Medicinrådet

Bilag til Medicinrådets anbefaling vedrørende mogamulizumab til behandling af mycosis fungoides og Sézarys syndrom

Vers. 1.0

Bilagsoversigt

1. Medicinrådets sundhedsøkonomiske afrapportering vedr. mogamulizumab, version 1.0
2. Forhandlingsnotat fra Amgros vedr. mogamulizumab
3. Høringssvar fra ansøger, inkl. efterfølgende dialog vedr. den sundhedsøkonomiske afrapportering
4. Medicinrådets vurdering vedr. mogamulizumab til behandling af voksne patienter med mycosis fungoides eller Sézarys syndrom, der har fået mindst to tidligere systemiske behandlinger, version 1.0
5. Ansøgers endelige ansøgning
6. Ansøgers tekniske dokument til den sundhedsøkonomiske ansøgning
7. Medicinrådets protokol for vurdering vedr. mogamulizumab til behandling af voksne patienter med mycosis fungoides eller Sézarys syndrom, der har fået mindst to tidligere systemiske behandlinger, version 1.0

Medicinrådet

Medicinrådets sundheds-økonomiske afrapportering

Mogamulizumab

Mycosis fungoides eller Sézarys syndrom

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

Den sundhedsøkonomiske analyse indeholder Medicinrådets vurdering af de inkrementelle omkostninger pr. patient og budgetkonsekvenserne ved anbefaling. 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.

Den sundhedsøkonomiske analyse er udarbejdet efter Metodevejledning for omkostningsanalyse af nye lægemidler og indikationsudvidelser i hospitalssektoren.

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1. Begreber og forkortelser

AIP	Apotekernes indkøbspris
DKK	Danske kroner
DRG	Diagnose Relaterede Grupper
EMA	European Medicines Agency
HR	Hazard ratio
KM	Kaplan-Meier
KTCL	Kutane T-cellelymfomer
MF	Mycosis fungoides
OS	Samlet overlevelse
PD	Progredieret sygdom
PFS	Progressionsfri overlevelse
SAIP	Sygehusapotekernes indkøbspris
SS	Sézarys syndrom
TOT	*Time on treatment*
TTNT	*Time to next treatment*

2. Konklusion

Inkrementelle omkostninger og budgetkonsekvenser
I det scenarie, Medicinrådet mener er mest sandsynligt, er de inkrementelle omkostninger for mogamulizumab ca. [redacted] DKK pr. patient sammenlignet med alemtuzumab. Når analysen er udført med apotekets indkøbspriser (AIP), er de inkrementelle omkostninger til sammenligning ca. -124.000 DKK pr. patient.

De inkrementelle omkostninger er næsten udelukkende drevet af lægemiddelomkostninger, [redacted] Analysens resultat er dog meget følsomt overfor ændringer i de antagelser som har ligget til grund for beregningen af lægemiddelomkostningerne. En følsomhedsanalyse viser, at behandling med mogamulizumab [redacted] sammenlignet med behandling med alemtuzumab, hvis spild ikke medregnes. Derved [redacted] de inkrementelle omkostninger til ca. [redacted] DKK. Anvendes brentuximab vedotin som komparator, viser analysen, at [redacted] forbundet med mogamulizumab. Her vil de inkrementelle omkostninger være ca. [redacted] DKK.

Analysen bygger på et meget usikkert datagrundlag, da der ikke er data tilgængeligt fra en relevant population for de targeterede behandlinger (alemtuzumab og brentuximab vedotin), som kan anvendes i den sundhedsøkonomiske analyse. Derfor er effekterne antaget at være ens for mogamulizumab og alle targeterede behandlinger. Dog viser følsomhedsanalyser, at denne usikkerhed ikke har væsentlig betydning for analysens resultat.

Medicinrådet vurderer, at budgetkonsekvenserne for regionerne ved anbefaling af mogamulizumab som mulig standardbehandling vil være ca. [redacted] DKK i år 5. Når analysen er udført med AIP, er budgetkonsekvenserne ca. -0,8 mio. DKK i år 5.

3. Introduktion

Formålet med analysen er at estimere de gennemsnitlige inkrementelle omkostninger pr. patient og de samlede budgetkonsekvenser for regionerne ved anbefaling af mogamulizumab som mulig standardbehandling på danske hospitaler til voksne patienter med mycosis fungoides (MF) eller Sézarys syndrom (SS).

Analysen er udarbejdet, fordi Medicinrådet har modtaget en endelig ansøgning fra Kyowa Kirin. Vi modtog ansøgningen den 12. november 2020.

3.1 Patientpopulation

MF er den hyppigste form af alle kutane T-cellelymfomer (KTCL). KTCL er en heterogen gruppe af sjældne non-Hodgkin lymfomer, hvor MF udgør omkring 50-60 % af alle KTCL. SS er den næstmest almindelige form for KTCL og udgør ca. 3-5 % af alle KTCL. MF viser sig i form af erythematøse patches, plaques og sjældnere tumorer i huden og er almin-

deligvis langsomt progredierende. SS er, sammenlignet med MF, en mere aggressiv leukæmisk variant, der primært adskiller sig fra MF ved tilstedeværelsen af høje niveauer af cirkulerende atypiske T-celler (Sézary-celler). Ved SS har patienten omfattende erythem og svær kløe [1].

Prognosen for MF er stadieafhængig. Stadie IA og IB har en god prognose (medianoverlevelse > 6 år). Omtrent 25 % af patienterne med stadie IA eller IB oplever med tiden progression til mere avancerede sygdomsstadier. Stadie IIB og III har en medianoverlevelse på 4-6 år, mens stadie IV har en medianoverlevelse på mindre end 4 år. Hos patienter med SS er det sværere at inducere remissioner, og disse patienter har derfor oftest en kortere forventet overlevelse. Den mediane overlevelse for patienter med SS er ca. 3 år, og ca. 25 % er i live efter 5 år [1].

I Danmark lever ca. 400-500 patienter med behandlingskrævende KTCL (lokal såvel som systemisk behandling) [1]. Fagudvalget vurderer, at der er omkring 24 MF-patienter og 12 SS-patienter, der er kandidater til mogamulizumab (prævalens), og at der vil være omkring 14 nye MF-patienter og 5 nye SS-patienter om året, som er kandidater til mogamulizumab.

Yderligere information om sygdomsområdet kan findes i Medicinrådets vurderingsrapport.

3.1.1 Komparator

Medicinrådet har defineret targeterede behandlinger (brentuximab vedotin, alemtuzumab, pembrolizumab og romidepsin) og kemoterapi (højdosis methotrexat, doxorubicin og gemcitabin) som komparatorer til mogamulizumab. Medicinrådet har vurderet den kliniske værdi af mogamulizumab på baggrund af følgende kliniske spørgsmål:

Klinisk spørgsmål 1:

Hvilken værdi har mogamulizumab sammenlignet med nuværende behandling for patienter med mycosis fungoides eller Sézarys syndrom, der har fået mindst to tidligere systemiske behandlinger?

4. Vurdering af den sundhedsøkonomiske analyse

I sin ansøgning har ansøger indsendt en sundhedsøkonomisk analyse, der består af en omkostningsanalyse og en budgetkonsekvensanalyse. I omkostningsanalysen estimeres de inkrementelle omkostninger pr. patient for mogamulizumab sammenlignet med hhv. targeterede behandlinger og kemoterapi. Medicinrådet vurderer nedenfor den sundhedsøkonomiske analyse, som ansøger har indsendt.

