (m^2) was 1,87, while average weight was 75.45 kg. In the trial, patients were treated with 6 to 8 cycles of A+CHP, at the center's discretion. Further, it is recommended that patients are administered prednisone, 100 mg on Days 1 to 5 of each 3-week cycle, orally for 6-8 cycles (4,12).

The CHOP regimen recommended in sALCL and administered in ECHELON-2 is comprised of 750 mg/m2 of cyclophosphamide, 50 mg/m2 of doxorubicin, and 1.4 mg/m2 of vincristine on Day 1 of each 21-day cycle and 100 mg of prednisone on Days 1 to 5 of each cycle (4).

Treatment with CHOEP consists of doxorubicin 50 mg/m2, cyclophosphamide 750 mg/m2 , and vincristine 1.4 mg/m2 by intravenous infusion on day 1, etoposide 100 mg/m2 intravenously days 1–3, and oral prednisone days 1–5. Cycles are repeated every 3 weeks for a maximum of six to eight courses(13).

Prophylactic use of G-CSF (in this report referred to as concomitant treatment) is mandatory for both CHOEP/CHOP treatments and A+CHP. G-CFS is used to reduce duration of neutropenia and cases of fibril neutropenia, which is shown to be a present adverse event in treatment of sALCL.

2.4.4 Salvage treatments and radiotherapy

CD30+ sALCL patients are the only subgroup of the PTCL patient population currently with a recommended standard of care for relapsed/refractory patients. Recommended treatment is A+CHP given in 6 to 8 cycles independent of ALK-status. In some cases, treatment with A+CHP as salvage therapy is also useful to bridge patients towards autologous stem cell transplantation (AutoSCT) when patients experience PR or CR.
In fit patients without severe comorbidities, combination chemotherapy regimes such as DHAP (dexamethasone, high-dose cytarabine, cisplatin), GDP (gemcitabine, dexamethasone, cisplatin), ESHAP (etoposide, methylprednisolone, cytarabine, cisplatin), or ICE (ifosfamide, etoposide, carboplatin) can be attempted in chemosensitive patients. This treatment approach is often aimed at preparing the patients for allogeneic stem cell transplantation (AlloSCT) if PR or CR is reached.
Patients with localized disease may be treated with local radiotherapy. However, in a Danish setting, this is used in very low frequencies and often with a palliative purpose to treat locally symptomatic disease (1,3).

2.4.5 Stem cell transplantation

AutoSCT can be used as consolidation as part of first-line treatment if patients experience PR or CR. Traditionally, ALK-positive patients have been excluded from receiving AutoSCT as part of first-line treatment due to their superior outcomes after traditional CHOP-like treatment. Based on expert opinions, this shows to still be evident in the Danish setting ([redacted]).

An alternative to AutoSCT is AlloSCT also given as part of first-line treatment. AlloSCT has shown the potential to cure PTCL patients, but data from the ECHELON-2 trial shows that AutoSCT is still the predominantly used method (3,4).
Very few relapsed/refractory patients receive SCT as part of second-line treatment, due to the staging and progression of disease, preventing them from being candidates for SCT (1,3).

3 OBJECTIVE

This analysis aims to evaluate the budget impact to assess the likely effect on resources and budget resulting from adopting A+CHP for the treatment of adults with previously untreated sALCL. The model assesses differences in cost of care in an environment with and without frontline A+CHP devided into the two clinical questions proposed by the Danish Miedicines Council.

Further, cost analysis based on extrapolated PFS and OS data from the ECHELON-2 trial has been conducted to estimate the lifetime cost of a patient treated on either of the three treatment regimens. A time horizon of 30 years has been chosen to reflect all important differences in costs between the technologies being compared.

4 METHOD

4.1 Budget impact model

The budget impact model (BIM) developed for this submission compares drug acquisition costs and adverse event costs associated with treatment with intervention and comparator as well as relevant hospital costs.

The budget impact analysis is based on a 5-year time horizon. The costs are either attributed based on the extrapolated data for the entire sALCL population, or as a one-off cost. It has not been possible to extrapolated data based on ALK-status due to very low patient numbers.

4.2 Cost Analysis

The cost analysis utilizes a partitioned survival approach (PartSA), which is a model structure commonly used in oncology. PartSAs are often used because the endpoints and survival curves reported (e.g. PFS and OS) can be directly used to model state membership. In this cost analysis, the proportion of patients in the PFS state over time (based on the primary endpoint of ECHELON-21) is estimated directly from the PFS curve reported in ECHELON-2 study. Standard parametric curves has been fitted to the PFS and OS data to extrapolate the outcomes observed in the ECHELON-2 trial for the estimation of long-term costs of each technology. A 21-day cycle length is applied, reflecting the duration of a CHOP/CHOEP or A+CHP treatment cycle. Half-cycle correction is implemented using the life table method, where the time in each cycle is

[1] PFS was defined as the time from the date of randomisation to the date of first documentation of progressive disease, death due to any cause, or receipt of subsequent anticancer chemotherapy to treat residual or progressive disease, whichever occurred first. Receipt of post-treatment consolidative radiotherapy, post-treatment chemotherapy for the purpose of mobilising peripheral stem cells, or consolidative autologous or allogeneic SCT was not considered disease progression or as having started new anticancer therapy.

estimated by taking the average of the number of people at the start and end of the cycle. The maximum time horizon of the cost analysis is 45 years.

Treatment of sALCL focuses on postponing progression of disease. Each drug thus delays the time until progression. Subsequent therapy costs such as retreatment with A+CHP can be selected in the model. Palliative care costs are assumed to be equal for both A+CHP and CHOP/CHOEP.

Results are presented for each of the two clinical questions proposed in the protocol.

1. What value does brentuximab vedotin in combination with cyclophosphamide, doxorubicin, and prednisolone (CHP) have compared to cyclophosphamide, doxorubicin, vincristine, etoposide, and prednisolone (CHOEP) or cyclophosphamide, doxorubicin, vincristine, and prednisolone (CHOP) cell lymphoma in patients who are candidates for HDT and ASCT?
    a. Population: Adults with previously untreated systemic anaplastic large cell T-cell lymphoma who are candidates for HDT and ASCT.
2. What value does brentuximab vedotin have in combination with cyclophosphamide, doxorubicin, and prednisolone (CHP) compared to cyclophosphamide, doxorubicin, vincristine, and prednisolone (CHOP) for previously untreated patients with systemic anaplastic large-cell T-cell lymphoma who are not candidates for HDT and AST?
    a. Adults with previously untreated systemic anaplastic large-cell T-cell lymphoma who are not candidates for HDT and ASCT and previously untreated ALK-positive adults with low IPI.

The model is developed in Microsoft Excel® 2010 using standard Excel® functions. The model consists of the following sheets:

1. Key results
2. Model design
3. Input section
    a. Eligible population
    b. Market share
    c. Efficacy & safety
    d. Time on treatment
    e. Acquisition
    f. Resource use
    g. Stem cell transplants
    h. Radiotherapy
    i. Indirect costs
4. Base-case results
5. Sensitivity analysis

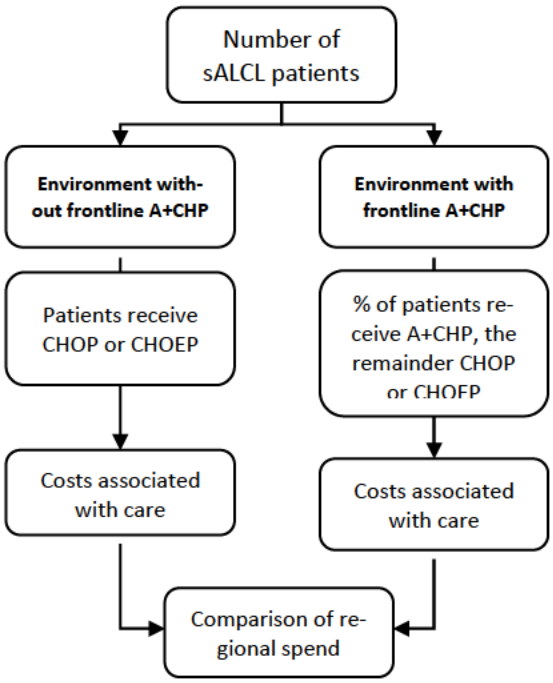
4.3 Model structure

A model overview is presented in the 'Model design' tab within the Excel model itself.

The model settings enable choosing between the full sALCL population, or sALCL ALK-positive and ALK-negative patients for the budget impact analysis. Further, the model gives the possibility to select if only patients who are candidates for CHOP treatment should be included in the model. Finally, the user can select which costs to include in the model by ticking off the boxes on the "Key results" tab.

For the cost analysis, it has not been feasible to satisfy the population based on ALK-status, due to very low patient numbers and risk of impacting the robustness of the analysis. The cost analysis is therefore only based on extrapolations of the survival data for the sALCL population. In the cost analysis, the user can still select which costs to include in the model by ticking off the boxes on the "Key results" tab. The base case settings for the model can be found in appendix 16.

Figure 1: model structure. The entire sALCL population is divided into two scenarios dependent on the recommendation of A+CHP as SoC.



4.4 Comparators

The comparators, CHOP and CHOEP, is specified by the Danish Medicines Council via the submission protocol for this application (10). The costs for CHOP and CHOEP are attributed to the eligible populations for the respective regimes based on the administration description given in section 2.4.3.

4.5 *Time on first-line treatment*

In the base case, the number of cycles of treatment is assumed identical to the mean number of cycles given in ECHELON-2 (i.e., 6,0 cycles for A+CHP and 5,8 cycles for CHOP; option 1). There are three additional options available as part of the scenario analysis (Table 1):

- The mean number of cycles received during ECHELON-2, capped at 6 cycles, meaning that patients that are given under 6 cycles in the trial are kept at their respective cycles, while patients that are above 6 cycles are reduced to only receiving 6 cycles in the model. The total average is therefore reduced compared to option 1 (option 2)
- All patients receive 6 cycles (option 3)
- All patients receive 8 cycles (option 4)

Table 1: Number of cycles per treatment arm: A+CHP=ADCETRIS and cyclophosphamide, doxorubicin, prednisone; CHOEP=cyclophosphamide, doxorubicin, vincristine, etoposide, prednisone; CHOP=cyclophosphamide, doxorubicin, vincristine, prednisone.

	A+CHP	CHOP	CHOEP
Option 1	5,99	5,84	5,84
Option 2	4,49	4,28	4,28
Option 3	6	6	6
Option 4	8	8	8

Reference: (4)

4.6 *Perspective*

The analysis is performed from the perspective of the Danish Regions and compares the drug acquisition cost, costs associated with adverse events as well as other relevant hospital costs. The indirect costs, such as transportation cost for the patient are not included in the budget impact analysis nor the cost analysis but are shown as individual analysis. No municipality costs have been identified as relevant for the purposes of this analysis.

5 5 MODEL INPUT

5.1 *Patients*

The total Danish population is derived from the Danish Statistics Population Projections (14). Patient numbers used in this analysis are derived from data from the Danish Lymphoma Database (DLD), and based on this data, the total Danish sALCL population is estimated to be 21 patients in 2021 (2). Further, it is estimated that 30 percent of sALCL patients will be ALK-positive, while 70 percent will be ALK-negative (2). The estimated number commensurate with the estimated number in the submission protocol of approximately 20 patients per year (10).

The rate of sALCL patients in Denmark is assumed to follow changes in the overall population, corresponding to an increase of 0,0218 % each year (14). Table 2 specifies the growth rate of sALCL patients and estimated number of A+CHP candidates used in the analysis.

Table 2: Epidemiological input. Overview of newly diagnosed patients per 100.000 from year 1 through 5, with an increase in the sALCL population of 0,0218 % each year, corresponding to the increase in the overall population in Denmark on a yearly basis.

Population	Year 1	Year 2	Year 3	Year 4	Year 5
sALCL	0,36	0,36	0,36	0,36	0,36
sALCL ALK+	0,11	0,11	0,11	0,11	0,11
sALCL ALK-	0,25	0,25	0,25	0,25	0,25

Reference: (2,14)

5.2 *Treatment mix and market shares*

5.2.1 sALCL population

The current distribution of patients receiving CHOP and CHOEP is assumed to be 40% receiving CHOP and 60% receiving CHOEP. The estimate of the distribution is based on expert opinions ([redacted]). As mentioned previously in this report, two scenarios are proposed in the model. The first scenario includes zero patients receiving A+CHP as a treatment for sALCL, and the market share for A+CHP is therefore set at 0%.

In the scenario where A+CHP is approved for the use in first-line treatment in Denmark, A+CHP is expected to gradually increase in market shares within the five-year time demarcation of the analysis. It is assumed that patients treated with A+CHP will increase with approximately 25 percentage points per year until the maximum of 100 percent is reached. Table 3 and table 4 list the estimated treatment mix with and without the presence of A+CHP, respectively.

Table 3: Treatment mix with A+CHP. A+CHP market share with A+CHP as a first-line indication.

Year	A+CHP	CHOP	CHOEP
Year 1	20%	25%	55%
Year 2	50%	10%	40%
Year 3	80%	0%	20%
Year 4	100%	0%	0%
Year 5	100%	0%	0%

Table 4: Treatment mix without A+CHP. It is assumed that A+CHP will have a 0 % market share in the situation where no reimbursement for SoC is given.

Year	A+CHP	CHOP	CHOEP
Year 1	0%	40%	60%
Year 2	0%	40%	60%
Year 3	0%	40%	60%
Year 4	0%	40%	60%
Year 5	0%	40%	60%

5.2.2 Treatment mix of clinical questions 1 and 2

In clinical question 1, only patients who are candidates for HDT and consolidate SCT should be included. However, in clinical practice, patients are not necessarily assessed candidates for SCT when first diagnosed

with sALCL. The decision to consolidate first-line treatment with SCT is based on the patient's response to the treatment (PR or CR). In the study by Ellin et al (2014) 32% of patients that up-front was intended for auto-SCT never received it, due to the patients not obtaining PR or CR (15). Therefore, to estimate the costs associated with clinical question 1, all patients who are candidates for CHOEP have been included in the treatment mix. The rationale for this grouping is, that patients that are treated with CHOEP are most likely to be candidates for consolidative SCT following the guidelines from the Danish Lymphoma Groups (DLG) recommendations for diagnostic and treatment of PTCL (1). The proportion of patients treated with CHOEP who receive consolidating SCT are based on input from clinical experts ([redacted]). It is assumed that the proportion receiving consolidative SCT in the A+CHP arm will be identical to those patients receiving SCT in the CHOEP arm. However, in a real-world setting, it is uncertain whether transplant rates will increase or decrease as a result of the addition of BV to CHP; more patients will achieve a CR which may increase the number of patients eligible for an SCT, conversely, the efficacy associated with BV may reduce the need for consolidation. As a precautionary measure, the proportions are identical for the two treatment arms. The treatment mix can be seen in the tables below. Table 5.1 shows the percentage split between the treatments, while table 5.2 presents the patient numbers.