4.1 Antagelser og forudsætninger for model

Ansøger har indsendt en analyse for den samlede population af både MF- og SS-patienter. Sammenligningen mellem mogamulizumab og targeterede behandlinger er lavet på baggrund af data fra MAVORIC-studiet [2], et fase III-, multinationalt, open-label-forsøg, der sammenligner mogamulizumab med vorinostat (randomiseret 1:1) hos 372 voksne patienter. Patienterne havde enten MF (n = 204) eller SS (n = 168), bekræftet ved histologi, og havde modtaget mindst én tidligere systemisk behandling. Der findes ikke tilgængeligt data, som kan anvendes i en sundhedsøkonomisk analyse til at modellere effekten af de targeterede behandlinger for de specificerede patientpopulationer. Ansøger antager derfor, at data for mogamulizumab fra MAVORIC-studiet kan benyttes som proxy for behandling med samtlige af de targeterede behandlinger, som Medicinrådet har valgt som komparatorer. Det indebærer, at progressionsfri overlevelse (PFS), samlet overlevelse (OS) og bivirkningsprofiler i modellen er ens for mogamulizumab og alle de targeterede behandlinger. Dermed antager ansøger, at hazard ratio (HR) for PFS = 1,0 og OS = 1,0, når mogamulizumab sammenlignes med alle targeterede behandlinger. Behandlingslængden er også antaget at være ens på nær for alemtuzumab, hvor behandlingslængden er begrænset til maksimalt 12 uger.

I sammenligningen mellem mogamulizumab og kemoterapierne (højdosis methotrexat, doxorubicin og gemcitabin) benytter ansøger data fra MAVORIC-studiet til beregning af omkostningerne for mogamulizumab [2]. Ansøger havde indledningsvist anvendt data for vorinostat fra MAVORIC-studiet som proxy for kemoterapi, men som beskrevet i vurderingsrapporten vurderer fagudvalget, at vorinostat ikke er en passende proxy for de kemoterapiregimer, der er valgt som komparatorer. Der findes ikke tilgængeligt forløbsdata, som kan benyttes i den sundhedsøkonomiske analyse til at modellere effekten af kemoterapi for den specificerede patientpopulation. I et forsøg på at approksimere omkostningerne forbundet med behandling med kemoterapi benytter ansøger derfor EORTC-studiet, et enkeltarmet fase II-studie, der undersøger behandling med intravenøs pegyleret liposomal doxorubicin hos 49 patienter med stadie IIB, IVA eller IVB avanceret MF [3]. Studiet anvendes til at estimere den gennemsnitlige behandlingslængde for doxorubicin. Denne behandlingslængde benyttes som proxy for behandlingslængden for alle inkluderede kemoterapiregimer i analysen.

Medicinrådets vurdering af antagelser og forudsætninger for modellen
Fagudvalget vurderer på baggrund af den kliniske data, at man i dansk klinisk praksis kun vil anvende mogamulizumab til MF- eller SS-patienter med blodinvolvering. Dette drejer sig om samtlige SS-patienter, da blodinvolvering er en del af diagnosen, og et fåtal af MF-patienter. Fagudvalgets vurdering bygger på, at den kliniske data indikerer, at effekten af mogamulizumab kan være dårligere end de behandlingsalternativer, der er til MF-patienter uden blodinvolvering. Ifølge fagudvalget behandler man hovedsageligt patienter med blodinvolvering med alemtuzumab, men i få tilfælde, hvis patienten er CD30-positiv, anvendes brentuximab vedotin. Medicinrådet vælger derfor at basere hovedanalysen på data fra patienter med blodinvolvering og anvender alemtuzumab som komparator i hovedanalysen. Medicinrådet præsenterer en følsomhedsanalyse, hvor brentuximab vedotin anvendes som komparator. Dermed ekskluderes pembrolizumab, romidepsin og kemoterapi som komparatorer i Medicinrådets hovedanalyse.

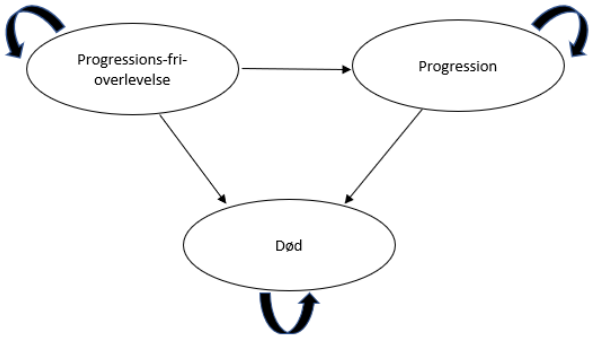
I ansøgers model er sammenligningen mellem mogamulizumab og de targeterede behandlinger baseret på antagelsen om, at PFS, OS, behandlingslængde og bivirkningsprofiler er ens for alle behandlinger (på nær behandlingslængden for alemtuzumab). Fagudvalget vurderer, at der i dansk klinisk praksis kan forventes at være forskel på PFS, OS, behandlingslængde og bivirkningsprofiler mellem de targeterede behandlinger, men det er usikkert, hvilken forskel der forventes. På grund af den yderst begrænsede datatilgængelighed accepterer fagudvalget antagelsen om ens effekt mellem mogamulizumab og de targeterede behandlinger, men gør opmærksom på at dette bidrager til stor usikkerhed i analysen. Medicinrådet præsenterer derfor følsomhedsanalyser, hvor HR for PFS og OS varieres samtidig for at belyse usikkerheden forbundet med effekten af mogamulizumab sammenlignet med targeterede behandlinger. Yderligere præsenteres følsomhedsanalyser, hvor behandlingslængden for mogamulizumab varieres med +/-10 %.

På baggrund af fagudvalgets vurdering baserer Medicinrådet egen hovedanalyse på data for patienter med blodinvolvering og anvender alemtuzumab som komparator. Medicinrådet præsenterer en følsomhedsanalyse, hvor brentuximab vedotin anvendes som komparator. Medicinrådet accepterer anvendelsen af data for mogamulizumab som proxy for targeteret behandling, men understreger at dette bidrager med usikkerhed i analysen. Medicinrådet præsenterer derfor følsomhedsanalyser, hvor HR for PFS, OS og behandlingslængden for mogamulizumab varieres.

4.1.1 Modelbeskrivelse

Ansøger benytter forskellige metoder til at beregne omkostningerne forbundet med behandling med mogamulizumab, targeterede behandlinger og kemoterapi. Dette skyldes begrænset tilgængelig data. Eftersom fagudvalget vurderer, at kemoterapi ikke er en relevant komparator til patienter med blodinvolvering, præsenteres ansøgers antagelser vedr. kemoterapi ikke i denne rapport.

Til sammenligningen mellem mogamulizumab og de targeterede behandlinger har ansøger indleveret en *partitioned survival model*, der estimerer omkostninger baseret på den tid, patienten er i de tre stadier: PFS, progression og død. Data stammer fra MAVORIC-studiet [2]. Figur 1 viser modellens struktur. En cyklus i modellen er en uge. Ansøgers analyse er ikke delt op i MF- og SS-patienter, men modellen indeholder muligheden for at dele analysen op.



Figur 1. Beskrivelse af modelstrukturen i omkostningsanalysen

Ansøger anvender Kaplan-Meier (KM)-data for PFS og OS til beregning af tiden, patienterne befinder sig i stadierne. KM-data er benyttet til at ekstrapolere data for PFS og OS for den samlede patientpopulation. Til ekstrapolering af PFS er [redacted] (rød kurve) anvendt som parametrisk funktion, se Figur 2, og til ekstrapolering af OS er [redacted] (rød kurve) anvendt, se Figur 3.

[redacted]

Figur 2. Ansøgers PFS-kurve for mogamulizumab for den samlede population (MF og SS)

[redacted]

Figur 3. Ansøgers OS-kurve for mogamulizumab for den samlede population (MF og SS)

Ansøger benytter KM-data for *time on treatment* (TOT) fra MAVORIC-studiet [2] til beregning af behandlingslængden. Alle patienter afsluttede behandling med mogamulizumab i studiet, og det var derfor ikke er nødvendigt at ekstrapolere behandlingslængden yderligere. Den samlede patientpopulation i MAVORIC-studiet modtog i gennemsnit behandling i ca. [redacted].