Table 5.1: Treatment mix with A+CHP (%). Clinical question 1

Year	A+CHP	CHOP	CHOEP
Year 1	20%	0%	80%
Year 2	50%	0%	50%
Year 3	80%	0%	20%
Year 4	100%	0%	0%
Year 5	100%	0%	0%

Table 6.2: Treatment mix with A+CHP. Clinical question 1

Year	A+CHP	CHOP	CHOEP	Total
Year 1	3	0	10	13
Year 2	6	0	6	13
Year 3	10	0	3	13
Year 4	13	0	0	13
Year 5	13	0	0	13

To assess clinical question 2, only patients receiving CHOP are included in the treatment mix. The rationale is similar to the one for clinical question 1; that patients receiving CHOP are less likely to receive consolidate SCT based on guidelines from DLG (1). Further, only patients who are ALK-positive are included in the

analysis, as requested in the protocol for this submission. The treatment mix is shown in the tables below. Table 6.1 shows the percentage split between the treatments, while table 6.2 presents the patient numbers.

Table 7.1: Treatment mix with A+CHP (%). Clinical question 2

Year	A+CHP	CHOP	CHOEP
Year 1	20%	80%	0%
Year 2	50%	50%	0%
Year 3	80%	20%	0%
Year 4	100%	0%	0%
Year 5	100%	0%	0%

Table 8.2: Treatment mix with A+CHP. Clinical question 2

Year	A+CHP	CHOP	CHOEP	Total
Year 1	1	2	0	3
Year 2	1	1	0	3
Year 3	2	1	0	3
Year 4	3	0	0	3
Year 5	3	0	0	3

5.3 *Clinical data*

The principal source of clinical data was the sALCL subgroup of the ECHELON-2 study. Patient-level data were accessed to inform:

- extrapolation of OS and PFS outcomes
- average duration of treatment (cycles)
- AEs and their duration and frequency.

5.3.1 Proportional hazards

The assumption of proportional odds, used in the accelerated failure time (AFT) metric models (log-normal, log-logistic, etc) was assessed visually using quantile-quantile plots and are presented in appendix 14 and 15.

In the base case, all models were estimated using joint statistical models containing a single covariate representing the treatment arm – despite the potential violation of the proportional hazards assumption for PFS outcomes. This decision was justified on the basis that:

- **early testing suggested results were most sensitive to OS data, and there was no evidence that the proportional hazards assumption was violated for OS**

- extrapolations based on subgroups of data when using independent statistical models were associated with unrealistic long-term outcomes. This is in part because of the reduction in sample size when considering subgroups, and also a consequence of the need to extrapolate a relatively large proportion of the data.

The proportional hazards assumption was assessed using plots of the log-cumulative hazard.

For OS in the sALCL population (Figure 2), the plots are relatively parallel throughout. For PFS in the sALCL population (Figure 3), the plots are similarly relatively parallel throughout. On the basis of these results, a joint modelling approach was adopted, in which the effect of treatment is represented by a coefficient estimated on data from both arms of ECHELON-2.

Figure 2: Log-cumulative hazard - OS, sALCL

Abbreviations: A+CHP; brentuximab vedotin, cyclophosphamide, doxorubicin and prednisone; CHOP; cyclophosphamide, doxorubicin, prednisone and vincristine; OS, overall survival, ITT; intention-to-treat; IRF, independent review facility, trt; treatment.

Figure 3: Log-cumulative hazard - PFS, sALC

Abbreviations: A+CHP; brentuximab vedotin, cyclophosphamide, doxorubicin and prednisone; CHOP; cyclophosphamide, doxo-rubicin, prednisone and vincristine; OS, overall survival, ITT; intention-to-treat; IRF, independent review facility, trt; treatment.

5.3.2 Extrapolations used for the cost analysis

As the follow-up period for ECHELON-2 was shorter than the model time horizon, extrapolation from the observed OS and PFS data was required. Standard parametric curves were fitted to the PFS and OS data to extrapolate the outcomes observed in the ECHELON-2 trial and estimate the long-term outcomes:

- Exponential
- generalized gamma
- Gompertz
- log-normal
- log-logistic
- Weibull

Extrapolations based are presented in figure 2 and figure 3.

Figure 4: Standard parametric extrapolation of OS data

Figure 5: Standard parametric extrapolation of PFS data

The input variables of sex and age of the extrapolations were based on the median baseline characteristics of the ECHELON-2 trial (age: 58, female: 37%).

Model diagnostics are reported in the table below. For OS, generalised gamma and Gompertz models were associated with the lowest AIC and BIC scores, respectively. For PFS, the generalised gamma distribution was associated with the lowest AIC and BIC scores. In general, models that were able to capture

the decreasing hazard over time outperformed those, such as the exponential model, which are unable to capture this trend.

Table 9: model diagnostics, sALCL

	N	ll	df	AIC	BIC
OS					
Gen. gamma	316	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	316	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	316	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	316	[redacted]	[redacted]	[redacted]	[redacted]
Lognormal	316	[redacted]	[redacted]	[redacted]	[redacted]
Loglogistic	316	[redacted]	[redacted]	[redacted]	[redacted]
PFS					
Gen. gamma	316	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	316	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	316	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	316	[redacted]	[redacted]	[redacted]	[redacted]
Lognormal	316	[redacted]	[redacted]	[redacted]	[redacted]
Loglogistic	316	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; df, degrees of freedom ll, log-likelihood; OS, overall survival; PFS, progression free survival; sALCL, systemic anaplastic large cell lymphoma.

Extrapolations were presented at an international advisory board (no Danish experts were included in the advisory board) and they were asked to identify the most plausible extrapolations amongst standard parametric curves. Clinical opinion suggested that the generalised gamma distribution was most reflective of long-term outcomes for PFS and OS. The generalised gamma distribution was consequently used in the base-case for both outcomes, with alternative distributions considered in scenario analysis.

5.3.3 General population life tables

Age- and gender-specific probabilities of death were taken from published national life tables for Denmark, using data from 2019 (14). The model includes functionality enabling a multiplier to be applied to age- and gender-specific life tables. This reflects the fact that those in long-term remission following sALCL may be expected to experience increased mortality as compared with the age- and gender-matched general population, reflecting increased rates of secondary primary malignancies and cardiac toxicity. The mortality multiplier is set at 1.21 and is based on Takeda estimates. The multiplier is not applied in the base case analysis but can be included by selection. An estimate of 5% was selected – this does not reflect the midway point of the range but aligns with the specific overall mortality observed by clinicians who has been part of an English advisory board.

5.4 *Costs*

Drug prices are based on pharmacy purchase price excluding value-added tax (PPP ex. VAT) as presented in www.medicinpriser.dk for each product used within the analysis. If more than one supplier or dosage is present within the system, the least costly alternative is used.

For the budget impact modeling, the number of first-line cycles chosen in the model, and the uptake of patients treated with A+CHP each year is determining the accusation cost. After year one, each subsequent calendar year is discounted by 4 % in the cost analysis, as per the guidance from the Danish Ministry of Finance (16). During the first year of treatment, A+CHP is modelled as being available from January 2021, following a recommendation as SoC.

5.4.1 Drug acquisition costs

All drug costs and doses are based on the lowest prices available on www.medicinpriser.dk. Costs and dose calculations are shown in the 'Acquisition' tab in the excel model. No wastage is included within the model. The price of BV is modeled as an upfront cost of DKK [redacted] per vial. Each frontline regimen cost is calculated as the cost per course for the number of treatment cycles, adjusted for the respective market share. G-CFS, also described as a concomitant medication is applied to 100% of patients in all treatment arms of this report (and identically for CHOP and CHOEP) in the base case. The dosing regimes for the concomitant medication are collected from the NICE technology appraisal guidance (TA478), while the price is from www.medicinpriser.dk (17,18).

Table 10.1: Drug acquisition costs. The frontline acquisition costs are specific for the different treatment regimes, while the concomitant medication costs are equal independent of treatment regimes.

		A+CHP	CHOP	CHOEP
Frontline acquisition costs	Per cycle	[redacted]	[redacted]	[redacted]
	Per course	[redacted]	[redacted]	[redacted]
Concomitant medication costs	Per cycle	[redacted]	[redacted]	[redacted]
	Per course	[redacted]	[redacted]	[redacted]

Table 11.2: Concomitant acquisition costs. The concomitant medication costs are equal independent of treatment regimes.

	G-CSF		
	Filgrastim	Levofloxacin	Aciclovir
Dose (micrograms)	300	500	400
Microgram/pack	300	500	200
Pack size	5	30	100
Price/pack	2,693.65 kr.	100.00 kr.	44.50 kr.
Admins/cycle	7.00	7.00	14.00
Cost/cycle	3,771.11 kr.	23.33 kr.	12.46 kr.

5.4.2 Administration costs

Both A+CHP, CHOP, and CHOEP are administrated intravenously at the outclinic. Patients receiving BV require a single infusion on Day 1 of each cycle. Doxorubicin and cyclophosphamide are administered on the same day as BV in patients receiving A+CHP, and on the same day as vincristine/etoposide in patients receiving CHOP/CHOEP. As a result, cost of administration is applied once per cycle for all treatments. The CHOEP regime is set to have an additional cost shown as a subsequent administration cost. The reason for the subsequent treatment cost, which also appears in Table 12, is due to etoposide being administered on days 1-3 (three times in one cycle), therefore, resulting in the additional cost shown as subsequent administration cost. Prednisone is taken orally and does not incur an administration cost. Resource use frequencies are taken directly from the ECHELON-2 trial clinical study report and matched with monitoring costs based on the Danish DRG-2020 system(4,5).

Table 12: Administration costs. The table shows number of cycles per treatment and the administration cost of the first- and subsequent treatments. The CHOEP regime is shown to have an additional cost shown as a subsequent administration cost. This is due to etoposide being administered three times per cycle.

	A+CHP	CHOP	CHOEP
Number of cycles	5,99	5,84	5,84
Administration costs first treatment	[redacted]	[redacted]	[redacted]
Administration cost subsequent treatments	[redacted]	[redacted]	[redacted]
Total administration costs per cycle	[redacted]	[redacted]	[redacted]
Total administration costs per course	[redacted]	[redacted]	[redacted]

Reference: (4)

5.4.3 Salvage chemotherapies and radiotherapy costs

A proportion of patients are modelled to receive salvage chemotherapies and/or radiotherapy as a subsequent treatment after progression. The salvage chemotherapy regimens given to patients were taken from the European Society for Medical Oncology (ESMO) guidelines for PTCL, and the Danish Lymphoma Groups (DLG) recommendations for diagnostic and treatment of PTCL (1,3). In the BIM, the salvage chemotherapies and the radiotherapy were calculated from individual patient data from the ECHELON-2 trial. Information about dosing and pricing of the chemotherapies can be found in appendix 10.

In the ECHELON-2 trial, at least 6 cycles of study treatment were to be given prior to initiating post-treatment radiotherapy. In the cost analysis, the cost of radiotherapy treatment was assumed to be incurred at 6-months post-initiation of treatment with A+CHP or CHOP/CHOEP, meaning that all radiotherapy was assumed to occur at Cycle 9 in the model; median time to receipt of consolidative chemotherapy was 175 days (8.3 cycles) in the trial. To estimate the cost of salvage chemotherapies the accumulated cost of the regimes was applied to all newly progressed patients in each cycle of the cost analysis. Of the subjects who received post-progression therapies, subjects in the A+CHP and CHOP arms received on average 1.55 and 1.56 lines of non-BV containing post-progression therapy, respectively.

Table 13: Salvage- and radiotherapy costs. The table shows the percentage of patients receiving radiotherapy. The fractions are based on numbers from the ECHELON-2 trial.

Population	A+CHP	CHOP	CHOEP
sALCL	8,6%	2,6%	2,6%
sALCL ALK+	10,2%	0,0%	0,0%
sALCL ALK-	8,0%	3,8%	3,8%

Table 14: Salvage chemotherapy. The table shows the percentage of patients receiving salvage chemotherapy. The fractions are based on numbers from the ECHELON-2 trial.

Population	A+CHP	CHOP	CHOEP
sALCL	22%	36%	36%
sALCL ALK+	8%	36%	36%
sALCL ALK-	28%	36%	36%

5.4.4 Subsequent BV cost

BV was given as a subsequent therapy to 10% of the patients in the sALCL population of the A+CHP arm. These patients are considered to have been re-treated with BV. BV is recommended by Medicinrådet and used in clinical practice for patients with relapsed/refractory sALCL; therefore, the use of subsequent BV for these patients in the CHOP arm is included in terms of costs (23% in the sALCL population of the CHOP arm received subsequent BV). The per-cycle acquisition and administration costs are assumed identical to BV in front-line. Patients receive an average of 8.23 cycles of subsequent BV. In the BIM, the cost of subsequent BV is applied to the proportion of patients who received it in ECHELON-2 as a one-off cost. In the cost analysis, it is applied to per cycle.

Table 15: Subsequent BV. The table shows the percentage of patients receiving subsequent BV. The fractions are based on numbers from the ECHELON-2 trial.

Population	Subsequent BV		
	A+CHP	CHOP	CHOEP
sALCL	10%	23%	23%
sALCL ALK+	2%	12%	12%
sALCL ALK-	14%	29%	29%

5.4.5 Stem cell transplant cost

A proportion of patients are shown to receive stem cell transplantation (SCT), either as a consolidative treatment or as part of second-line treatment. The SCT input parameters have been included as part of the sensitivity analysis. The division of patients receiving SCT for CHOP or CHOEP, respectively, is based on verified inputs from clinical experts ([redacted]), while the proportions represented for A+CHP are based on assumptions from Takeda Pharma regarding the ALK-negative population and data inputs from the ECHELON-2 trial concerning the ALK-positive population. The split between patients receiving autologous stem cell transplantation and patients receiving allogeneic stem cell transplantation is based on data from the ECHELON-2 trial.

In the BIM, both the salvage SCT and consolidative SCT are attributed as a one-off cost. In the ECHELON-2 trial, at least 6 cycles of study treatment were to be given prior to initiating post-treatment consolidative SCT in the cost analysis. Consolidative SCT is therefore also attributed as a one-off cost in the cost analysis. As stated by the DLG, patients achieving a complete (CR) or partial response (PR) to salvage therapy would be considered for transplant. Subsequent SCTs are therefore included as a component of the costs of progressive disease in the cost analysis and attributed per cycle.

Further, all patients receiving SCT also receives HDT in the form of the BEAM regime. The dosing and cycle numbers are based on recommendations from Danish Hematological society (19). The cost are based on www.medicinpriser.dk. The dosing and cost of the BEAM regime are listed below.

Table 16: Stem cell transplant cost. The table shows the percentage of patients receiving SCT as a consolidative treatment.

Population	Proportion of consolidative SCT		
	A+CHP	CHOP	CHOEP
sALCL	48%	14%	43%
sALCL ALK+	8%	0%	0%
sALCL ALK-	60%	17%	60%

Reference: (4)

Table 17: Stem cell transplant cost. The table shows the percentage of patients receiving SCT as part of second-line treatment.

Population	Proportion of 2L SCT			% 2L SCT auto vs allo
	BV+CHP	CHOP	CHOEP	
sALCL	7%	10%	10%	62,96%
sALCL ALK+	4%	10%	10%	57,14%
sALCL ALK-	8%	21%	21%	65,00%

Reference: (4)

Table 18: BEAM regime costs

Drug	Mg/m^2	Product size (mg)	Number of cycles	Price/Pack	Cost per regime
Carmustine	300	100	1	6.995 kr.	39.346,52 kr.
Etopodside	200	50	1	1.690 kr.	12.674,89 kr.
Cytosar	200	100	2	150 kr.	1.124,99 kr.
Melphalan	140	50	1	4.500 kr.	23.624,79 kr.

Reference: (19)

5.4.6 Adverse events costs

All grade 3/4 treatment-emergent AEs observed in ECHELON-2 due to treatment with A+CHP or CHOP were modeled at the rates reported in the ECHELON-2 trial (4). Total AE duration in the sALCL population amounts to 24.7 days in the A+CHP arm and 20.77 days in the CHOP arm. AE numbers were assessed during the safety period of ECHELON-2, from Day 1 through to the end of treatment visit or 30-days after the last study treatment, whichever was later. As patients are no longer on treatment after this point, AEs have not been extrapolated beyond the safety period and all costs associated with AEs are assumed to occur in the first cycle of the cost analysis and budget impact model.

No RCTs are investigating the efficacy or safety of CHOEP. However, according to S. Deng et al. the addition of etoposide to the CHOP regime is associated with an increase in the toxicity and side effects experienced by patients (20). Still, due to uncertainty and lack of available data, the efficacy of CHOEP is set equal to CHOP in the base-case. Alternative assumptions are tested in the scenario analysis. All AE costs are calculated using Danish DRG-2020 codes (5).

Table 19: TEAEs grade ≥ 3 for A+CHP. The table is modified from the A+CHP and CHOP rates observed in the ECHELON-2 trial. The table represents grade ⩾ 3 TEAEs.

Adverse event	Average number of events per patient			Cost per AE	DRG2020
	A+CHP	CHOP	CHOEP		
Anaemia	0,20	0,19	0,19	4.732 kr.	16PR02
Febrile neutropenia	0,20	0,16	0,16	58.620 kr.	01MA03
Leukopenia	0,09	0,21	0,21	6.114 kr.	16PR01
Pneumonia	0,04	0,03	0,03	37.050 kr.	04MA13
Thrombocytopenia	0,07	0,06	0,06	37.603 kr.	16MA03

Reference: (4,5)

5.4.7 Monitoring costs

Monitoring costs primarily refer to routine consultations and clinical tests. The number of units during treatment is based on the guideline from DLG (1). However, a precautionary principle has been used when estimating the number of units attributed per patient, meaning that the highest expected usage is used as input for the respective procedures. The unit cost is based on the Danish DRG2020 catalog and can be seen in Table 20 together with the procedures and the number of units during treatment for each of the three treatment arms (5).

In the cost analysis, the monitoring cost was calculated as a single cost during treatment (applied as an up-front cost), and an additional cost in the first- to fifth-year post-treatment after either of the A+CHP or CHOP-like regimes. The cost was applied based on the extrapolated data and only to patients who were progression-free. The frequency of follow-up was assumed identical to that reported in the Danish lymphoma group recommendations regarding treatment of PTCL (Patients are followed up quarterly **for the**

first two years. After the first two years, tests are preformed bi-yearly until the five-year mark (1))[2]. The full blood count, clinical biochemistry test, and urea and electrolytes tests are all assumed to fall under the same DRG-code and it is assumed they are all done simultaneously, the DRG-code is therefore only attributed once.

Table 20: Monitoring costs. The table lists the primary activities driving monitoring costs.

	Unit cost	Number of units during treatment			DRG2020
Procedure		A+CHP	CHOP	CHOEP	
CT scan	2,032 kr.	2	2	2	30PR06
PET scan (3+ areas)	2,470 kr.	2	2	2	36PR07
Consultation	1,512 kr.	11	11	11	23MA04
Full blood count/clinical biochemistry/urea and electrolytes	28,271 kr.	6	6	6	17MA03
Bone marrow biopsy	14.935 kr.	3	3	3	17PR01
Liver function test	28,271 kr.	6	6	6	17MA03

Reference: (5)

[2] There is scars documentation of how often to preform clinical tests and imaging control after completion of primary treatment with PTCL. Clinical tests are preformed quarterly for the first two years. After the first two years, tests are preformed bi-yearly until the five-year mark (1). It is assumed that follow-up ceases after year five in the model.

5.4.8 Indirect costs

The average time a patient spends at hospital during first line treatment of sALCL is based on number of treatment cycles chosen in the model. Each visit is attributed transportation time to and from hospital, waiting time at the clinic, and time of administration. The total time consumption is multiplied with the unit costs defined by the Medicine Council (21).

Transportation time and patient time per cycle is assumed to be 3.5 hours for patients in the A+CHP and CHOP arm, including buffer time to find a parking spot, etc. For patients in the CHOEP arm, the total time consumption per cycle is estimated to be 7 hours due to the extra time spend receiving etoposide (22). According to the Medicine Council, patient transportation cost is estimated to be 100 kr. per hospital visit (includes the hospital visit itself) (21). Table 21 lists the indirect costs used within the model. None of the costs mapped out in this section of the document are included in the budget impact analysis. However, they are included in the cost analysis.

Table 21: Indirect costs. The tables list the time consumption related to patient time, including unit costs as defined by Amgros

	A+CHP	CHOP	CHOEP
Number of cycles	5.99	5.84	5.84
Transportation time 2W (hours)	1.00	1.00	1.00
Waiting time at hospital	0.50	0.50	0.50
Administration time (hours)	2.00	2.00	2.00
Time consumption (per visit)	3.50	3.50	3.50
Time consumption (per cycle)	3.50	3.50	7.00
Time consumption (all visits)	20.97	20.43	40.85
Patient salary per hour	179 kr.	179 kr.	179 kr.
Indirect costs (per cycle)	627 kr.	627 kr.	1,253 kr.
Indirect costs (time)	3,753 kr.	3,656 kr.	7,313 kr.
Travel reimbursement (per visit)	100 kr.	100 kr.	100 kr.
Travel reimbursement (all visits)	599 kr.	584 kr.	1,167 kr.

Reference: (21)

Patients who receives second line chemotherapy are also attributed a transportation- and patient cost. It is assumed that patients spend 3.5 hours per cycle of second line chemotherapy as transportation- and patient time, independent of the chemo-regime administered. The costs and distributions can be seen in Table 22.

Table 22: Indirect costs. The table shows the transportation- and patient time used when receiving second line chemotherapy

	2L chemo. After A+CHP	2L chemo. After CHOP	2L chemo. After CHOEP
Transportation time 2W (hours)	1.00	1.00	1.00

Waiting time at hospital	0.50	0.50	0.50
Administration time (hours)	2.00	2.00	2.00
Time consumption (per visit)	3.50	3.50	3.50
Patient salary per hour	179 kr.	179 kr.	179 kr.
Indirect costs (per cycle)	627 kr.	627 kr.	627 kr.
Travel reimbursement (per visit)	100 kr.	100 kr.	100 kr.

6 RESULTS

The result section is split into the budget impact analysis showing the impact of the two scenarios; 1) where A+CHP is not recommended as SoC for first-line treatment, and 2) where A+CHP is recommended as SoC first-line treatment, and the cost analysis presenting the estimated lifetime cost per patient in each treatment arm. Finally, the sensitivity analysis is presented, firstly as a univariate analysis, and secondly as scenario analysis. The results are as mentioned in the method section of this document divided into the two clinical questions proposed by the Danish Medicines council.

6.1 Budget impact

6.1.1 Scenarios of treatment with and without A+CHP

The following section covers the results of the budget impact estimates when considering two scenarios for the frontline sALCL indication; the potential costs of patients treated with A+CHP if A+CHP is recommended as SoC versus the potential costs of CHOP/CHOEP if A+CHP is not recommended as SoC. The scenarios are presented based on clinical questions 1 and 2. For the comparison, all costs described in the cost section of this report, are compared over 5 years.

6.1.1.1 Clinical question 1

To estimate the budget impact of clinical question 1, appendix 1 considers the scenario in which only patients who are candidates for CHOEP are included and in which A+CHP is not recommended as SoC for the EMA-approved indication. As shown in appendix 1, the total budget for the population converts to [redacted]

Appendix 2 considers the scenario in which A+CHP is recommended as SoC for the EMA-approved indication for patients who receive SCT. As shown in appendix 2, especially acquisition costs, medical resource use, and consolidative SCT costs represent a substantial part of the total cumulative budget. The total budget for the population converts to [redacted] kr. over 5 years. The costs are based on the base case scenario, where the number of treatment cycles selected is the mean number of cycles from the ECHELON-2 trial.

Appendix 3 presents the incremental budget impact for years 1-5 in the case of a recommendation as SoC for A+CHP. As already indicated, acquisition costs drive the majority of the cost increase of the budget impact. However, administration costs and second-line acquisition costs impact the budget as a decreasing factor. The total incremental budget impact for the population converts to [redacted] kr. The costs are based on the base case scenario, where the number of treatment cycles selected is the mean number of cycles from the ECHELON-2 trial.

6.1.1.2 Clinical question 2

To estimate the budget impact of clinical question 2, appendix 4 considers the scenario in which only patients who are candidates for CHOP and who are ALK-positive are included. Appendix 4 considers a scenario in which A+CHP is not recommended as SoC for the EMA-approved indication. As shown in appendix 4, the total budget for the population converts to [redacted] kr. over 5 years. As seen in the appendix, consolidative SCT cost have been excluded for the budget. The costs are based on the base case scenario, where the number of treatment cycles selected is the mean number of cycles from the ECHELON-2 trial.

Appendix 5 considers the scenario in which A+CHP is recommended as SoC for the EMA-approved indication for patients who are not candidates for SCT. The total budget for the population converts to [redacted] kr. The costs are based on the base case scenario, where the number of treatment cycles selected is the mean number of cycles from the ECHELON-2 trial.

Appendix 6 presents the incremental budget impact for years 1-5 in the case of a recommendation as SoC for A+CHP. The total incremental budget impact for the population converts to [redacted] kr. The costs are based on the base case scenario, where the number of treatment cycles selected is the mean number of cycles from the ECHELON-2 trial.

6.1.1.3 Total sALCL population

Appendix 7 considers the scenario in which all patients in the sALCL population is included. Appendix 7 considers a scenario in which A+CHP is not recommended as SoC for the EMA-approved indication. The total budget for the population converts to [redacted] kr. over 5 years. The costs are based on the base case scenario, where the number of treatment cycles selected is the mean number of cycles from the ECHELON-2 trial.

Appendix 8 considers the scenario in which A+CHP is recommended as SoC for the EMA-approved indication for patients who are not candidates for SCT. The total budget for the population converts to [redacted] kr. The costs are based on the base case scenario, where the number of treatment cycles selected is the mean number of cycles from the ECHELON-2 trial.

Appendix 9 presents the incremental budget impact for years 1-5 in the case of a recommendation as SoC for A+CHP. The total incremental budget impact for the population converts to [redacted] kr. The costs are based on the base case scenario, where the number of treatment cycles selected is the mean number of cycles from the ECHELON-2 trial.

6.2 *Cost analysis*

6.2.1 Incremental cost per patient

6.2.1.1 Clinical question 1

Table 23 shows the cost per patient based on the extrapolated data from the ECHELON-2 trial comparing A+CHP with CHOEP. The Gamma distribution is selected as the base case distribution. As shown in the table, the majority of the costs associated with the treatments fall within year one. The reason why the majority of the costs fall within year one is, that first line acquisition costs, administration costs, consolidative SCT- and radiotherapy costs, and adverse event costs all are charged within year one. Only monitoring costs, second-line chemotherapies, and salvage SCT are attributed after year one. The table shows that the cost per patient treated in the A+CHP arm accumulates to [redacted] kr. in year 1, and [redacted] kr. over a lifetime period. The cost per patient treated in the CHOEP arm accumulates to [redacted] kr. in year 1, and [redacted] kr. over a lifetime period. The difference in cost accumulates to [redacted] kr. The differentiated costs can be found in appendix 11.

Table 23: Clinical question 1

	Year 1	Remaining years	Total (30 years)	Difference
A+CHP	[redacted]	[redacted]	[redacted]	[redacted]
CHOEP	[redacted]	[redacted]	[redacted]	[redacted]

6.2.1.2 Clinical question 2

Table 24 shows the cost per patient based on the extrapolated data from the ECHELON-2 trial comparing CHOP til A+CHP, and where consolidative SCT costs have been excluded from the analysis. However, the extrapolation is based on the entire sALCL population and not only ALK-positive patients. It has not been possible to perform the extrapolation based ALK-status due to lack of data. The gamma distribution has been selected as the base case option. The table shows that the cost per patient treated in the A+CHP arm accumulates to [redacted] kr. in year 1, and [redacted] kr. over a lifetime period. The cost per patient treated in the CHOP arm accumulates to [redacted] kr. in year 1, and [redacted] kr. over a lifetime period. The difference in cost accumulates to [redacted] kr. The differentiated costs can be found in appendix 12.

Table 24: Clinical question 2

	Year 1	Remaining years	Total (30 years)	Difference
A+CHP	[redacted]	[redacted]	[redacted]	[redacted]
CHOP	[redacted]	[redacted]	[redacted]	[redacted]

6.2.1.3 Total sALCL population

Table 25 shows the outcome of the cost analysis if the entire sALCL population is included and consolidative treatment with SCT hasn't been excluded from the analysis. The differentiated costs can be found in appendix 13.

Table 25: sALCL population

	Year 1	Remaining years	Total (30 years)	Difference
A+CHP	[redacted]	[redacted]	[redacted]	[redacted]
CHOP	[redacted]	[redacted]	[redacted]	[redacted]
CHOEP	[redacted]	[redacted]	[redacted]	[redacted]

6.3 *Sensitivity analysis*

This section focuses on a simple evaluation of the impact changes in the most influential input parameters. Sensitivity analysis has been conducted for both the budget impact analysis and the cost analysis.

6.3.1 Univariate sensitivity analysis

Results for the most influential parameters identified by univariate sensitivity analysis are presented in table 26 for the budget impact analysis. The first row shows the base-case value, while the rows below show the input parameters at lower and upper values.

Table 26: Univariate sensitivity analysis. The table lists the lower and upper value of parameters impacting the budget

Parameter	Budget impact at lower value of parameter	Budget impact at upper value of parameter
Base case	[redacted]	
BV price per vial		
sALCL incidence		
Proportion of consolidative SCT - A+CHP		
Proportion of consolidative SCT - CHOEP		
Proportion of patients recieving subsequent A+CHP - CHOEP		
Proportion of patients recieving subsequent A+CHP - A+CHP		
Cost of SCT		
Subsquent BV cycles		

Figure 6: Univariate sensitivity analysis. The figure graphically illustrates the lower and upper value of parameters impacting the budget.