Ansøger antager, at romidepsin ikke anvendes i dansk klinisk praksis, da lægemidlet ikke har fået markedsføringstilladelse af Det Europæiske Lægemiddelagentur (EMA). Ansøger antager, at behandling med de resterende targeterede behandlinger er ligeligt fordelt mellem brentuximab vedotin (33,3 %), alemtuzumab (33,3 %) og pembrolizumab (33,3 %).

Medicinrådets vurdering af ansøgers modelantagelser

Som tidligere beskrevet vælger Medicinrådet at basere egen hovedanalyse på data for patienter med blodinvolvering, og Medicinrådet vælger derfor at revurdere valgene af parametriske funktioner til ekstrapolering af PFS og OS for begge populationer. Medicinrådet har vurderet det statistiske fit, mens fagudvalget har vurderet den kliniske plausibilitet af de ekstrapolerede PFS- og OS-kurver. Til ekstrapolering af PFS er [redacted] valgt (rød kurve), og til OS er [redacted] (rød kurve) valgt som parametrisk funktion, se Figur 4 og Figur 5. Disse er valgt, da fagudvalget vurderer, at de andre parametriske funktioner er for optimistiske ift. sygdommes alvorlighed.

[redacted]

Figur 4: PFS-kurve for mogamulizumab for patienter med blodinvolvering

Figur 5: OS-kurve for mogamulizumab for patienter med blodinvolvering

Tabel 1 viser den gennemsnitlige behandlingsvarighed, PFS og OS for patienter med blodinvolvering ved behandling med mogamulizumab. Eftersom data for mogamulizumab anvendes som proxy for targeterede behandlinger, har alemtuzumab samme gennemsnitlige PFS og OS i analysen. Alemtuzumab administreres i maksimalt 12 uger, og denne begrænsning er anvendt i analysen.

Tabel 1. Gennemsnitlig behandlingsvarighed, PFS og OS for mogamulizumab for patienter med blodinvolvering

Behandling	Behandlingsvarighed	PFS	OS
Mogamulizumab	[redacted]	[redacted]	[redacted]

Medicinrådet accepterer ansøger antagelser vedr. modelantagelser, men baserer egen hovedanalyse på data for patienter med blodinvolvering og anvender kun alemtuzumab som komparator i hovedanalysen.

4.1.2 Analyseperspektiv

I overensstemmelse med metoderne har ansøger valgt et begrænset samfundsperspektiv til sin analyse. Analysen har en tidshorisont på 30 år, da ansøger vurderer, at alle patienter vil være døde efter 30 år. Omkostninger, der ligger efter det første år, er diskonteret med en rate på 4 % pr. år.

Medicinrådets vurdering af ansøgers analyseperspektiv

Fagudvalget vurderer, at det er usandsynligt, at MF- eller SS-patienter med blodinvolvering er i live efter 30 år.

[redacted], og Medicinrådet anvender i stedet en tidshorisont på 20 år. Denne ændring har ingen betydning for analysens resultat. Det er kun omkostninger forbundet med den aktive behandling, der er forskellig mellem mogamulizumab og de targeterede behandlinger, da de omkostninger, der ikke er relateret til den aktive behandling, antages at være ens for mogamulizumab og de targeterede behandlinger.

Siden ansøger har indsendt sin sundhedsøkonomiske analyse, har Finansministeriet ændret den samfundsøkonomiske diskonteringsrente. Medicinrådet ændrer derfor analysen, så omkostningerne diskonteres med en rate på 3,5 % efter år 1.

Medicinrådet ændrer tidshorisonten til 20 år og ændrer diskonteringsrenten til 3,5 % efter år 1.

4.2 Omkostninger

I det følgende er ansøgers antagelser for omkostningerne i den sundhedsøkonomiske analyse af mogamulizumab sammenlignet med alemtuzumab og brentuximab vedotin præsenteret. Ansøger har inkluderet lægemiddelomkostninger, hospitalsomkostninger, bivirkningsomkostninger, patientomkostninger og omkostninger til efterfølgende behandling. Omkostningerne er cyklusbestemt, hvilket betyder, at omkostningerne påregnes for hver cyklus, patienten befinder sig i stadiet.

4.2.1 Lægemiddelomkostninger

Ansøger har jf. *Metodevejledning for omkostningsanalyser af nye lægemidler og indikationer i hospitalssektoren* estimeret lægemiddelomkostninger på baggrund af apotekets indkøbspris (AIP). Ansøger anvender gennemsnitsvægten på 76,8 kg og det gennemsnitlige kropsfladeareal (BSA) på 1,91 m^2 fra MAVORIC-studiet til beregning af lægemiddelomkostningerne. Følgende doseringer er anvendt:

- Mogamulizumab: 1 mg/kg på dag 1, 8, 15 og 22 i den første 28-dages cyklus, efterfulgt af infusioner hver 2. uge på dag 1 og 15 i hver af de efterfølgende 28-dages cykler
- Alemtuzumab: 10 mg, 3 gange om ugen i 12 uger
- Brentuximab vedotin: 1,8 mg/kg hver 3. uge

Ansøger antager, at alle lægemidler har en relativ dosisintensitet på [redacted] %. Dette baserer ansøger på MAVORIC-studiet. Spild er medregnet for alle komparatorer i analysen. Til beregning af lægemiddelomkostningerne for mogamulizumab antager ansøger, at der minimum skal være brug for 10 % af et hætteglas, før der tages et nyt hætteglas i brug. Dermed antages det, at hvis en patient har brug for < 10 % af et nyt hætteglas med mogamulizumab, vil det ikke blive taget i brug.

Medicinrådets vurdering af ansøgers antagelser vedr. lægemiddelomkostninger
Medicinrådet har udskiftet AIP med sygehusapotekets indkøbspris (SAIP), se Tabel 2.

Tabel 2. Anvendte lægemiddelpriser, SAIP, (maj 2021)

Lægemiddel	Styrke	Pakningsstørrelse	Pris [DKK]	Kilde
Mogamulizumab	4 mg/ml	5 ml	[redacted]	Amgros
Alemtuzumab	12 mg/1,2 ml	1 stk.	[redacted]	Amgros
Brentuximab vedotin	50 mg	1 stk.	[redacted]	Amgros

Ifølge fagudvalget giver man i dansk praksis patienterne den nøjagtige dosis mogamulizumab, som patienterne skal have ift. deres vægt. Dermed er det ikke dansk praksis, at en patient skal have brug for minimum 10 % af et hætteglas med mogamulizumab, før hætteglasset tages i brug. Dog kan fagudvalget ikke afvise, at der kan være tilfælde fremover, hvor den behandlende læge vil beslutte ikke at tage et ekstra hætteglas i brug, hvis patienten kun mangler få mg for at opnå den optimale dosis. Da dette endnu ikke har været aktuelt, vælger Medicinrådet at basere hovedanalysen på antagelsen, at patienterne modtager den nøjagtige dosis ift. deres vægt, og at der potentielt kan være spild i forbindelse med administrationen af mogamulizumab. Dette har nogen betydning for analysens resultat.

Da der er usikkerhed omkring, hvordan man i dansk praksis vil administrere lægemidlerne, således at spildet mindskes, repræsenterer hovedanalysen potentielt en overestimering af lægemiddelomkostningerne forbundet med både mogamulizumab og de targeterede behandlinger. Medicinrådet præsenterer derfor en følsomhedsanalyse, hvor det antages, at der ikke vil være spild forbundet med administrationen af hverken mogamulizumab eller targeterede behandlinger.

Da der er usikkerhed omkring RDI for de targeterede behandlinger, ændrer Medicinrådet RDI til at være 100 % for alle lægemidler i analysen. Dette har ingen betydning for hovedanalysens resultat.