The total budget impact estimate is most sensitive to BV price per vial. The base case parameter input of [redacted] kr. has been varied by the arbitrary range of +/- 15%, resulting in the difference in budget impact as shown in the table. Another influential input parameter is the proportion of patients receiving

subsequent A+CHP. In the base case, 10% of the patients who are treated with first-line A+CHP also receive A+CHP as subsequent treatment. In the sensitivity analysis, the input parameters are set as 5% for the lower value and 15% for the upper value. For patients who are treated with CHOP/CHOEP as first-line treatment, the patients who receive A+CHP as a subsequent treatment are placed at 23% in the base case and varied from 18-28% for the lower and upper values, respectively. The intervals for both the A+CHP and CHOP/CHOEP arm are based on Takeda base case estimates and each value is varied by five percentage points. The proportion of patients receiving consolidative SCT also imposes a significant budget impact. In the base case, 48% of the patients treated with A+CHP receive consolidative SCT, and for the analysis, the input parameter has been varied with 38-58%. For the patients treated with CHOEP, 43% receive SCT in the base case scenario, while the parameter is varied by 33-53% in the univariate analysis. The ranges for both A+CHP and CHOEP vary by ten percentage points and are arbitrarily selected.

For the final input parameters; sALCL incidence, number of cycles given to patients receiving subsequent A+CHP, and cost of SCT, the upper and lower alternatives are simple +/- 15 % changes from the base case values. Table **26: Univariate sensitivity analysis. The table lists the lower and upper value of parameters impacting the budget** 26 lists the different input parameters and their impact on the incremental difference in the budget. The same data is graphically illustrated in Figure 6.

Table 27 and Table 28 shows the impact of adjusting four of the cost parameters for the cost analysis. The adjusted parameters are listed in the tables below. All inputs have been altered by +/- 30% to show their impact on the incremental results. Table 27 shows the results of comparing A+CHP to CHOEP, while table 28 shows the results of comparing A+CHP to CHOP.

Table 27: Univariate sensitivity analysis. The table list the upper and lower value of the parameters impacting the cost analysis of A+CHP vs. CHOEP

CHOEP	Budget impact at lower value of parameter	Budget impact at upper value of parameter
Medical ressource use - CHOEP		
Medical ressource use - A+CHP		
Accusition cost - A+CHP		
Administraion cost - CHOEP		
Administraion cost - A+CHP		
Consolidative SCT - A+CHP		
Consolidative SCT - CHOEP		
Accusition cost - CHOEP		

Table 28: Univariate sensitivity analysis. The table list the upper and lower value of the parameters impacting the cost analysis of A+CHP vs. CHOP

CHOP	Budget impact at lower value of parameter	Budget impact at upper value of parameter
Medical ressource use - CHOP		
Medical ressource use - A+CHP		

Accusition cost - A+CHP		[redacted]			[redacted]	
Administraion cost - CHOP						
Administraion cost - A+CHP						
Consolidative SCT - A+CHP						
Consolidative SCT - CHOP						
Accusition cost - CHOP						

Figure 7 and Figure 8 below graphically presents the output of table 27 and 28. Figure 7 shows the incremental difference for A+CHP versus CHOEP, while figure 8 shows the incremental difference between A+CHP and CHOP.

Figure 7: Univariate sensitivity analysis. The figure graphically illustrates the lower and upper value of parameters impacting the incremental difference between A+CHP and CHOEP

[redacted]

Figure 8: Univariate sensitivity analysis. The figure graphically illustrates the lower and upper value of parameters impacting the incremental difference between A+CHP and CHOP

[redacted]

6.3.2 Scenario analysis

Three different scenarios are presented in table 29 for the budget impact analysis. Different extremes have been chosen for selected input parameters, showing how the budget impact will change from the base case scenario. The first scenario illustrates that excluding infusion of subsequent BV treatment has a

correspondingly large decrease in the cumulative net budget impact, as expected (-2.96%). The second scenario shows, that if all sALCL patients treated with frontline A+CHP receive SCT, it results in a 67.81% change from the base case budget impact. Finally, the third scenario shows that if the adverse event profile for CHOEP is identical to the average number of adverse events per patient in the A+CHP arm, a -0.59% change from the base-case budget impact will occur.

Table 29: Scenario analysis. The table lists the base case and three potential scenarios impacting the budget

	Budget impact	% change from base-case budget impact
Base-case	[redacted]	[redacted]
Exclusion of subsequent BV treatment	[redacted]	[redacted]
All ALCL patients treated with L1 A+CHP recieves SCT	[redacted]	[redacted]
CHOEP patients with same AE profile as A+CHP	[redacted]	[redacted]

Table 30 shows two potential scenarios and their impact on the cost analysis between A+CHP and CHOEP. Exclusion of subsequent BV treatment is shown to result in the biggest impact of the cost analysis, while the second scenario only shows minor impact on the cost analysis.

Table 30: Scenario analysis. The table lists the base case and two potential scenarios impacting the cost analysis of A+CHP versus CHOEP

	Incremental difference	% change from base-case cost analysis
Base-case	[redacted]	[redacted]
Exclusion of subsequent BV treatment	[redacted]	[redacted]
CHOEP patients with same AE profile as A+CHP	[redacted]	[redacted]

7 DISCUSSION

7.1 General overview

The cohort-based BIM presented in this report assesses the financial impact of introducing A+CHP as an additional intervention in the treatment of adult patients previously untreated for sALCL, compared to the current SoC represented by CHOP and CHOEP. The model compares the total budget impact in the Danish Regions via two scenarios; one in which A+CHP receives a recommendation as SoC versus one in which A+CHP does not receive the recommendation as SoC.

7.2 Structure

The structure of the BIM allows for the assessment of annual cohorts of patients who are considered eligible for treatment with A+CHP. A+CHP is expected to replace current SoC by year 4 and has been modeled as such, in the BIM.

Overall, the economic evaluation is a limited societal cost analysis focusing on relevant costs associated with drug acquisition, hospital care, adverse event costs, and indirect costs. The results of the model are driven largely by increased acquisition costs associated with BV, however, the analysis also estimated substantial cost savings associated with reduced administration costs both first- and second-line. Further, results were most sensitive to the parameters which determined the size of the eligible population, the price of an Adcetris vial, and the proportion of patients receiving subsequent A+CHP. The principal determinant of a budget impact remains estimates of market share assumed; these assumptions about the future use of A+CHP in clinical practice are uncertain. A conservative approach to the modeling was preferred throughout the model development, to avoid an underestimation of the costs incurred by a recommendation of A+CHP as SoC.

For the cost analysis, a PartSAs approach was taken. PartSAs are often used because the endpoints and survival curves reported (e.g. PFS and OS) can be directly used to model state membership. The main limitation of this approach is the lack of dependence between endpoints, reducing the validity of extrapolations and sensitivity analyses. For instance, adjusting the PFS curve has no effect on OS, which is biologically implausible. Statistical analyses that requires extrapolation beyond follow-up remains a fundamental source of uncertainty; however, the analysis and extrapolation were based on a relatively large dataset, allowing sufficient patient numbers to perform economically analyses in on the sALCL population. The PartSA approach was selected for consistency with other BV indications and ease of interpretation.

7.3 Data

The model is based on publicly available material and published articles as well as the product EPARs available through the EMA. To support the understanding of how the published data translates into clinical reality, expert opinions were used to understand the real-world clinical impact of the data. Specifically, expert opinions were used to assess market share and the quantities used as input parameters for stem cell transplantation ([redacted]).

The main strengths of the analysis are derived from the robustness of the ECHELON-2 trial, which was used to estimate key clinical parameters in the analysis. ECHELON-2 provides data for 452 subjects with a median follow-up of 36.2 months and compares A+CHP with one of the two current standards of care regimes, CHOP. As such, analyses are based on a relatively large dataset, allowing sufficient patient numbers to perform economically relevant subgroup analyses. However, all models are a simplification of the real treatment process. The model estimates resource use and costs for an average patient and does not consider other factors such as disease severity, patient characteristics, or other prognostic factors.

Finally, as there is no head-to-head study comparing CHOEP to A+CHP, the comparison becomes indirect based on assumptions about equality between CHOP and CHOEP. Safety data and time on treatment data are therefore equal for the two CHOP-like regimes in the base-case scenario. The overall level of robustness of data decreases as a consequence. However, a complex model increases the scope of the analysis but also risk introducing uncertainties.

8 CONCLUSION

8.1 Clinical question 1

The total eligible patient population for clinical question 1 for the A+CHP treatment arm over a five-year time horizon is 44 patients based on the assumed market share of the model, leaving 19 to be treated in the CHOEP arm. By year 4 the model expects that all patients will be treated with A+CHP. The total budget impact is estimated to be [redacted] kr. over 5-years. These costs are associated with a treatment time of 5.99 cycles equivalent to the mean number of cycles from the ECHELON-2 trial. For the cost analysis, the A+CHP treatment had an estimated lifetime cost per patient of [redacted] kr., while the CHOEP arm had a lifetime cost per patient of [redacted] kr. The incremental difference between the treatments was [redacted] kr.

8.2 Clinical question 2

The total eligible patient population for clinical question 2 for the A+CHP treatment arm over a five-year time horizon is 9 patients based on the assumed market share of the model, leaving 4 to be treated in the CHOP arm. By year 4 the model expects that all patients will be treated with A+CHP. The total budget impact is estimated to be [redacted] kr. over 5-years. These costs are associated with a treatment time of 5.99 cycles equivalent to the mean number of cycles from the ECHELON-2 trial. For the cost analysis, the A+CHP treatment had an estimated lifetime cost per patient of [redacted] kr., while the CHOP arm had a lifetime cost per patient of [redacted] kr. The incremental difference between the treatments was [redacted] kr.

8.3 sALCL population

The total eligible patient population for the sALCL population for the A+CHP treatment arm over a five-year time horizon is 74 patients based on the assumed market share of the model, leaving 31 patients to be treated either CHOP or CHOEP. By year 4 the model expects that all patients will be treated with A+CHP. The total budget impact is estimated to be [redacted] kr. over 5-years. These costs are associated with a treatment time of 5.99 cycles equivalent to the mean number of cycles from the ECHELON-2 trial. For the cost analysis, the A+CHP treatment had an estimated lifetime cost per patient of [redacted] kr., while the CHOP and CHOEP arm had a lifetime cost per patient of [redacted] kr. and [redacted] kr., respectively. The incremental difference between the treatments was [redacted] kr. and [redacted] kr., respectively.

1. om PTCL A. 2017 Dansk Lymfomgruppe Arbejdsgruppe om PTCL PERIFERE T-CELLE LYMFOMER (PTCL) [Internet]. [cited 2020 Aug 28]. Available from: www.lymphoma.dk

2. Dansk Lymfom Database [Internet]. [cited 2020 Sep 1]. Available from: https://www.danishhealthdata.dk/find-sundhedsdata/Dansk-Lymfom-Database

3. D'amore F, Gaulard P, Trümper L, Corradini P, Kim W-S, Specht L, et al. Peripheral T-cell lymphomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up †. 2015;

4. Horwitz S, O'Connor OA, Pro B, Illidge T, Fanale M, Advani R, et al. Brentuximab vedotin with chemotherapy for CD30-positive peripheral T-cell lymphoma (ECHELON-2): a global, double-blind, randomised, phase 3 trial. Lancet [Internet]. 2019 Jan 19 [cited 2020 Aug 27];393(10168):229–40. Available from: http://www.thelancet.com/article/S0140673618329842/fulltext

5. DRG-takster 2020 - Sundhedsdatastyrelsen [Internet]. [cited 2020 Aug 27]. Available from: https://sundhedsdatastyrelsen.dk/da/afregning-og-finansiering/takster-drg/takster-2020

6. EMA Recommends Extension of Indications for Brentuximab Vedotin [Internet]. [cited 2020 Aug 28]. Available from: https://www.esmo.org/oncology-news/ema-recommends-extension-of-indications-for-brentuximab-vedotin3

7. EU/3/08/596 | European Medicines Agency [Internet]. [cited 2020 Aug 28]. Available from: https://www.ema.europa.eu/en/medicines/human/orphan-designations/eu308596

8. Brentuximab vedotin (Adcetris) [Internet]. [cited 2020 Aug 28]. Available from: https://medicinraadet.dk/igangvaerende-vurderinger/laegemidler-og-indikationsudvidelser/brentuximab-vedotin-adcetris-voksne-cd30-positive-ptcl-patienter

9. Produktvisning - www.medicinpriser.dk [Internet]. [cited 2020 Aug 28]. Available from: https://medicinpriser.dk/Default.aspx?id=15&vnr=132488

10. Medicinrådets protokol for vurdering af brentuximab vedotin i kombination med doxorubicin og prednisolon til behandling af tidligere ubehandlet systemisk anaplastisk storcellet T- cellelymfom. :0–17.

11. CHMP. ANNEX I SUMMARY OF PRODUCT CHARACTERISTICS.

12. HIGHLIGHTS OF PRESCRIBING INFORMATION [Internet]. 2018 [cited 2020 Aug 27]. Available from: www.fda.gov/Safety/MedWatch.

13. Wöhrer S, Chott A, Drach J, Püspök A, Hejna M, Hoffmann M, et al. Chemotherapy with cyclophosphamide, doxorubicin, etoposide, vincristine and prednisone (CHOEP) is not effective in patients with enteropathy-type intestinal T-cell lymphoma. Ann Oncol [Internet]. 2004 Nov [cited 2020 Aug 27];15(11):1680–3. Available from: https://pubmed.ncbi.nlm.nih.gov/15520071/

14. Danmarks Statistik [Internet]. [cited 2020 Aug 27]. Available from: https://www.dst.dk/da/

15. Ellin F, Landström J, Jerkeman M, Relander T. Real-world data on prognostic factors and treatment in peripheral T-cell lymphomas: A study from the Swedish Lymphoma Registry. Blood [Internet]. 2014 Sep 4 [cited 2020 Sep 15];124(10):1570–7. Available from: https://ashpublications.org/blood/article-pdf/124/10/1570/1379431/1570.pdf

16. Vejledning i samfundsøkono- miske konsekvens- vurderinger. 2017.

17. Technology appraisal guidance: Brentuximab vedotin for treating relapsed or refractory systemic anaplastic large cell lymphoma [Internet]. 2019 [cited 2020 Oct 13]. Available from: https://www.nice.org.uk/terms-and-

18. Forside - www.medicinpriser.dk [Internet]. [cited 2020 Oct 5]. Available from:

https://medicinpriser.dk/default.aspx

19. Rekommandationer for stamcellemobilisering/høst og højdosis kemoterapi med autolog stamcelletransplantation hos voksne Udarbejdet af udvalg under Dansk Haematologisk Selskab 2018.

20. Deng S, Lin S, Shen J, Zeng Y. Comparison of CHOP vs CHOPE for treatment of peripheral T-cell lymphoma: A meta-analysis. Onco Targets Ther [Internet]. 2019 [cited 2020 Aug 27];12:2335–42. Available from: /pmc/articles/PMC6445243/?report=abstract

21. Medicinrådet. Vaerdisaetning af enhedsomkostninger [Internet]. [cited 2020 Aug 28]. Available from: www.medicinraadet.dk

22. Undersøgelser og behandlinger i Hæmatologisk Ambulatorium [Internet]. [cited 2020 Nov 24]. Available from: https://aalborguh.rn.dk/afsnit-og-ambulatorier/haematologisk-afdeling/afsnit/haematologisk-ambulatorium/undersoegelser-og-behandlinger

23. Zelenetz AD, Hamlin P, Kewalramani T, Yahalom J, Nimer S, Moskowitz CH. Ifosfamide, carboplatin, etoposide (ICE)-based second-line chemotherapy for the management of relapsed and refractory aggressive non-Hodgkin's lymphoma. Ann Oncol. 2003;14(SUPPL. 1):5–10.

24. Velasquez WS, Cabanillas F, Salvador P, McLaughlin P, Fridrik M, Tucker S, et al. Effective salvagae therapy for lymphoma with cisplatin in combination with high-dose ara-C and dexamethasone (DHAP). Blood. 1988;71(1):117–22.

25. Dong M, He XH, Liu P, Qin Y, Yang JL, Zhou SY, et al. Gemcitabine-based combination regimen in patients with peripheral T-cell lymphoma. Med Oncol [Internet]. 2013 Mar [cited 2020 Oct 13];30(1). Available from: https://pubmed.ncbi.nlm.nih.gov/23269584/

26. Velasquez WS, McLaughlin P, Tucker S, Hagemeister FB, Swan F, Rodriguez MA, et al. ESHAP - An effective chemotherapy regimen in refractory and relapsing lymphoma: A 4-year follow-up study. J Clin Oncol [Internet]. 1994 [cited 2020 Oct 13];12(6):1169–76. Available from: https://pubmed.ncbi.nlm.nih.gov/8201379/

9 Appendix

Appendix 1: Budget impact. The table shows the estimated total budget impact over 5 years in a scenario without A+CHP for clinical question 1.

Frontline	Year 1	Year 2	Year 3	Year 4	Year 5	Total
A+CHP						
Acqusition cost						
Administration cost						
Medical ressource use						
AE cost						
Consolidative SCT						
2L BV						
2L Chemotherapy						
Consolidative radiotherapy						
Non-consolidative SCT						
CHOP						
Acqusition cost						
Administration cost						
Medical ressource use						
AE cost						
Consolidative SCT						
2L BV						
2L Chemotherapy						
Consolidative radiotherapy						
Non-consolidative SCT						
CHOEP						
Acqusition cost						
Administration cost						
Medical ressource use						
AE cost						

Consolidative SCT		[redacted]			[redacted]			[redacted]			[redacted]			[redacted]			[redacted]	
2L BV		[redacted]			[redacted]			[redacted]			[redacted]			[redacted]			[redacted]	
2L Chemotherapy		[redacted]			[redacted]			[redacted]			[redacted]			[redacted]			[redacted]	
Consolidative radiotherapy		[redacted]			[redacted]			[redacted]			[redacted]			[redacted]			[redacted]	
Non-consolidative SCT		[redacted]			[redacted]			[redacted]			[redacted]			[redacted]			[redacted]	
Total		[redacted]			[redacted]			[redacted]			[redacted]			[redacted]			[redacted]	

Appendix 2: Budget impact. The table lists the estimated total budget impact over 5 years in a scenario with A+CHP for clinical question 1.

Frontline	Year 1	Year 2	Year 3	Year 4	Year 5	Total
A+CHP total						
Acqusition cost						
Administration cost						
Medical ressource use						
AE cost						
Consolidative SCT						
2L BV						
2L Chemotherapy						
Consolidative radiotherapy						
Non-consolidative SCT						
CHOP total						
Acqusition cost						
Administration cost						
Medical ressource use						
AE cost						
Consolidative SCT						
2L BV						
2L Chemotherapy						
Consolidative radiotherapy						
Non-consolidative SCT						
CHOEP total						
Acqusition cost						
Administration cost						

Medical ressource use	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AE cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Consolidative SCT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2L BV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2L Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Consolidative radiotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-consolidative SCT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Appendix 3: Budget Impact. The table lists the estimated incremental budget impact over 5 years for clinical question 1.

Frontline	Year 1	Year 2	Year 3	Year 4	Year 5	Total
A+CHP						
Acqusition cost						
Administration cost						
Medical ressource use						
AE cost						
Consolidative SCT						
2L BV						
2L Chemotherapy						
Consolidative radiotherapy						
Non-consolidative SCT						
CHOP						
Acqusition cost						
Administration cost						
Medical ressource use						
AE cost						
Consolidative SCT						
2L BV						
2L Chemotherapy						
Consolidative radiotherapy						
Non-consolidative SCT						
CHOEP						
Acqusition cost						
Administration cost						
Medical ressource use						
AE cost						
Consolidative SCT						

2L BV												
2L Chemotherapy												
Consolidative radiotherapy												
Non-consolidative SCT												
Total												

Appendix 4: Budget impact. The table shows the estimated total budget impact over 5 years in a scenario without A+CHP for clinical question 2.

Frontline	Year 1			Year 2			Year 3			Year 4			Year 5			Total		
A+CHP																		
Acqusition cost																		
Administration cost																		
Medical ressource use																		
AE cost																		
Consolidative SCT																		
2L BV																		
2L Chemotherapy																		
Consolidative radiotherapy																		
Non-consolidative SCT																		
CHOP																		
Acqusition cost																		
Administration cost																		
Medical ressource use																		
AE cost																		
Consolidative SCT																		
2L BV																		
2L Chemotherapy																		
Consolidative radiotherapy																		
Non-consolidative SCT																		

CHOEP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Acqusition cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Administration cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Medical ressource use	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AE cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Consolidative SCT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2L BV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2L Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Consolidative radiotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-consolidative SCT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Appendix 5: Budget impact. The table lists the estimated total budget impact over 5 years in a scenario with A+CHP for clinical question 2.

Frontline	Year 1	Year 2	Year 3	Year 4	Year 5	Total
A+CHP total						
Acqusition cost						
Administration cost						
Medical ressource use						
AE cost						
Consolidative SCT						
2L BV						
2L Chemotherapy						
Consolidative radiotherapy						
Non-consolidative SCT						
CHOP total						
Acqusition cost						
Administration cost						
Medical ressource use						
AE cost						
Consolidative SCT						
2L BV						
2L Chemotherapy						
Consolidative radiotherapy						
Non-consolidative SCT						
CHOEP total						
Acqusition cost						
Administration cost						
Medical ressource use						

AE cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Consolidative SCT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2L BV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2L Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Consolidative radiotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-consolidative SCT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Appendix 6: Budget impact. The table lists the estimated incremental budget impact over 5 years for clinical question 2.

Frontline	Year 1	Year 2	Year 3	Year 4	Year 5	Total
A+CHP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Acqusition cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Administration cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Medical ressource use	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AE cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Consolidative SCT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2L BV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2L Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Consolidative radiotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-consolidative SCT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CHOP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Acqusition cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Administration cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Medical ressource use	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AE cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Consolidative SCT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2L BV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2L Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Consolidative radiotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-consolidative SCT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CHOEP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Acqusition cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Administration cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Medical ressource use	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AE cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Consolidative SCT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

2L BV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2L Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Consolidative radiotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-consolidative SCT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Appendix 7: Budget impact. The table shows the estimated total budget impact over 5 years in a scenario without A+CHP for the entire sALCL population.

Frontline	Year 1	Year 2	Year 3	Year 4	Year 5	Total
A+CHP						
Acqusition cost						
Administration cost						
Medical ressource use						
AE cost						
Consolidative SCT						
2L BV						
2L Chemotherapy						
Consolidative radiotherapy						
Non-consolidative SCT						
CHOP						
Acqusition cost						
Administration cost						
Medical ressource use						
AE cost						
Consolidative SCT						
2L BV						
2L Chemotherapy						
Consolidative radiotherapy						
Non-consolidative SCT						
CHOEP						
Acqusition cost						
Administration cost						
Medical ressource use						
AE cost						

Consolidative SCT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2L BV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2L Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Consolidative radiotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-consolidative SCT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Appendix 8: Budget impact. The table shows the estimated total budget impact over 5 years in a scenario with A+CHP for the entire sALCL population.

Frontline	Year 1	Year 2	Year 3	Year 4	Year 5	Total
A+CHP total						
Acqusition cost						
Administration cost						
Medical ressource use						
AE cost						
Consolidative SCT						
2L BV						
2L Chemotherapy						
Consolidative radiotherapy						
Non-consolidative SCT						
CHOP total						
Acqusition cost						
Administration cost						
Medical ressource use						
AE cost						
Consolidative SCT						
2L BV						
2L Chemotherapy						
Consolidative radiotherapy						
Non-consolidative SCT						
CHOEP total						
Acqusition cost						
Administration cost						
Medical ressource use						
AE cost						

Consolidative SCT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2L BV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2L Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Consolidative radiotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-consolidative SCT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Appendix 9: Budget impact. The table lists the estimated incremental budget impact over 5 years for the entire sALCL population.

Frontline	Year 1	Year 2	Year 3	Year 4	Year 5	Total
A+CHP						
Acqusition cost						
Administration cost						
Medical ressource use						
AE cost						
Consolidative SCT						
2L BV						
2L Chemotherapy						
Consolidative radiotherapy						
Non-consolidative SCT						
CHOP						
Acqusition cost						
Administration cost						
Medical ressource use						
AE cost						
Consolidative SCT						
2L BV						
2L Chemotherapy						
Consolidative radiotherapy						
Non-consolidative SCT						
CHOEP						
Acqusition cost						
Administration cost						
Medical ressource use						
AE cost						
Consolidative SCT						
2L BV						

2L Chemotherapy	[redacted]		[redacted]		[redacted]		[redacted]		[redacted]		[redacted]		[redacted]	
Consolidative radiotherapy	[redacted]		[redacted]		[redacted]		[redacted]		[redacted]		[redacted]		[redacted]	
Non-consolidative SCT	[redacted]		[redacted]		[redacted]		[redacted]		[redacted]		[redacted]		[redacted]	
Total	[redacted]		[redacted]		[redacted]		[redacted]		[redacted]		[redacted]		[redacted]	

Appendix 10. Cost of chemotherapy

	Method	Units/pack	Cost/pack	mg/unit	Cost/unit	mg/m2/per administration	mg/kg/day	units/day	Administrations per cycle	Cycles	Cycle Length	Cost per cycle	Total cost	Proportion of patients
ICE (4,23)													**11,325.33 kr.**	
Ifosfamide	IV	1	308 kr.	1000	308.00 kr.	5000		9.37	1	3	14	2,887.47 kr.	8,662.42 kr.	28%
Carboplatin	IV	1	96 kr.	150	95.68 kr.		800	6.00	1			574.08 kr.	1,722.24 kr.	
Etoposide	IV	1	279 kr.	500	278.72 kr.	100		0.37	3			313.56 kr.	940.67 kr.	
DHAP (4,24)													**9,697.48 kr.**	
Dexamethasone	Oral	1	63 kr.	4	63.00 kr.		40	10.00	4	3	21	2,520.00 kr.	7,560.00 kr.	15%
Cytarabine	IV	1	150 kr.	2000	150.00 kr.	2000		1.87	2			562.49 kr.	1,687.48 kr.	

Cisplatin	IV	1	80 kr.	100	80.00 kr.	100		1.87	1			150.00 kr.	450.00 kr.	
GDP (4,25)		1											**21,779.89 kr.**	
Gemcitabine	IV	1	1,200 kr.	2000	1,200.00 kr.	1250		1.17	2	4	21	2,812.47 kr.	11,249.90 kr.	33%
Dexamethasone	Oral	1	63 kr.	4	63.00 kr.		40	10.00	4			2,520.00 kr.	10,080.00 kr.	
Cisplatin	IV	1	80 kr.	100	80.00 kr.	25		0.47	3			112.50 kr.	450.00 kr.	
ESHAP(4,26)													**4,468.29 kr.**	
Etoposide	IV	1	279 kr.	500	278.72 kr.	40		0.15	4	7	21	167.23 kr.	1,170.61 kr.	24%
Methylprednisolone	IV	10	80 kr.	500	7.97 kr.		500	1.00	5			39.85 kr.	278.95 kr.	
Cytarabine	IV	1	150 kr.	2000	150.00 kr.	2000		1.87	1			281.25 kr.	1,968.73 kr.	
Cisplatin	IV	1	80 kr.	100	80.00 kr.	25		0.47	4			150.00 kr.	1,049.99 kr.	

Appendix 11. Differentiated cost data for clinical question 1.

Part 1

Frontline acquisition	Accusition cost	Administration cost	Medical ressource use	AE cost	Consolidative SCT
A+CHP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CHOEP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Part 2

2L BV	2L Chemotherapy	Consolidative radiotherapy	Non-consolidative SCT	Patient- and transport cost	Total
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Appendix 12. Differentiated cost data for clinical question 2.

Part 1

Frontline acquisition	Accusition cost	Administration cost	Medical ressource use	AE cost	Consolidative SCT
A+CHP lifetime cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CHOP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

2L BV	2L Chemotherapy	Consolidative radiotherapy	Non-consolidative SCT	Patient- and transport cost	Total
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Appendix 13. Differentiated cost data for the entire sALCL population.

Part 1

Frontline acquisition	Accusition cost	Administration cost	Medical ressource use	AE cost	Consolidative SCT
A+CHP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CHOP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CHOEP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Part 2

2L BV	2L Chemotherapy	Consolidative radiotherapy	Non-consolidative SCT	Patient- and transport cost	Total
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Appendix 14. Quantile-quantile plotes sALCL OS

Abbreviations: A+CHP, brentuximab vedotin and cyclophosphamide, doxorubicin, and prednisone; CHOP, cyclophosphamide, doxorubicin, vincristine and prednisone; OS, overall survival; sALCL, systemic anaplastic large cell lymphoma.

Appendix 15. Quantile-quantile plotes sALCL PFS

Abbreviations: A+CHP, brentuximab vedotin and cyclophosphamide, doxorubicin, and prednisone; CHOP, cyclophosphamide, doxorubicin, vincristine and prednisone; IRF, Independent Review Facility; PFS, progression-free survival; sALCL, systemic anaplastic large cell lymphoma.