Medicinrådet accepterer ikke antagelsen om, at en patient skal have behov for minimum 10 % af et hætteglas med mogamulizumab, før hætteglasset tages i brug og vælger i Medicinrådets hovedanalyse at antage, at patienterne får den nøjagtige dosis ift. deres vægt og inkluderer spild. Medicinrådet præsenterer en følsomhedsanalyse, hvor det antages, at der ikke er noget spild forbundet med nogen af lægemidlerne. Medicinrådet sætter RDI til 100 % for alle lægemidler i analysen.

4.2.2 Hospitalsomkostninger

Administrationsomkostninger

Alle lægemidler administreres ved intravenøs infusion, og ansøger anvender DRG-taksten 3.235 DKK (DRG 2020: 17MA98) for omkostninger til administration på hospitalet ved et ambulant besøg.

Medicinrådets vurdering af ansøgers antagelser vedr. administrationsomkostninger
Medicinrådet accepterer ansøgers tilgang til estimering af administrationsomkostninger. Ansøger indsendte sin ansøgning i 2020 og anvender derfor DRG-takster for 2020. Medicinrådet opdaterer DRG-takster til takster for 2021. Dette har minimal betydning for analysens resultat.

Medicinrådet accepterer ansøgers tilgang vedr. administrationsomkostninger.

Monitoreringsomkostning

På baggrund af kliniske eksperters vurdering antager ansøger, at MF- og SS-patienter skal monitoreres på samme måde. Det antages, at alle patienter starter behandling efter en PET/CT-scanning ved første konsultation, og herefter har patienten en månedlig konsultation (20 min.) med en læge og månedlige blodtællinger og prøver på leverfunktion, urin og elektrolytter samt lactatdehydrogenase. Frekvensen af monitorering gælder, både når patienterne er progressionsfri, og efter de er progredieret.

Medicinrådets vurdering af ansøgers antagelser vedr. monitoreringsomkostninger
Da der ikke antages at være forskel på monitoreringen af patienter, afhængig af hvilken behandling de modtager, har omkostningerne ikke betydning for analysens resultat, og Medicinrådet ekskluderer derfor omkostningerne i egen analyse.

Medicinrådet ekskluderer monitoreringsomkostninger fra Medicinrådets hovedanalyse.

Bivirkningsomkostninger

Ansøger har inkluderet bivirkningsomkostninger for uønskede hændelser af grad 3 og 4 og anvender DRG-takster til beregning af bivirkningsomkostningerne. Til sammenligningen med targeterede behandlinger antager ansøger, at alle targeterede behandlinger vil have den samme bivirkningsprofil som mogamulizumab i MAVORIC-studiet.

Medicinrådets vurdering af ansøgers antagelser vedr. bivirkningsomkostninger
Fagudvalget vurderer, at der sandsynligvis vil være forskel på bivirkningerne mellem mogamulizumab og de targeterede behandlinger, men det er usikkert, hvilken forskel der forventes. I mangel på data accepteres ansøgers tilgang til estimering af bivirkningsomkostninger. Da bivirkningerne antages at være ens, ekskluderer Medicinrådet bivirkningsomkostninger i egen analyse.

Medicinrådet accepterer ansøgers tilgang vedr. bivirkningsomkostninger, men ekskluderer omkostningerne fra Medicinrådets hovedanalyse.

4.2.3 Efterfølgende behandling

Ansøger har inkluderet omkostninger til behandling efter patienterne er progredieret. De inkluderede omkostninger til efterfølgende behandling dækker over lægemiddelomkostninger, administrationsomkostninger og patientomkostninger. Hvis patienten har modtaget targeteret behandling, vil den efterfølgende behandling både kunne bestå af enten kemoterapi eller anden targeteret behandling. Tabel 3 viser ansøgers antagede fordeling mellem de efterfølgende behandlinger på baggrund af, hvilken behandling patienten modtog inden progression.

Tabel 3. Ansøgers estimat for fordeling af efterfølgende behandling

Efterfølgende behandling	Fordeling [%]
Højdosis methotrexat	22,2
Doxorubicin	22,2
Gemcitabin	22,2
Brentuximab vedotin	11,1
Alemtuzumab	11,1
Pembrolizumab	11,1

Ansøger antager, at behandlingslængden for efterfølgende behandling med alle targeterede behandlinger og mogamulizumab svarer til *time to next treatment* (TTNT), som blev estimeret for mogamulizumab i MAVORIC-studiet [2]. Det vil sige tiden, indtil patienten modtog en ny form for behandling efter mogamulizumab i MAVORIC-studiet. Dermed benyttes TTNT som proxy for behandlingslængden for den efterfølgende behandling for de targeterede behandlinger. Behandlingslængden antages at være ca. 28 uger ved behandling med targeterede behandlinger eller mogamulizumab. Dette gælder dog ikke for alemtuzumab, som har en maksimal behandlingslængde på 12 uger. Ved behandling med kemoterapi antager ansøger, at behandlingslængden svarer til TTNT, som blev estimeret for vorinostat i MAVORIC-studiet. Det vil sige tiden, indtil patienten modtog en ny form for behandling, efter vorinostat i MAVORIC-studiet. Den gennemsnitlige behandlingslængde ved behandling med kemoterapi antages at være ca. 17 uger [2].

Medicinrådets vurdering af ansøgers antagelser vedr. efterfølgende behandling
Medicinrådet vurderer, at der er store usikkerheder forbundet med estimeringen af omkostningerne til efterfølgende behandling. Fagudvalget vurderer, at der er usikkerhed omkring den reelle fordeling mellem behandlingerne, efter patienterne har modtaget mogamulizumab eller anden targeteret behandling. Yderligere er der usikkerhed forbundet med estimeringen af behandlingslængden for de efterfølgende behandlinger. For targeterede behandlinger antager ansøger, at den gennemsnitlige behandlingslængde svarer til TTNT efter behandling med mogamulizumab i MAVORIC. For kemoterapi antager ansøger, at den gennemsnitlige behandlingslængde svarer til TTNT efter behandling med vorinostat i MAVORIC. Medicinrådet vurderer, at denne antagelse har været nødvendige for at kunne beregne en omkostning til efterfølgende behandling, men at der ikke er evidens for, at de gennemsnitlige behandlingslængder for efterfølgende behandling vil afspejle dansk klinisk praksis. Medicinrådet ekskluderer derfor omkostninger til efterfølgende behandling i egen hovedanalyse.

Medicinrådet accepterer ikke ansøgers tilgang vedr. efterfølgende behandling og ekskluderer omkostningerne i Medicinrådets hovedanalyse.

4.2.4 Patientomkostninger

Patientomkostninger er estimeret på baggrund af lægemiddeladministrationsbesøg på hospitalet og tid til monitorering. Ansøger benytter enhedsomkostningen på 179 DKK pr. time for patienttid, og for transportomkostninger er der antaget en omkostning på 3,52 DKK pr. km med en gennemsnitlig distance på 28 km til hospitalet. Antagelserne for patienttid gælder både før og efter progression.

Medicinrådets vurdering af ansøgers antagelser vedr. patientomkostninger
Medicinrådet accepterer ansøgers estimerede patienttid, som kan ses i Tabel 4.

Tabel 4. Ansøgers estimat af patienttid til lægemiddeladministration og monitorering

	Patienttid
IV-administration	2 timer
Lægekonsultation	20 min.
Blodtælling	20 min.
Parakliniske tests	20 min.

Medicinrådet accepterer ansøgers tilgang vedr. patientomkostninger.

4.3 Følsomhedsanalyser

Formålet med følsomhedsanalyserne er at undersøge usikkerhederne i analysen og de økonomiske konsekvenser af at justere de parametre, der er usikre.

Ansøger har udarbejdet en række følsomhedsanalyser, hvor effekten af variation i forskellige parametre undersøges. Ansøger har udført følsomhedsanalyser, som er præsenteret i Tabel 5.