Appendix 16. Base case model settings

Clinical question 1

Parameter	Selection	Sheet
Population	sALCL	Key results
CHOP/CHOEP	CHOEP	Key results
Frontline cycles	Mean number of cycles for ECHELON-2	Key results
PFS fit	Gamma	Key results
OS fit	Gamma	Key results
Subsequent BV retreatment	Included	Key results
Included costs	All	Key results
Including long-term remission multiplier	No	Clinical data - Mortality

Clinical question 2

Parameter	Selection	Sheet
Population	sALCL ALK-positive	Key results
CHOP/CHOEP	CHOP	Key results
Frontline cycles	Mean number of cycles for ECHELON-2	Key results
PFS fit	Gamma	Key results
OS fit	Gamma	Key results
Subsequent BV retreatment	Included	Key results
Included costs	All except stem cell transplant costs	Key results
Including long-term remission multiplier	No	Clinical data - Mortality

Medicinrådet

BESTIL PDF/UA

Medicinrådets protokol for vurdering af brentuximab vedotin i kombination med cyclophosphamid, doxorubicin og prednisolon til behandling af tidligere ubehandlet systemisk anaplastisk storcellet T-cellelymfom

Versionsnr.: 1.0

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 protokollen

Protokollen beskriver, hvordan Medicinrådet vil foretage vurderingen af lægemidlets værdi for patienterne. Den indeholder et eller flere kliniske spørgsmål, som den ansøgende virksomhed skal besvare i deres endelige ansøgning. Til hvert spørgsmål knytter sig en definition af patientgruppen, det lægemiddel vi undersøger, den behandling vi sammenligner med og effektmålene. Udover de(t) kliniske spørgsmål indeholder protokollen også en beskrivelse af, hvordan litteratursøgning, -selektion og databehandling skal foregå.

Protokollen er udarbejdet med udgangspunkt i Håndbog for Medicinrådets proces og metode, som du kan finde på Medicinrådets hjemmeside under siden Metoder, og den ansøgende virksomheds foreløbige ansøgning, der fortæller, hvilke data der findes for lægemidlet.

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.

Godkendt af Medicinrådet 8. juli 2020
Dokumentnummer 80059
Versionsnummer 1.0

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

Indhold

1 Begreber og forkortelser

ALK	Anaplastisk lymfomkinase
ASCT	Autolog stamcelletransplantation
CD30	*Cluster of Differentiation 30*
CHOEP	Cyclophosphamid, doxorubicin, vincristin, etoposid og prednisolon
CHOP	Cyclophosphamid, doxorubicin, vincristin og prednisolon
CHP	Cyclophosphamid, doxorubicin og prednisolon
CI	Konfidensinterval
EMA	Det Europæiske Lægemiddelagentur (*European Medicines Agency)*
EPAR	*European Public Assessment Report*
GRADE	System til at vurdere evidens (*Grading of Recommendations, Assessment, Development and Evaluation*)
HDT	Højdosiskemoterapi
HR	*Hazard ratio*
IPI	International Prognostisk Index
ITT	*Intention to Treat*
MMAE	Monomethyl auristatin E
OR	*Odds ratio*
PICO	Population, intervention, komparator og effektmål (*Population, Intervention, Comparator and Outcome)*
PP	*Per-protocol*
PTCL	Perifere T-cellelymfomer
RCT	Randomiseret kontrolleret studie *(Randomised Controlled Trial)*
RR	Relativ risiko
sALCL	Systemisk anaplastisk storcellet T-cellelymfom
SMD	*Standardized Mean Difference*

2 Introduktion

Protokollen er udarbejdet, fordi Medicinrådet har modtaget en foreløbig ansøgning fra Takeda Pharma a/s, som ønsker, at Medicinrådet vurderer brentuximab vedotin i kombination med cyclophosphamid, doxorubicin og prednisolon (CHP) til behandling af tidligere ubehandlet systemisk anaplastisk storcellet T-cellelymfom (sALCL). Vi modtog den foreløbige ansøgning den 28. februar 2020.

2.1 Systemisk anaplastisk storcellet T-celle lymfom

SALCL et aggressivt lymfom, som hører til gruppen af perifere T-cellelymfomer (PTCL). PTCL er en heterogen gruppe af lymfekræftsygdomme, som udgør ca. 10-15 % af alle non-Hodgkin-lymfomer. SALCL er den tredje hyppigst forekommende PTCL og udgør ca. 10-15 %. SALCL er næsten altid CD30 positiv (CD30+), hvilket betyder, at tumorcellerne næsten altid udtrykker receptoren CD30 i varierende grad [1].

SALCL har to overordnede undertyper, der defineres ved forekomsten af anaplastisk lymfomkinase (ALK) i de maligne celler. De to undertyper betegnes ALK-positiv og ALK-negativ. ALK-positiv sALCL udgør ca. 40 % og rammer hyppigst yngre (medianalder 34 år), mens ALK-negativ udgør ca. 60 % og oftest rammer ældre (medianalder 54-61 år). ALK-positiv sALCL har en bedre prognose end ALK-negativ sALCL. Begge har, sammenlignet med de øvrige PTCL'er, en relativ god prognose [1,2]. ALK-positiv sALCL har en 5-års overlevelse på 70-93 %, mens ALK-negativ sALCL har en 5-års overlevelse på 37-49 %. Hos yngre patienter (< 40 år) er der ikke observeret forskelle i overlevelse blandt ALK-positive og ALK-negative patienter [3]. Det er således uklart, hvorvidt forskel i prognose mellem ALK-positive og ALK-negative udelukkende skyldes forskel i aldersfordeling, eller om der er andre faktorer med indflydelse på prognosen.

SALCL diagnosticeres oftest i et fremskredent stadium (stadie III og IV) med sygdom påviselig flere steder. Lokaliseret sygdom (stadie I-II) er sjælden. Sygdomsbyrden er derfor ofte stor med deraf følgende almensymptomer, herunder såkaldte B-symptomer (nattesved, ikke tilsigtet vægttab og feber uden anden forklaring). Sygdommen ses oftest lokaliseret til lymfeknuder (nodal sygdom), men kan dog også ses i regioner uden for det lymfatiske system (ekstranodal sygdom, herunder knoglemarv). Sygdommen opdages sædvanligvis på baggrund af hævede lymfeknuder og/eller almensymptomer. SALCL risikostratificeres oftest ved hjælp af det Internationale Prognostiske Index (IPI). IPI-scoren bestemmes ud fra fem risikofaktorer, som omfatter: alder, niveau af lactatdehydrogenase, sygdomsstadie, generel helbredsstatus og udbredelse af sygdommen. Scoren går fra 0-5, hvor en højere score er forbundet med en dårligere prognose. IPI-scoren kan anvendes til at gruppere patienterne efter deres prognose, hvor en score på 0-1 svarer til lav IPI-score, 2-3 svarer til intermediær IPI-score og 4-5 til en høj IPI-score. Patienter med ALK-positiv sALCL og lav IPI har en markant bedre prognose end resten af gruppen af sALCL. Diagnosen stilles på baggrund af en histopatologisk vurdering af vævsmateriale fra en biopsi. Billeddiagnostik bruges på diagnosetidspunktet til stadieinddeling, men også under og efter behandlingsforløbet til vurdering af behandlingseffekt og sygdomskontrol. Der diagnosticeres ca. 1.400 nye tilfælde af lymfekræft om året i Danmark, ca. 90 % af dem er non-Hodgkin lymfom, og ca. 10 % er Hodgkins lymfom. Fagudvalget skønner, at der diagnosticeres ca. 20 nye tilfælde af sALCL om året i Danmark.

2.2 Brentuximab vedotin

Brentuximab vedotin er et antistoflægemiddelkonjugat bestående af et CD30-rettet monoklonalt antistof, som er kovalent bundet til antimikrotubulusmidlet monomethyl auristatin E (MMAE) [4]. Efter binding til CD30 optages brentuximab vedotin hurtigt i cellerne og transporteres til lysosomerne, hvor MMAE frigives og binder til tubulin. Som en konsekvens heraf dør cellerne [5].

Lægemidlet administreres som intravenøs infusion 1,8 mg/kg hver tredje uge i 6-8 serier.

Protokollen vedrører en indikationsudvidelse til patienter med tidligere ubehandlet sALCL, hvor brentuximab vedotin gives i kombination med CHP.

Brentuximab vedotin er også indiceret til behandling af voksne patienter med:

- ikke tidligere behandlet CD30+ Hodgkins lymfom stadie IV i kombination med doxorubicin, vinblastin og dacarbazin.
- CD30+ Hodgkins lymfom med øget risiko for recidiv eller progression efter autolog stamcelletransplantation (ASCT).
- recidiverende eller refraktært CD30+ Hodgkins lymfom:
    - Efter ASCT eller
    - efter mindst to tidligere behandlinger, når ASCT eller flerstofskemoterapibehandling ikke er en behandlingsmulighed.
- recidiverende eller refraktært sALCL.
- CD30+ kutant T-cellelymfom efter mindst 1 forudgående systemisk behandling.

Brentuximab vedotin har således allerede indikationen sALCL, blot i en senere behandlingslinje. Lægemidlet er behandlet som *orphan drug* hos EMA, men ikke i accelereret proces.

2.3 Nuværende behandling

De danske retningslinjer for behandling af sALCL lægger sig op ad retningslinjer fra ESMO [2]. Behandlingsmålet er helbredelse med samtidig fokus på at undgå uacceptabel toksicitet ikke mindst hos ældre og ved væsentlig komorbiditet.

Valg af behandling afhænger af alder, komorbiditet, om lymfomet er ALK-positiv eller ALK-negativ, samt risiko vurderet ud fra IPI. Patienter, som er ALK-negative og under 65 (-70) år uden markant komorbiditet, behandles med cyclophosphamid, doxorubicin, vincristin, etoposid og prednisolon (CHOEP), i alt 6 serier som gives hver 14. dag (CHOEP-14). Opnås et tilfredsstillende respons, efterfølges dette af højdosiskemoterapi (HDT) og ASCT. Patienter, som er ALK-positive og under 65 (-70) år, behandles på tilsvarende vis med CHOEP i 6 serier eventuelt efterfulgt af HDT og ASCT ved høj IPI. Patienter over 60 år anbefales dog cyclophosphamid, doxorubicin, vincristin og prednisolon (CHOP) frem for CHOEP grundet toksicitet. Ved tilfredsstillende respons hos ældre i god almen tilstand uden væsentlig komorbiditet efterfølges CHOP også af HDT og ASCT. HDT består af carmustin 300 mg/m^2 IV på dag 1, etoposid 100 mg/m^2 IV to gange daglig på dag 2 til 5, cytarabin 200 mg/m^2 IV to gange daglig på dag 2 til 5 og melphalan 140 mg/m^2 IV på dag 6 (kaldet BEAM).

Patienter, som ikke vurderes egnet til HDT og ASCT (ældre patienter, patienter med dårlig almen tilstand og/eller væsentlig komorbiditet), behandles med CHOP hver 14. eller 21. dag (CHOP-14 eller CHOP-21), i alt 6 serier [1]. Patienter, som er ALK-positive med lav IPI (IPI < 2), har en markant bedre prognose og her kan intensive strategier (CHOEP efterfulgt af HDT og ASCT) eventuelt udelades.

Disse retningslinjer baserer sig ikke på solid evidens. Enkelte studier har vist en bedre *event free survival* (men ikke *overall survival*) med CHOEP frem for CHOP til patienter under 60 år. Et studie fra den Nordiske Lymfomgruppe viste positive resultater med HDT og ASCT hos yngre patienter [6]. Sidstnævnte støttes af retrospektive populationsbaserede data. Imidlertid er den overordnede evidens på området svag.

3 Kliniske spørgsmål

Medicinrådet bruger kliniske spørgsmål til vurdering af lægemidlers værdi for patienterne. Til hvert spørgsmål knytter sig en definition af patientgruppen (population), af det lægemiddel vi undersøger (intervention), af den behandling vi sammenligner med (komparator(er)) og af effektmålene.

3.1 Klinisk spørgsmål 1

Hvilken værdi har brentuximab vedotin i kombination med cyclophosphamid, doxorubicin og prednisolon (CHP) sammenlignet med cyclophosphamid, doxorubicin, vincristin, etoposid og prednisolon (CHOEP) eller cyclophosphamid, doxorubicin, vincristin og prednisolon (CHOP) for tidligere ubehandlede patienter med systemisk anaplastisk storcellet T-cellelymfom som kandiderer til HDT og ASCT?

Population
Voksne med tidligere ubehandlet systemisk anaplastisk storcellet T-cellelymfom som kandiderer til HDT og ASCT.

Intervention
Brentuximab vedotin i kombination med cyclophosphamid, doxorubicin og prednisolon.

- Brentuximab vedotin, 1,8 mg/kg hver 3. uge i 6-8 serier
- Cyclophosphamid, 750 mg/m^2 hver 3. uge i 6-8 serier
- Doxorubicin, 50 mg/m^2 hver 3. uge i 6-8 serier
- Prednisolon, 100 mg fra dag 1-5 i hver 3-ugers serie i 6-8 serier.

Komparator
Cyclophosphamid, doxorubicin, vincristin, etoposid og prednisolon (CHOEP-14).

- Cyclophosphamid, 750 mg/m^2 hver 2. uge i 6 serier
- Doxorubicin, 50 mg/m^2 hver 2. uge i 6 serier
- Vincristin, 1,4 mg/m^2 hver 2. uge i 6 serier
- Etoposid, 200 mg/m^2 peroralt dag 1-3 hver 2. uge i 6 serier
- Prednisolon, 100 mg fra dag 1-5 i hver serie hver 2. uge i 6 serier.

Cyclophosphamid, doxorubicin, vincristin og prednisolon (CHOP-14/-21).

- Cyclophosphamid, 750 mg/m^2 hver 2. eller 3. uge i 6 serier
- Doxorubicin, 50 mg/m^2 hver 2. eller 3. uge i 6 serier
- Vincristin, 1,4 mg/m^2 hver 2. eller 3. uge i 6 serier
- Prednisolon, 100 mg fra dag 1-5 i hver serie hver 2. eller 3. uge i 6 serier.

Ved tilfredsstillende respons efterfølges intervention og komparator af HDT og ASCT.

Effektmål
De valgte effektmål fremgår af tabel 1.

3.2 Klinisk spørgsmål 2

Hvilken værdi har brentuximab vedotin i kombination med cyclophosphamid, doxorubicin og prednisolon (CHP) sammenlignet med cyclophosphamid, doxorubicin, vincristin og prednisolon (CHOP) for tidligere ubehandlede patienter med systemisk anaplastisk storcellet T-cellelymfom som ikke kandiderer til HDT og ASCT?

Population
Voksne med tidligere ubehandlet systemisk anaplastisk storcellet T-cellelymfom som ikke kandiderer til HDT og ASCT og tidligere ubehandlede ALK-positive voksne med lav IPI.

Intervention
Brentuximab vedotin i kombination med cyclophosphamid, doxorubicin og prednisolon.

- Brentuximab vedotin, 1,8 mg/kg hver 3. uge i 6-8 serier
- Cyclophosphamid, 750 mg/m^2 hver 3. uge i 6-8 serier
- Doxorubicin, 50 mg/m^2 hver 3. uge i 6-8 serier
- Prednisolon, 100 mg fra dag 1-5 i hver 3-ugers serie i 6-8 serier.

Komparator
Cyclophosphamid, doxorubicin, vincristin og prednisolon (CHOP-14/-21).

- Cyclophosphamid, 750 mg/m^2 hver 2. eller 3. uge i 6 serier
- Doxorubicin, 50 mg/m^2 hver 2. eller 3. uge i 6 serier
- Vincristin, 1,4 mg/m^2 hver 2. eller 3. uge i 6 serier
- Prednisolon, 100 mg fra dag 1-5 i hver serie hver 2. eller 3. uge i 6 serier.

Effektmål
De valgte effektmål fremgår af tabel 1.

3.3 Effektmål

Medicinrådet mener, at vurderingen af lægemidlets værdi bliver bedst understøttet af de effektmål, vi har nævnt i tabel 1. For hver effektmål har Medicinrådet fastsat en mindste klinisk relevant forskel (MKRF). MKRF er den forskel mellem intervention og komparator, der som minimum skal opnås for at det vurderes at være klinisk relevant. I det følgende afsnit argumenterer vi for valget af effektmål og de mindste klinisk relevante forskelle.

Tabel 1. Oversigt over valgte effektmål. For hvert effektmål er angivet deres vigtighed, måleenhed og mindste klinisk relevante forskel samt indplacering i de tre effektmålsgrupper (dødelighed, livskvalitet samt alvorlige symptomer og bivirkninger, ikkealvorlige symptomer og bivirkninger), som anvendes ved Medicinrådets vurdering af lægemidlets kliniske værdi.

Effektmål	Vigtighed	Effektmålsgruppe	Måleenhed	Mindste klinisk relevante forskel
Samlet overlevelse (OS)	Kritisk	Dødelighed	Median OS i måneder	6 måneder
			Andel af patienter, der opnår 2-års overlevelse	5 %-point
Progressionsfri overlevelse (PFS)	Vigtig	Livskvalitet samt alvorlige symptomer og bivirkninger	Median PFS i måneder	6 måneder
			Andel af patienter, der opnår 2-års progressionsfri overlevelse	5 %-point
Livskvalitet	Vigtig	Livskvalitet samt alvorlige symptomer og bivirkninger	Gennemsnitlig ændring fra baseline på EORTC QLQ-C30 til efter endt behandling	10 point
			Gennemsnitlig ændring fra baseline på EORTC QLQ-C30 til efter endt opfølgning	10 point
Uønskede hændelser	Vigtig	Livskvalitet samt alvorlige symptomer og bivirkninger	Andel som ophører behandlingen pga. uønskede hændelser (behandlingsophør)	5 %-point
			Andel patienter med uønskede hændelser grad 3 og grad 4	10 %-point
			Kvalitativ gennemgang af rapporterede bivirkninger	Ikke relevant

For alle effektmål ønsker vi data baseret på længst mulig opfølgningstid, med mindre andet er angivet.

3.3.1 Kritiske effektmål

Samlet overlevelse (OS)

OS er standard til at vise klinisk effekt i cancerstudier, herunder lymfekræft. Det er et patientrelevant effektmål, der belyser patientpopulationens levetid. Derfor er OS et kritisk effektmål for vurderingen. OS defineres som tiden fra randomisering eller opstart af behandling til død uanset årsag. Den forventede overlevelse hos patienter med sALCL afhænger af forekomsten af ALK. Prognosen er generelt god sammenlignet med andre T-cellelymfomer, med en 5-års OS på henholdsvis 37-49 % og 70-93 % for ALK-negativ og ALK-positiv sALCL [7]. Det vil således kræve en betydelig opfølgningstid (formentlig mere end 5 år) for at vise effekt på patienternes mediane OS. Derfor vurderer fagudvalget, at OS, foruden median OS, også skal vurderes på andelen af patienter, der opnår 2-års OS. Dette vurderer fagudvalget er en realistisk tidshorisont i studiesammenhæng og samtidig tilstrækkelig lang tid til at vurdere lægemidlets effekt på OS fra et klinisk perspektiv, idet langt de fleste tilbagefald finder sted indenfor de første 2 år. Observationelle studier fra Tyskland og Sverige, hvor patienterne behandles med CHOP-/CHOEP-lignende regimer har vist 2-års OS-rater på ca. 50-65 % og ca. 80-95 % for henholdsvis ALK-negativ og ALK-positiv sALCL [8,9]. Fagudvalget vurderer, at 5 %-point vil være en klinisk relevant forskel i andelen af patienter, der opnår 2 års OS.

3.3.2 Vigtige effektmål

Progressionsfri overlevelse (PFS)

PFS er defineret som tiden fra initiering af behandling til progression eller død uafhængigt af årsag. PFS anvendes i vurderingen af brentuximab vedotin som et udtryk for graden og længden af sygdomskontrol, som opnås under og efter 1. linje behandling. PFS er et komplementært effektmål til OS, idet OS kan være påvirket af de efterfølgende behandlingslinjer. Med nuværende standardbehandling opnår ca. 40 % af patienterne fem års PFS [7]. Et større tysk studie, hvor patienterne behandles med CHOP-/CHOEP-lignende regimer har vist en 3-års *event free survival* (et effektmål svarende til PFS) på 76 % og 46 % for henholdsvis ALK-positiv og ALK-negativ sALCL [9], mens en svensk registerundersøgelse viser 5-års PFS-rater på henholdsvis 63 % og 31 % for ALK-positiv og ALK-negativ sALCL [8]. Som for OS vil det kræve en betydelig opfølgningstid for at vise effekt på median PFS. Det vurderes dog realistisk indenfor den forventede opfølgningstid. Fagudvalget vurderer, at en forskel på 6 måneder i median PFS er en klinisk relevant forbedring. Fagudvalget ønsker også at se data for 2-års PFS. To-års PFS vurderes at være rationelt fra et klinisk perspektiv, idet langt de fleste tilbagefald finder sted indenfor de første 2 år. De før omtalte svenske og tyske studier har vist 2-års PFS-rater i størrelsesordenen 40-50 % hos ALK-negative patienter og ca. 65-80 % hos ALK-positive patienter. For andelen af patienter, der opnår 2 års PFS, anses en forskel på 5 %-point derfor som klinisk relevant.

Livskvalitet

Livskvalitet er en vigtig parameter som effektmål ved introduktion af ny kræftbehandling. Ved sALCL kan både sygdomsbyrde og toksicitet af behandlingen have markant indflydelse på patienternes livskvalitet. I vurderingen af brentuximab vedotin vurderes livskvalitet derfor som et vigtigt effektmål. EORTC QLQ-C30 er et spørgeskema til vurdering af helbredsrelateret livskvalitet hos patienter med kræft, der deltager i internationale kliniske forsøg. QLQ-C30 indeholder ni skalaer fordelt indenfor forskellige emner: fem funktionelle skalaer (fysisk, rolle, kognitiv, følelsesmæssig og social), tre symptomskalaer (træthed, smerte og kvalme og opkast) og en global livskvalitetsskala. Hertil kommer seks enkeltsymptomskalaer, som vurderer: dyspnø, tab af appetit, søvnforstyrrelse, forstoppelse, diarré og den økonomiske konsekvens af behandlingen [10]. Alle skalaer scores fra 0-100. Med undtagelse af enkeltsymptomskalaerne indikerer en højere score en bedre tilstand, f.eks. en bedre livskvalitet på den globale skala. For enkeltsymptomskalaerne

indikerer en højere score værre symptomer. Fagudvalget ønsker livskvalitet opgjort som ændring fra baseline på den globale EORTC QLQ-C30 livskvalitetsskala frem til 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. Fagudvalget har ikke kendskab til publicerede mindste klinisk relevante forskelle specifikt for patienter med sALCL. En oversigtsartikel har gennemgået tolkning af resultater fra EORTC QLQ-C30, og denne viser, at den hyppigst anvendte grænse for klinisk relevans er en ændring på > 10 point [11]. Denne tolkning stammer fra et studie, som har vist, at ændringer på mellem 5-10 point modsvarer en lille forskel, en ændring på 10-20 point en moderat forskel, mens en ændring på > 20 svarer til en stor forskel [12]. Der kan dog være forskel på klinisk relevante forskelle, afhængigt af om der er tale om forbedringer i livskvalitetsscoren, eller om der er tale om at undgå en forringelse. Fælles gælder dog, at der som minimum skal opnås en ændring på 5 point på den globale skala, for at det kan opfattes som klinisk relevant [13]. Fagudvalget fastsætter den mindste klinisk relevante forskel til 10 point i ændringen fra baseline mellem grupperne. Dette gælder til begge opfølgningstidspunkter.

Hvis der ikke foreligger data fra EORTC QLQ-C30, foretrækkes data fra et andet valideret instrument, som er relevant for patienter med sALCL, eksempelvis det generiske EQ-5D eller andre sygdomsspecifikke værktøjer.

Uønskede hændelser

Bivirkninger har stor betydning for den enkelte patients livskvalitet og vilje til at forblive i en behandling over længere tid. Til tidligere ubehandlede patienter med sALCL gives brentuximab vedotin i 6-8 serier svarende til op til 24 uger, så eventuelle bivirkninger skal tolereres over en længere periode.

Fagudvalget ønsker at vurdere lægemidlets toksicitet ved den samlede mængde af grad 3-4-uønskede hændelser samt andelen af patienter, som ophører med behandling pga. uønskede hændelser. Andelen af patienter, der ophører behandlingen pga. uønskede hændelser, er et effektmål, der udtrykker, hvor godt behandlingen tolereres af patienterne, mens forekomsten af uønskede hændelser grad 3-4 er et udtryk for alvorlig toksicitet af lægemidlerne. Uønskede hændelser er et vigtigt effektmål, fordi patienterne er villige til at acceptere en risiko for alvorlige bivirkninger, når behandlingsmålet er helbredelse. Uønskede hændelser, herunder grad 3-4 uønskede hændelser observeres ofte med de nuværende behandlinger. Det er dog sjældent, at behandlingen helt afbrydes på grund af toksicitet. Fagudvalget betragter en forskel på 5 %-point mellem grupperne som den mindste klinisk relevante forskel for behandlingsophør pga. uønskede hændelser, idet det er afgørende for patientens efterfølgende prognose, at behandlingen ikke afbrydes. For grad 3-4 uønskede hændelser vil fagudvalget acceptere en lidt højere forskel mellem grupperne, når behandlingen samtidig forventes at have en gevinst på OS og/eller PFS. Derfor fastsættes den mindste klinisk relevante forskel til 10 %-point mellem grupperne.

Fagudvalget vil udover ovenstående opgørelser vurdere håndterbarhed og tyngde af bivirkningsprofilen i en narrativ gennemgang.

4 Litteratursøgning

Medicinrådet har på baggrund af den foreløbige ansøgning undersøgt, om der findes en eller flere randomiserede studier, hvor brentuximab vedotin i kombination med cyclophosphamid, doxorubicin og prednisolon er sammenlignet direkte med henholdsvis CHOEP-14/21 og CHOP-14/21.

Medicinrådet har fundet følgende fuldtekstartikel, som indeholder en direkte sammenligning mellem brentuximab vedotin i kombination med cyclophosphamid, doxorubicin og prednisolon og CHOP:

- *Brentuximab Vedotin with Chemotherapy for CD30-Positive Peripheral T-cell Lymphoma (ECHELON-2): a global, double-blind, randomised, phase 3 trial.* [14]

Det er tilstrækkeligt datagrundlag til at besvare klinisk spørgsmål 2. Ansøger skal derfor ikke søge efter yderligere studier til besvarelse af dette spørgsmål.

Det er ikke tilstrækkeligt datagrundlag til en komplet besvarelse af klinisk spørgsmål 1, da studiet ikke har sammenlignet effekten af brentuximab vedotin i kombination med CHP mod CHOEP.

Derfor skal ansøger søge efter artikler til en indirekte sammenligning. Søgestrengen fremgår nedenfor.

Søgestreng til PubMed (https://pubmed.ncbi.nlm.nih.gov/advanced/):

#	**Søgetermer**	**Kommentar**
#1	Lymphoma, Large-Cell, Anaplastic[mh] OR Lymphoma, T-Cell, Peripheral[mh]	Søgetermer for indikationen (P)
#2	(Lymphom*[tiab] AND (Anaplastic[tiab] OR (Peripheral[tiab] AND T-Cell[tiab]))) OR PTCL[tiab] OR ALCL[tiab]	
#3	#1 OR #2	
#4	Brentuximab Vedotin[mh] OR brentuximab[tiab] OR adcetris*[tiab] OR SGN-35[tiab] OR cAC10-vcMMAE[tiab] OR A+CHP[tiab]	Intervention (I)
#5	CHOEP protocol[nm] OR EPOCH protocol[nm] OR CHOEP[tiab] OR CHOPE[tiab] OR CHOP-E[tiab] OR VACPE[tiab] OR EPOCH[tiab] OR CAVPE[tiab] OR DA-EPOCH[tiab]	Komparator (C)
#6	Cyclophosphamide[mh] OR B-518[tiab] OR Cyclophospha*[tiab] OR Cytophosphan*[tiab] OR Cytoxan[tiab] OR Endoxan[tiab] OR NSC-26271[tiab] OR Neosar[tiab] OR Procytox[tiab] OR Sendoxan[tiab]	
#7	Doxorubicin[mh] OR Doxorubicin[tiab] OR Adriablastin*[tiab] OR Adriamycin[tiab] OR Adriblastin*[tiab] OR DOXO-cell[tiab] OR Doxorubicin*[tiab] OR Myocet[tiab] OR Rubex[tiab] OR Urokit Doxo-cell[tiab]	
#8	Etoposide[mh] OR Etopos*[tiab] OR Celltop[tiab] OR Eposid*[tiab] OR Lastet[tiab] OR NSC-141540[tiab] OR Toposar[tiab] OR VP-16*[tiab] OR Vepesid*[tiab]	
#9	Prednisone[mh] OR Prednisolone[mh] OR Predni*[tiab] OR Pronison*[tiab] OR Dacorti*[tiab] OR Cortan*[tiab] OR Dehydrocortison*[tiab] OR Encorto*[tiab] OR Deltasone[tiab] OR Liquid Pred[tiab] OR Meticorten[tiab] OR Orasone[tiab] OR Panafcort[tiab] OR Panasol[tiab] OR Rectodelt[tiab] OR Sterapred[tiab] OR Ultracorten[tiab] OR Winpred[tiab] OR delta-Cortisone[tiab]	
#10	Vincristine[mh] OR Vincris*[tiab] OR Citomid[tiab] OR Farmistin[tiab] OR Oncovin*[tiab] OR Onkocristin[tiab] OR Vintec[tiab]	
#11	#5 OR (#6 AND #7 AND #8 AND #9 AND #10)	
#12	#3 AND (#4 OR #11)	Kombination af P, I og C
#13	Case Reports[pt] OR Comment[pt] OR Editorial[pt] OR Letter[pt] OR Review[pt] OR Systematic Review[pt]	Eksklusion af specifikke publikationstyper
#14	#12 NOT #13	Linje #14 = endelig søgning

Søgestreng til CENTRAL – Cochrane Library (https://www.cochranelibrary.com/advanced-search/search-manager):