Tabel 5. Følsomhedsanalyser og beskrivelse

Følsomhedsanalyse	Beskrivelse
Tidshorisont	10 år / 20 år
Lægemiddelomkostninger	Spild medregnes ikke
Variation i parametriske funktioner	Resultater beregnes, når parametriske funktioner for PFS, OS, TOT og TTNT varieres

Medicinrådets vurdering af ansøgers valg af følsomhedsanalyser
Medicinrådet præsenterer ikke følsomhedsanalysen, hvor tidshorisonten sættes til 10 år og 20 år, da Medicinrådet har ændret tidshorisonten til 20 år i egen hovedanalyse. Som tidligere beskrevet har denne ændring ingen betydning for analysens resultat, da om-

kostninger, der ikke er relateret til den aktive behandling, antages at være ens for mogamulizumab og targeteret behandling. Medicinrådet præsenterer følsomhedsanalysen, hvor spild ikke medregnes i lægemiddelomkostningerne.

Medicinrådet vælger ikke at præsentere ansøgers følsomhedsanalyser, hvor de parametriske funktioner varieres, da Medicinrådet har udført egen analyse for MF- og SS-patienter med blodinvolvering. De parametriske funktioner, der var mest klinisk plausible og havde gode statistiske fit, er valgt til ekstrapolering af PFS og OS. Valg af parametrisk funktion har derudover lille betydning for analysens resultat.

Medicinrådet vælger at præsentere en følsomhedsanalyse, hvor effekten af behandlingen med mogamulizumab ikke antages at være den samme som for de targeterede behandlinger. Ansøger antager, at effekten af mogamulizumab svarer til behandling med alle targeterede behandlinger. Dermed antages det, at HR for PFS = 1,0 og HR for OS = 1,0. Denne antagelse bygger ikke på data, og der er dermed stor usikkerhed forbundet med antagelsen. Medicinrådet vælger derfor at præsentere en følsomhedsanalyse, hvor HR varieres. HR for PFS og OS sættes til 0,9 i én følsomhedsanalyse og 1,1 i en anden analyse. Yderligere præsenterer Medicinrådet en følsomhedsanalyse, hvor behandlingslængden for mogamulizumab reduceres med 10 % og øges med 10 %.

Fagudvalget vurderer, at patienter med blodinvolvering oftest behandles med alemtuzumab, men at der er patienter, som er CD30-positive, som vil blive behandlet med brentuximab vedotin. Medicinrådet præsenterer derfor en følsomhedsanalyse, hvor brentuximab vedotin anvendes som komparator.

Medicinrådet præsenterer følsomhedsanalyser, hvor spild ikke medregnes i lægemiddelomkostningerne, hvor HR for PFS og OS sættes til hhv. 0,9 og 1,1, og hvor behandlingslængden reduceres og øges med 10 %. Medicinrådet præsenterer derudover en følsomhedsanalyse, hvor brentuximab vedotin anvendes som komparator.

4.4 Opsummering af basisantagelser

I Tabel 6 opsummeres basisantagelserne i henholdsvis ansøgers og Medicinrådets hovedanalyse.

Tabel 6. Basisantagelser for ansøgers og Medicinrådets hovedanalyse

Basisantagelser	Ansøger	Medicinrådet
Tidshorisont	30 år	20 år
Diskonteringsrate	4 %	3,5 %
Dosis for mogamulizumab	1 mg/kg	1 mg/kg
RDI for mogamulizumab og targeteret behandling	[redacted] %	100 %

Basisantagelser	Ansøger	Medicinrådet
Population	Samlet analyse for MF- og SS-patienter	MF- og SS-patienter med blodinvolvering
Komparator	Targeteret behandling: Brentuximab vedotin: 33,3 % Alemtuzumab: 33,3 % Pembrolizumab: 33,3 % Kemoterapi: Højdosis methotrexat: 0 % Doxorubicin: 100 % Gemcitabin: 0 %	Alemtuzumab 100 %
Parametriske funktioner for PFS for mogamulizumab	[redacted]	[redacted]
Parametriske funktioner for OS for mogamulizumab	[redacted]	[redacted]
Inkludering af spild	Ja	Ja
Efterfølgende behandling	Inkluderes	Ekskluderes
Andre vigtige antagelser	Samme effekt, behandlingslængde og bivirkningsprofil mellem mogamulizumab og de targeterede behandlinger (på nær behandlingslængden for alemtuzumab)	Samme effekt, behandlingslængde og bivirkningsprofil mellem mogamulizumab og de targeterede behandlinger (på nær behandlingslængden for alemtuzumab)

5. Resultater

5.1 Resultatet af Medicinrådets hovedanalyse

Medicinrådets hovedanalyse bygger på samme antagelser som ansøgers hovedanalyse med undtagelse af de ændringer, der er beskrevet igennem denne afrapportering.

Den gennemsnitlige inkrementelle omkostning pr. patient bliver ca. [redacted] DKK i Medicinrådets hovedanalyse. Er analysen udført med AIP, bliver den inkrementelle omkostning pr. patient ca. -124.000 DKK.

Resultaterne fra Medicinrådets hovedanalyse er præsenteret i Tabel 7.

Tabel 7. Resultatet af Medicinrådets hovedanalyse, DKK, diskonterede tal

	Mogamulizumab	Alemtuzumab	Inkrementelle omkostninger
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Hospitalsomkostninger	122.979	131.526	-8.547
Patientomkostninger	30.010	31.228	-1.218
Totale omkostninger	[redacted]	[redacted]	[redacted]

5.1.1 Resultatet af Medicinrådets følsomhedsanalyser

Ved samme antagelser som i Medicinrådets hovedanalyse for meromkostninger har Medicinrådet udført en følsomhedsanalyse på parametrene listet i Tabel 8.

Tabel 8. Resultatet af Medicinrådets følsomhedsanalyse sammenlignet med hovedanalysen, DKK

Scenarie	Inkrementelle omkostninger
Resultatet af hovedanalysen	[redacted]
Spild medregnes ikke	[redacted]
HR for PFS og OS varieres: 0,9 1,1	[redacted]
Behandlingslængden for mogamulizumab varieres: +10 % -10 %	[redacted]
Brentuximab vedotin anvendes som komparator	[redacted]

6. Budgetkonsekvenser

Budgetkonsekvenserne pr. år er baseret på antagelsen om, at mogamulizumab vil blive anbefalet som mulig standardbehandling. Man ser derfor på to scenarier:

- Mogamulizumab bliver anbefalet som mulig standardbehandling af Medicinrådet til indikationen, som denne analyse omhandler.
- Mogamulizumab bliver ikke anbefalet som mulig standardbehandling.

Budgetkonsekvenserne udgør forskellen mellem de samlede omkostninger i de to scenarier.

6.1 Ansøgers estimat af patientantal og markedsandel

Ansøger antager, jf. protokollen, at 15 patienter kandiderer til behandling med mogamulizumab i den samlede patientpopulation (MF- og SS-patienter), og at der årligt vil være 5 nye patienter, der kandiderer til behandlingen. Såfremt mogamulizumab anbefales som standardbehandling, antager ansøger, at mogamulizumab vil have et markedsoptag på 40 % i år 1, hvilket stiger til 100 % i år 5.

Medicinrådets vurdering af ansøgers budgetkonsekvensanalyse
Som nævnt i afsnit 4.1 vurderer fagudvalget, at man kun vil anvende mogamulizumab til MF- og SS-patienter med blodinvolvering i dansk praksis. Medicinrådet vælger derfor kun at inkludere patienter med blodinvolvering i budgetkonsekvensanalysen. Fagudvalget vurderer, at dette drejer sig om 15 patienter, og at der årligt vil være 7 nye patienter. Fagudvalget anslår, at markedsoptaget for mogamulizumab vil være på 50 % i år 1, 75 % i år 2 og 100 % i år 3 og fremadrettet, se Tabel 9.

Tabel 9. Medicinrådets estimat af antal nye patienter pr. år

	År 1	År 2	År 3	År 4	År 5
			Anbefales		
Mogamulizumab	8	5	7	7	7
Alemtuzumab	7	2	0	0	0
			Anbefales ikke		
Mogamulizumab	0	0	0	0	0
Alemtuzumab	15	7	7	7	7

Medicinrådet har udført sin egen budgetkonsekvensanalyse, der kun inkluderer patienter med blodinvolvering, og markedsoptaget er ændret jf. fagudvalgets vurdering.

6.2 Medicinrådets budgetkonsekvensanalyse

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

- Analysen inkluderer kun patienter med blodinvolvering
- Markedsoptaget er ændret jf. fagudvalgets vurdering

Medicinrådet estimerer, at anvendelse af mogamulizumab vil resultere i budgetkonsekvenser på ca. [redacted] DKK i år 5. Resultatet er præsenteret i Tabel 10.

Er analysen udført med AIP, bliver budgetkonsekvenserne ca. -0,8 mio. DKK i år 5.

Tabel 10. Medicinrådets analyse af totale budgetkonsekvenser, mio. DKK, ikkediskonterede 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 mogamulizumab er forbundet med inkrementelle omkostninger på ca. [redacted] DKK sammenlignet med behandling med alemtuzumab. Medicinrådets hovedanalyse viser derfor, at der er tale om [redacted] omkostninger på ca. [redacted] DKK ved behandling med mogamulizumab sammenlignet med alemtuzumab. De inkrementelle omkostninger er næsten udelukkende drevet af lægemiddelomkostninger, [redacted]. Følsomhedsanalyser viser dog, at resultatet er meget følsomt overfor ændringer i de antagelser, der har ligget til grund for beregningen i lægemiddelomkostningerne.

Det har således stor betydning for analysens resultat, om spild medregnes i lægemiddelomkostningerne. Hvis det antages, at der ikke er noget lægemiddelspild ved behandling med mogamulizumab og alemtuzumab, [redacted] de inkrementelle omkostninger fra ca. [redacted] DKK til ca. [redacted] DKK, og behandling med mogamulizumab er i dette scenarie [redacted] end behandling med alemtuzumab. Medicinrådet vurderer derfor, at der ikke med sikkerhed vil være tale om [redacted] ved anvendelse af mogamulizumab sammenlignet med alemtuzumab, og at behandling med mogamulizumab i nogle tilfælde kan være [redacted] end behandling med alemtuzumab.

Medicinrådet har udført en scenarieanalyse, hvor brentuximab vedotin anvendes som komparator, da et lille antal patienter, der er CD30-positive, ifølge fagudvalget vil blive behandlet med brentuximab vedotin i stedet for alemtuzumab. Anvendes brentuximab vedotin som komparator bliver de inkrementelle omkostninger ca. [redacted] DKK, og der er dermed [redacted] ved behandling med mogamulizumab sammenlignet med brentuximab vedotin. Dette skyldes, at lægemiddelomkostningerne for brentuximab vedotin samlet set er [redacted] end lægemiddelomkostningerne ved behandling med mogamulizumab.

Sammenligningen af mogamulizumab med targeteret behandling (alemtuzumab og brentuximab vedotin) bygger på et meget usikkert datagrundlag. Der er ikke data tilgængeligt for de targeterede behandlinger, som kan anvendes i den sundheds-økonomiske analyse, og derfor er effekterne antaget at være ens. Analysens resultat afhænger derfor næsten udelukkende af lægemiddelpriserne. Fagudvalget vurderer, at

der i praksis sandsynligvis vil være forskel på PFS, OS, behandlingslængder og bivirkninger mellem de targeterede behandlinger, men kan ikke vurdere, om de anvendte antagelser potentielt overestimerer eller underestimerer effekten af mogamulizumab. På trods af store usikkerheder omkring effekten af alemtuzumab, viser følsomhedsanalyserne, hvor HR for PFS og OS varieres, at mindre forskelle i effekt har minimal betydning for analysens resultat. Derimod har behandlingslængden for mogamulizumab nogen betydning, hvilket skyldes, at det er lægemiddelomkostningerne, der driver analysens resultat.

8. Referencer

1. Medicinrådet. Medicinrådets protokol for vurdering af mogamulizumab til behandling af voksne med mycosis fungoides eller Sézarys syndrom , der har fået mindst to tidligere systemiske behandlinger. 2020;0–17.

2. Kim YH, Bagot M, Pinter-Brown L, Rook AH, Porcu P, Horwitz SM, et al. Mogamulizumab versus vorinostat in previously treated cutaneous T-cell lymphoma (MAVORIC): an international, open-label, randomised, controlled phase 3 trial. Lancet Oncol. 2018;19(9):1192–204.

3. Dummer R, Quaglino P, Becker JC, Hasan B, Karrasch M, Whittaker S, et al. Prospective international multicenter phase II trial of intravenous pegylated liposomal doxorubicin monochemotherapy in patients with stage IIB, IVA, or IVB advanced mycosis fungoides: Final results from EORTC 21012. J Clin Oncol. 2012;30(33):4091–7.

9. Versionslog

Versionslog		
Version	**Dato**	**Ændring**
1.0	17. juni 2021	Godkendt af Medicinrådet.

10. Bilag

10.1 Resultatet af ansøgers hovedanalyse

I ansøgers hovedanalyse bliver den inkrementelle omkostning pr. patient ca. [redacted] DKK over en tidshorisont på 30 år. Resultaterne fra ansøgers hovedanalyse er præsenteret i Tabel 11.

Tabel 11. Resultatet af ansøgers hovedanalyse, DKK, diskonterede tal

	Mogamulizumab	Targeterede behandlinger	Inkrementelle omkostninger
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Hospitalsomkostninger	[redacted]	[redacted]	[redacted]
Patientomkostninger	[redacted]	[redacted]	[redacted]
Totale omkostninger	[redacted]	[redacted]	[redacted]

10.2 Resultatet af ansøgers budgetkonsekvensanalyse

Ansøger har inkluderet de samme omkostninger i budgetkonsekvensanalysen, som er inkluderet i omkostningsanalysen, dog uden patientomkostninger.

Med de ovenstående antagelser om patientantal og markedsandel estimerer ansøger, at anvendelse af mogamulizumab vil resultere i budgetkonsekvenser på ca. [redacted] DKK i år 5. Ansøgers estimat af budgetkonsekvenserne fremgår af Tabel 12.

Tabel 12. Ansøgers hovedanalyse for totale budgetkonsekvenser, mio. DKK, ikkediskonterede 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]

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Forhandlingsnotat

Dato for behandling i Medicinrådet	26-05-2021
Leverandør	Kyowa Kirin
Lægemiddel	Mogamulizumab (poteligeo)
Ansøgt indikation	Behandling af voksne med mycosis fungoides eller Sézarys syndrom, der har fået mindst to tidligere systemiske behandlinger.

Forhandlingsresultat

Amgros har opnået følgende pris på mogamulizumab.

Lægemiddel	Styrke/dosis	Pakningsstørrelse	AIP	Forhandlet SAIP	Rabatprocent ift. AIP
Mogamulizumab	4 mg/ml	5 ml.	11.494,46	[redacted]	[redacted]

Amgros har indgået en aftale med Kyowa Kirin som løber til 31.8.2022. Aftalen indeholder en simpel flad rabat skitseret i tabellen ovenfor.

Vurdering af forhandlingsresultatet

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

- Virksomheden lægger i forhandlingen vægt på, at en godkendelse af mogamulizumab som standardbehandling vil bidrage med en besparelse i forhold til dansk klinisk praksis.

[redacted]

Konklusion

Det er Amgros vurdering at vi på nuværende tidspunkt ikke har opnået den bedst mulige pris på mogamulizumab.

[redacted]

Status fra andre lande

Sagen er under behandling i Norge[1] og Sverige[2].

[1] Mogamulizumab (Poteligeo) (nyemetoder.no)

[2] https://www.tlv.se/lakemedel/kliniklakemedelsuppdraget/pagaende-halsoekonomiska-bedomningar.html

Response from Kyowa Kirin regarding the draft assessment reports for mogamulizumab (Poteligeo®) for mycosis fungoides (MF) and Sézary syndrome (SS)

Date: 22-Jan-2021

Dear Danish Medicine Council.