#	Søgetermer	Kommentar
#1	[mh "Lymphoma, Large-Cell, Anaplastic"] OR [mh "Lymphoma, T-Cell, Peripheral"]	Søgetermer for indikationen (P)
#2	((Lymphom* AND (Anaplastic OR (Peripheral AND T-Cell))) OR PTCL OR ALCL):ti,ab,kw	
#3	#1 OR #2	
#4	[mh "Brentuximab Vedotin"]	Intervention (I)
#5	(brentuximab* OR adcetris* OR SGN-35):ti,ab,kw	Komparator (C)
#6	#4 OR #5	
#7	(CHOEP OR CHOPE OR CHOP-E OR VACPE OR EPOCH OR CAVPE OR DA-EPOCH):ti,ab,kw	
#8	[mh "Cyclophosphamide"]	
#9	(B-518 OR Cyclophospha* OR Cytophosphan* OR Cytoxan OR Endoxan OR NSC-26271 OR Neosar OR Procytox OR Sendoxan):ti,ab,kw	
#10	#8 OR #9	
#11	[mh "Doxorubicin"]	
#12	(Doxorubicin OR Adriablastin* OR Adriamycin OR Adriblastin* OR DOXO-cell OR Doxorubicin* OR Myocet OR Rubex OR Urokit Doxo-cell):ti,ab,kw	
#13	#11 OR #12	
#14	[mh "Etoposide"]	
#15	(Etopos* OR Celltop OR Eposid* OR Lastet OR NSC-141540 OR Toposar OR VP-16* OR Vepesid*):ti,ab,kw	
#16	#14 OR #15	
#17	[mh "Prednisone"] OR [mh "Prednisolone"]	
#18	(Predni* OR Pronison* OR Dacorti* OR Cortan* OR Dehydrocortison* OR Encorto* OR Deltasone OR Liquid Pred OR Meticorten OR Orasone OR Panafcort OR Panasol OR Rectodelt OR Sterapred OR Ultracorten OR Winpred OR delta-Cortisone):ti,ab,kw	
#19	#17 OR #18	
#20	[mh "Vincristine"]	
#21	(Vincris* OR Citomid OR Farmistin OR Oncovin* OR Onkocristin OR Vintec):ti,ab,kw	
#22	#20 OR #21	
#23	#7 OR (#10 AND #13 AND #16 AND #19 AND #22)	
#24	#3 AND (#6 OR #23)	Kombination af P, I og C
#25	(clinicaltrials.gov or trialsearch):so	Eksklusion af specifikke publikationstyper
#26	"conference abstract":pt	
#27	#25 or #26	
#28	#24 NOT #27	Linje #28 = endelig søgning

Derudover skal ansøger konsultere Det Europæiske Lægemiddelagenturs (EMA) European public assessment reports (EPAR) for både det aktuelle lægemiddel og dets komparator(er).

Ansøger skal ekskludere artikler med andre populationer end de, der er specificeret i protokollen, og artikler der ikke rapporterer mindst ét af de kritiske eller vigtige effektmål.

Hvis der ikke findes studier, som muliggør en sammenligning mellem CHOEP og brentuximab vedotin kombineret med CHP baseret på statistiske metoder, opfordres ansøger til at redegøre for, om effekten af CHOP (komparator i ECHELON-2) er sammenlignelig med effekten af CHOEP efterfulgt af HDT og ASCT, som anvendes i Dansk klinisk praksis. Redegørelsen bør indeholde en beskrivelse af studie- og

patientkarakteristika samt resultater fra de inkluderede studier i tekst og tabelform med angivelse af resultater pr. effektmål for både CHOP og CHOEP. Ansøger skal beskrive eventuelle forskelle mellem studier og vurderer, hvorvidt resultaterne er sammenlignelige.

Kriterier for litteratursøgning

Ansøger skal søge relevant litteratur i databaserne PubMed og CENTRAL (via Cochrane Library). Ansøger skal dokumentere søgningen for hver af de to databaser, f.eks. i form af et skærmklip eller en downloadet søgestrategi. Eventuelle ændringer/tilføjelser til søgestrategien skal fremgå af dokumentationen.

Kriterier for udvælgelse af litteratur

Ansøger skal screene de artikler, der identificeres ved databasesøgningerne, for overensstemmelse med de i protokollen definerede kliniske spørgsmål samt kriterier for studie- og publikationstype(r). Det vil sige, at ansøger skal ekskludere artikler med andre populationer end de i protokollen specificerede. Dette gælder ligeledes for artikler, som ikke rapporterer mindst ét af de kritiske eller vigtige effektmål.

Den ansøgende virksomhed skal ved screening af artikler ekskludere først på titel- og abstractniveau, dernæst ved gennemlæsning af fuldtekstartikler. Artikler, der ekskluderes ved fuldtekstlæsning, skal fremgå af en eksklusionsliste, hvor eksklusionen begrundes kort. Den samlede udvælgelsesproces skal afrapporteres ved brug af et flowdiagram som beskrevet i PRISMA-Statement (http://prisma-statement.org/PRISMAStatement/FlowDiagram.aspx).

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

5 Databehandling og -analyse

Ansøger skal bruge Medicinrådets ansøgningsskema til sin endelige ansøgning. Vær opmærksom på følgende:

Studier og resultater

- Beskriv de inkluderede studier og baselinekarakteristikken af studiepopulationerne.
- Angiv hvilke studier/referencer der er benyttet til at besvare hvilke kliniske spørgsmål.
- Brug som udgangspunkt ansøgningsskemaet til ekstraktion af al relevant data.
- Krydstjek de ekstraherede data med de resultater, der fremgår af de relevante EPARs.
- Angiv årsager, hvis der er uoverensstemmelser mellem resultaterne fra artikler og EPARs.
- Angiv årsager, hvis der er uoverensstemmelser i forhold til PICO mellem protokollen og studierne.
- Vurdér, hvordan uoverensstemmelserne påvirker estimaterne.

Statistiske analyser

- Begrund valget af syntesemetode (metaanalyse eller narrativ beskrivelse), og lad specifikke analysevalg fremgå tydeligt.
- Udfør en komparativ analyse for hvert enkelt effektmål på baggrund af de ekstraherede data.
- Hvis data for et effektmål ikke er baseret på alle deltagere i et studie, skal ansøger ikke gøre forsøg på at erstatte manglende data med en meningsfuld værdi.
- Angiv for hvert effektmål og studie, hvilken analysepopulation (f.eks. intention to treat (ITT), per-protocol) der er anvendt.

- Angiv en sensitivitetsanalyse baseret på ITT-populationen, hvis den komparative analyse ikke er baseret herpå.
- Angiv for hvert effektmål og studie, hvilken statistisk analysemetode, der er anvendt.
- Basér de statistiske analyser for dikotome effektmål på den relative forskel.
- Beregn den absolutte forskel med udgangspunkt i den estimerede relative forskel for et antaget niveau på hændelsesraten i komparatorgruppen (jævnfør Appendiks 5 i Håndbog for Medicinrådets proces og metode vedr. nye lægemidler og indikationsudvidelser).
- Foretag eventuelt en indirekte analyse, hvis der ikke foreligger direkte sammenlignende studier, og hvis intervention og komparator er sammenlignet med samme alternative komparator i separate studier. Anvend eventuelt Buchers metode for indirekte justeret sammenligning.

Metaanalyser

- Foretag en metaanalyse for de effektmål, hvor det er metodemæssigt forsvarligt, hvis der er mere end ét sammenlignende studie.
- Basér metaanalyser vedr. effektmål, hvor forskellige måleinstrumenter er brugt på tværs af de inkluderede studier, på standardized mean difference (SMD). Omregn den estimerede SMD til den foretrukne skala for effektmålet (jævnfør Appendiks 7 i Håndbog for Medicinrådets proces og metode vedr. nye lægemidler og indikationsudvidelser).
- Udfør alene netværksmetaanalyse i de undtagelsesvise situationer, hvor Medicinrådet specifikt beder om det i protokollen. Redegør i disse tilfælde for, i hvilken grad antagelserne om transitivitet og konsistens er opfyldt (gerne ved hjælp af passende statistiske metoder).
- Begrund for alle statistiske analyser valget mellem 'fixed effects'- og 'random effects'-modeller.
- Beskriv den anvendte metode detaljeret.

Narrative analyser

- Begrund valget af syntesemetode (metaanalyse eller narrativ beskrivelse), og lad specifikke analysevalg fremgå tydeligt.
- Syntetisér data narrativt, hvis det ikke er en mulighed at udarbejde komparative analyser baseret på statistiske metoder.
- Beskriv studie- og patientkarakteristika samt resultater fra de inkluderede studier narrativt og i tabelform med angivelse af resultater pr. effektmål for både intervention og komparator(er).
- Beskriv forskelle mellem studier og vurdér, hvorvidt resultaterne er sammenlignelige.

Vær opmærksom på, at Medicinrådets sekretariat forbeholder sig retten til at foretage sensitivitets- og subgruppeanalyser på baggrund af studiernes validitet og relevans, uanset valg af analysemetode.

6 Evidensens kvalitet

Medicinrådet anvender GRADE (Grading of Recommendations, Assessments, Development and Evaluation) til at foretage en systematisk og transparent vurdering af kvaliteten af evidensen. Evidensens kvalitet fortæller, i hvor høj grad vi kan have tiltro til den evidens, vi baserer vurderingen af lægemidlets værdi på.

7 Andre overvejelser

7.1 Opgørelse af effekt for ALK-ekspression, IPI og alder

Fagudvalget ønsker subgruppedata for OS og PFS stratificeret efter ALK-status (ALK-negativ og ALK-positiv). Data skal inkludere:

- Kaplan Meier-kurver for intervention og komparator for hhv. ALK-positive og ALK-negative.
- Effektestimater for effektforskellen mellem intervention og komparator for hhv. ALK-positive og ALK-negative, herunder HR, medianer og OS/PFS-rater ved 2 år.
- Oversigt over baselinekarakteristika, herunder relevante prognostiske faktorer.
- Oversigt over antal patienter der behandles med HDT og ASCT efter behandling med henholdsvis intervention og komparator.

Fagudvalget ønsker subgruppedata for OS og PFS stratificeret efter IPI-score (lav (0-1), intermediær (2-3) og høj IPI-score (>3)). Data skal inkludere:

- Kaplan Meier-kurver for intervention og komparator for hhv. lav (0-1), intermediær (2-3) og høj IPI (> 3).
- Effektestimater for effektforskellen i hver af subgrupperne, herunder HR, medianer og OS/PFS-rater ved 2 år.
- Oversigt over baselinekarakteristika, herunder relevante prognostiske faktorer.
- Oversigt over antal patienter der behandles med HDT og ASCT efter behandling med henholdsvis intervention og komparator.

Fagudvalget ønsker subgruppedata for OS og PFS stratificeret efter alder (≤ 60 år og > 60 år). Data skal inkludere:

- Kaplan Meier-kurver for intervention og komparator for hhv. patienter ≤ 60 år og > 60 år.
- Effektestimater for effektforskellen i hver af subgrupperne, herunder HR, medianer og OS/PFS-rater ved 2 år.
- Oversigt over antal patienter der behandles med HDT og ASCT efter behandling med henholdsvis intervention og komparator.

Fagudvalget ønsker desuden overlevelsesdata for ALK-status yderligere stratificeret på IPI-score.

7.2 Efterfølgende behandlingslinjer

Fagudvalget ønsker informationer, der kan belyse, hvorvidt og hvordan indførelsen af den ansøgte intervention i dansk klinisk praksis vil påvirke behandlinger i efterfølgende behandlingslinjer, hvad angår type, varighed og forventet effekt.

8 Relation til behandlingsvejledning

Der findes ikke en relevant behandlingsvejledning.

9 Referencer

1. Dansk Lymfomgruppe. ANBEFALINGER FOR DIAGNOSTIK OG BEHANDLING AF PERIFERE T-CELLE LYMFOMER (PTCL). 2017;
2. d'Amore F, Gaulard P, Trümper L, Corradini P, Kim W-S, Specht L, et al. Peripheral T-cell lymphomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2015;26:v108–15.
3. Sibon D, Fournier M, Brière J, Lamant L, Haioun C, Coiffier B, et al. Long-Term Outcome of Adults With Systemic Anaplastic Large-Cell Lymphoma Treated Within the Groupe d'Étude des Lymphomes de l'Adulte Trials. J Clin Oncol. 2012;30(32):3939–46.
4. EMA- European Medicines Agency. Produktresumé Adcetris. London; 2018.
5. Francisco JA, Cerveny CG, Meyer DL, Mixan BJ, Klussman K, Chace DF, et al. cAC10-vcMMAE, an anti-CD30-monomethyl auristatin E conjugate with potent and selective antitumor activity. Blood. 2003;102(4):1458–65.
6. d'Amore F, Relander T, Lauritzsen GF, Jantunen E, Hagberg H, Anderson H, et al. Up-Front Autologous Stem-Cell Transplantation in Peripheral T-Cell Lymphoma: NLG-T-01. J Clin Oncol. 2012;30(25):3093–9.
7. Savage KJ, Harris NL, Vose JM, Ullrich F, Jaffe ES, Connors JM, et al. ALK− anaplastic large-cell lymphoma is clinically and immunophenotypically different from both ALK+ ALCL and peripheral T-cell lymphoma, not otherwise specified: report from the International Peripheral T-Cell Lymphoma Project. Blood. 2008;111(12):5496–504.
8. Ellin F, Landström J, Jerkeman M, Relander T. Real-world data on prognostic factors and treatment in peripheral T-cell lymphomas: a study from the Swedish Lymphoma Registry. Blood. 2014;124(10):1570–7.
9. Schmitz N, Trümper L, Ziepert M, Nickelsen M, Ho AD, Metzner B, et al. Treatment and prognosis of mature T-cell and NK-cell lymphoma: an analysis of patients with T-cell lymphoma treated in studies of the German High-Grade Non-Hodgkin Lymphoma Study Group. Blood. 2010;116(18):3418–25.
10. Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst. 1993;85(5):365–76.
11. Cocks K, King MT, Velikova G, Fayers PM, Brown JM. Quality, interpretation and presentation of European Organisation for Research and Treatment of Cancer quality of life questionnaire core 30 data in randomised controlled trials. Eur J Cancer. 2008;44(13):1793–8.
12. Osoba D, Rodrigues G, Myles J, Zee B, Pater J. Interpreting the significance of changes in health-related quality-of-life scores. J Clin Oncol. 1998;16(1):139–44.
13. Cocks K, King MT, Velikova G, de Castro G, Martyn St-James M, Fayers PM, et al. Evidence-based guidelines for interpreting change scores for the European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30. Eur J Cancer. 2012;48(11):1713–21.
14. Horwitz S, O'Connor OA, Pro B, Illidge T, Fanale M, Advani R, et al. Brentuximab vedotin with chemotherapy for CD30-positive peripheral T-cell lymphoma (ECHELON-2): a global, double-blind, randomised, phase 3 trial. Lancet. 2019;393(10168):229–40.

10 Sammensætning af fagudvalg og kontaktinformation til Medicinrådet

Medicinrådets fagudvalg vedrørende 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

11 Versionslog

Version	Dato	Ændring
1.0	8. juli 2020	Godkendt af Medicinrådet.