Kyowa Kirin appreciates the opportunity to comment on the Danish Medicines Council's draft clinical and health economic assessment reports of mogamulizumab for the treatment of MF and SS cutaneous T-cell lymphoma (CTCL).

Summary

We have several comments for the draft documents that we consider critical to address. These are summarized in the following bullets:

- There is inconsistency between the comparators included in the protocol and the final assessment report.
- There is a lack of conclusion around the value of mogamulizumab compared to the relevant comparators.
- Incorrect list prices are used for alemtuzumab. This is not in line with the methods guideline.
- The compassionate use price (0 DKK) has been used for alemtuzumab in the base-case. This is highly questionable and without precedence.
- The comparison for the SS population is not supported by evidence and is highly biased in favour of alemtuzumab.

Each of these points are elaborated in the following.

Inconsistency between protocol and assessment report

The protocol defines pembrolizumab as a comparator to mogamulizumab and was defined as an "equal treatment alternative" to brentuximab, alemtuzumab and romidepsin by the expert committee.

In the health economic (HE) assessment report, the expert committee states that the primary comparators are brentuximab or alemtuzumab. The expert committee states that only a small proportion of patient will receive pembrolizumab and the DMC secretariat has therefore excluded pembrolizumab from the HE assessment. However, the two expert clinicians in CTCL [redacted] and [redacted]) consulted on by Kyowa Kirin to validate the model assumptions mentioned pembrolizumab as a relevant treatment alternative for MF patients. We have difficulty understanding the rationale behind the deviation from the DMC protocol to remove pembrolizumab as a comparator. What specifically has made the expert committee change on this matter from the protocol criteria until this draft evaluation?

Clinical assessment "Udkast Medicinrådets vurdering vedr. mogamulizumab til mycosis fungoides eller Sézarys syndrom-vers. 1.0.pdf"

Lack of conclusion

The expert committee's assessment is lacking comprehensive clinical judgements and conclusions on the value of mogamulizumab compared to the comparators. As the expert committee has decided to conduct a

narrative comparison, this is considered highly reliant on a clinical judgment on the value, and considerations whether mogamulizumab is considered a better, an equal, or a less optimal treatment alternative than the comparators in each population. The lack of value-based statements on the value makes it impossible to conduct a meaningful negotiation with Amgros. In situations where the intervention cannot be categorized, standard practice is to reflect on the expected value to make it relevant for decision making.

Overall survival (OS)

The clinical expert committee concludes that there is no reason to distinguish between the effectiveness of mogamulizumab and chemotherapy in the treatment of MF patients, due to the poor evidence available for off-label use of chemotherapy. In the assessment of OS, the expert committee states that it does not consider it relevant to compare the data from MAVORIC with the available data from the chemotherapy studies due to differences in the study populations. Given the lack of comparable studies, it would be valuable to have the expert committee reflect and discuss the results of mogamulizumab compared to their experience with chemotherapy in Danish clinical practice. Based on a naïve comparison of OS estimates provided in table 5 in the assessment report, mogamulizumab provides much better efficacy for OS than the chemotherapy regimens.

The expert committee states, that due to differences in the study populations it is not considered relevant to compare OS estimates. However, with the protocol stating OS as the critical outcome for the assessment, it would be highly valuable for the expert committees to examine to which extent they consider that the differences in OS can be purely driven by differences in study populations given the large differences OS estimates. It is important to note that difficulty of the comparison is derived from a lack of data for the chemotherapy regimens, since these are used off-label.

Progression-free survival (PFS)

In the assessment of mogamulizumab versus chemotherapy the expert committee states, that there do appear to be an improved median PFS for mogamulizumab compared to chemotherapy in the overall population, but also notes that PFS increases in higher disease stages and blood involvement. It is important to stress the differences in the definition of PFS in MAVORIC and the chemotherapy studies. In MAVORIC, a global composite response criteria was used in the assessment of PFS, that accounted for all potentially affected disease compartments (skin, blood, lymph nodes and viscera). The global composite response criteria is perceived as the most appropriate way to assess response and PFS of CTCL in clinical trials MAVORIC is the only study to date to have this primary endpoint across all 4 compartments for this rare disease. Whereas the elder chemotherapy trials used skin only response criteria in the assessment. This difference in PFS response criteria makes it challenging to compare the results in a direct naïve comparison, as the global composite response criteria reduces the percentage of patients reaching the response criteria compared to the skin only criteria.

Again, given the lack of clinical data for chemotherapy, it would be expected of the expert committee to use their clinical experience to reflect on the effectiveness of chemotherapy in patients with higher disease stages and blood involvement, and compare this to the mogamulizumab data.

Despite the observed improvement in PFS for patients with higher disease stages and blood involvement, this is not reflected in the overall conclusion for the comparison with chemotherapy in MF patients, which states: "*there is no reason to distinguish between the effect of mogamulizumab and chemotherapy in the treatment of MF patients*". Has the clinical expert committee considered the differences in PFS for the

more severe disease stages in their overall assessment and how does it relate to the Danish clinical experience with chemotherapy?

For the comparison with targeted therapy, the clinical expert committee concludes that PFS is longer for brentuximab vedotin than mogamulizumab based on a naive comparison of the PFS estimates. As previously described in the assessment report there are several differences in the study populations that potentially could impact the comparison e.g. CD-30 status, distribution of disease stages, blood involvement and different timepoints for the assessment of PFS. These have not been considered or described in the assessment report. Extrapolating the brentuximab vedotin outcome from a 100% CD-30+ patient population to reflect all MF patients is truly overstating the effect of brentuximab vedotin.

The overall conclusion of the clinical expert committee is that mogamulizumab is less effective than brentuximab vedotin. We find this conclusion highly questionable as it is based on a naive comparison which does not account for the major differences in study populations (CD-30 status, no SS patients in ALCANZA, disease stages and different definitions of PFS) nor that brentuximab vedotin is only indicated for CD30-positive patients and not all CTCL patients.

Other remarks

None of the included comparators, except brentuximab vedotin, are licenced for this indication (i.e. used off-label). As they are used off-label no pivotal trials have been developed and/or have published evidence for these interventions efficacy and safety in CTCL. Therefore, it is essential for the assessment report that the expert committee provides a clinical judgment on the value, and considerations on whether mogamulizumab is considered a better, an equal, or a less optimal treatment alternative than the comparators based on their clinical experience with the respective treatments.

Mogamulizumab has been investigated in the largest clinical trial programme within MF and SS patients, has regulatory approval and therefore provides more solid evidence for the efficacy and safety than any of the cohort studies available for the chemotherapies and most targeted therapies.

We find it hard to understand the rationale behind challenging the evidence base for mogamulizumab to such a high extent, when the challenge in this assessment is the lack of relevant evidence for the comparator treatments.

Health economic assessment "Udkast Medicinrådets sundhedsøkonomisk afrapportering vedr. mogamulizumab-vers. 1.0.pdf"

Use of AIP

There is inconsistency between the methods used in the preliminary assessment report and the methods guidelines set out by the DMC. It is stated that the drug costs must be reported by using AIP in the method guidelines for cost analyses of new drugs and indication by the DMC[1]. In the report, the results on page 26, it is stated that the incremental result (mogamulizumab vs. targeted therapy in MF) with AIP is approx. 322.000 DKK, however, this is not with the AIP of alemtuzumab. The results presented on AIP-level are incorrect, since an AIP of 0 DKK is used for alemtuzumab. This is not the official AIP of alemtuzumab, which is 45.699,31 DKK, as can be found on www.medicinpriser.dk. The same applies to the remaining reported results, which should be reported with AIP.

[1] 2.6.1 https://medicinraadet.dk/media/jgbiri0j/metodevejledning-for-omkostningsanalyser-af-nye-l%C3%A6gemidler-og-indikationer-i-hospitalssektoren-vers-1-6_adlegacy.pdf

Use of compassionate use program prices

The DMC secretariat has applied an assumption of zero drug acquisition costs for alemtuzumab. This assumption has been made based on the inputs from the expert committee, which stated that alemtuzumab is being given to the departments free of charge in a compassionate use programme. The assumption applied would imply that the DMC expects that the manufacturer of alemtuzumab will continue to provide the drug free of charge for the foreseeable future. This is a highly uncertain assumption that drives the entire outcome of the analysis. In addition, using compassionate use/clinical trial prices in the health economic assessment is highly questionable and without precedence. To comply with the standard DMC methods, we request the Amgros-price (AMKP/SAIP) of alemtuzumab is used for the base-case assessment.

SS-population comparison

We fail to understand the rationale behind the DMC base-case comparison for this population. Here mogamulizumab followed by alemtuzumab is compared with alemtuzumab followed by mogamulizumab, basically a comparison of the costs of the same therapies in reverse sequence. How can mogamulizumab be justified as a relevant comparator when the intervention is mogamulizumab? The methods guideline states that the relevant comparator should current standard treatment. Surely, mogamulizumab cannot be current standard treatment in Denmark, as this would deem this assessment redundant. In addition, there is no data available for the efficacy of alemtuzumab in these patients, so the validity of this comparison is highly questionable. The unfavourable safety profile of alemtuzumab is not accounted for in this comparison that assumes a 100% compliance and full treatment duration of alemtuzumab in 4th treatment line. This is highly unrealistic.

When setting the cost of alemtuzumab to 0 DKK, the comparison in the SS-population is basically a comparison between the cost of mogamulizumab in the 3rd treatment line with the cost of mogamulizumab in the 4th treatment line. This will imply that mogamulizumab will be used in the 4th treatment line if it not recommended as standard treatment in 3rd line. Is this correct?

Also, the approach adopted by the DMC in this comparison is highly questionable and likely biased. In the model, the patients who receive alemtuzumab in the subsequent treatment line (4th line) is assumed to receive the full 12-week regimen without any discontinuation. These costs are applied as a one-off cost. However, in the alemtuzumab treatment arm (3rd line), the drug costs are estimated using the time-to-treatment discontinuation curve of mogamulizumab and therefore a shorter treatment duration and associated lower treatment cost is estimated for this treatment line. This assumption is not supported by evidence, and generally treatment durations shorten the more previous lines of treatment the patient has received. The opposite is assumed for patient who receive mogamulizumab in the subsequent treatment line (4th line) following alemtuzumab. Here, the treatment duration of mogamulizumab is assumed significantly shorter than the 3rd line treatment duration of mogamulizumab. We fail to understand the rationale behind this, as these assumptions are highly biased in favour of alemtuzumab.

To generate a fair comparison between mogamulizumab and alemtuzumab in SS patients, subsequent treatment lines should be excluded from this comparison. This would allow to make a direct comparison of mogamulizumab versus alemtuzumab in the 3rd line treatment and would eliminate the uncertainty around treatment durations in the subsequent treatment lines.

We hope our comments will be considered by the DMC and expert committee to better clarify the draft assessment for treating MF and SS patients with mogamulizumab. These CTCL diseases today have minimal licensed and effective therapies that positively improve patient lives in Denmark.

[redacted]
[redacted]
Kyowa Kirin Ltd.

M: [redacted]
E: [redacted]

3rd February 2021

Dear Danish Medicine Council,

Response from Kyowa Kirin regarding the assessment reports for mogamulizumab (Poteligeo®) for mycosis fungoides (MF) and Sézary syndrome (SS)

Kyowa Kirin appreciates the opportunity to comment on the Danish Medicines Council's clinical and health economic assessment reports of mogamulizumab for the treatment of MF and SS cutaneous T-cell lymphoma (CTCL). As in our previous response, we would like to address some critical issues in the assessment of mogamulizumab.

In general, the assessment report lacks conclusions from the expert committee regarding the value of mogamulizumab, based on their clinical experience in CTCL. As the DMC assessment resulted in an uncategorised clinical benefit of mogamulizumab, it is of importance that the assessment report includes a discussion and conclusions on the value of the intervention, in comparison to the comparators. The lack of information of the expected value of mogamulizumab makes it very challenging to enter a negotiation with Amgros and is also not in line with standard practice and method guidance.

According to the protocol by the DMC, pembrolizumab is a comparator to mogamulizumab and was defined as an "equal treatment alternative" to brentuximab, alemtuzumab and romidepsin by the expert committee. However, in the health economic assessment report by the DMC, pembrolizumab is not included as a comparator and only brentuximab and alemtuzumab are considered comparators to mogamulizumab. Thus, there is an inconsistency between the protocol and the assessment report by the DMC. The rationale for removing pembrolizumab is stated to be the small number of patients treated with pembrolizumab, which is in contrast to the statements from two leading CTCL clinical experts.

Most of the comparators to mogamulizumab do not have a regulatory EMA license for CTCL and are used off-label for CTCL patients. As a result, there is limited or no data on the efficacy and tolerance of these products in CTCL and comparisons between studies are therefore difficult. The clinical expert committee concludes in the assessment report that there is no reason to distinguish between the

effectiveness of mogamulizumab and chemotherapy in the treatment of MF patients, due to the poor evidence available for off-label use of chemotherapy. Further, due to differences in the study populations it is not considered relevant to compare overall survival (OS) estimates, although the protocol states that OS is a critical outcome for the assessment. Given the lack of data for the comparators, it would be valuable to have the expert committee reflect and discuss the efficacy and tolerability of mogamulizumab compared to their experience with chemotherapy in Danish clinical practice.

In the assessment of progression-free survival (PFS) for mogamulizumab compared to chemotherapy, the assessment report states that there seem to be an improved median PFS for mogamulizumab compared to chemotherapy in the overall population, specifically in patients with more severe disease and blood involvement in both MF and SS. However, this is not reflected in the overall conclusion for the comparison with chemotherapy in MF patients, which states: "there is no reason to distinguish between the effect of mogamulizumab and chemotherapy in the treatment of MF patients". Again, given the lack of clinical data for chemotherapy, it would be expected of the expert committee to use their clinical experience to reflect on the effectiveness of chemotherapy in patients with higher disease stages and blood involvement, and compare this to the mogamulizumab data.

For the comparison of PFS for mogamulizumab compared to targeted therapy, the clinical expert committee concludes that mogmulizumab is less effective than brentuximab vedotin based on a naïve comparison of PFS estimates between mogamulizumab and brentuximab vedotin. As the clinical expert committee previously stated regarding comparisons between studies, there are several differences in the study populations that potentially could impact the comparison, such as CD-30 status, distribution of disease stages, blood involvement and different timepoints for assessment of PFS, which has not been considered in the assessment. Extrapolating the brentuximab vedotin outcome from a 100% CD-30+ patient population to reflect all MF patients is truly overstating the effect of brentuximab vedotin and is also not according to the approved label of brentuximab vedotin.

As mentioned above, none of the included comparators except brentuximab vedotin, are licensed for this indication and there is no published evidence for these interventions available. Mogamulizumab has been investigated in the largest clinical trial programme within MF and SS patients, has regulatory approval and therefore provides more solid evidence for the efficacy and safety than any of the cohort studies available for the chemotherapies and most targeted therapies. Given the lack of available evidence for the comparator treatments, it is essential that the expert committee provides a conclusion on the value and whether mogamulizumab is considered a better, an equal, or a less optimal treatment alternative than the comparators based on their clinical experience with the respective treatments.

In the method guidelines for cost analyses of new drugs and indication issued by the DMC, it is clearly stated that the drug costs must be reported by using AIP. However, in the health economic report, the AIP of the comparator alemtuzumab is not used. Instead the DMC secretariat applies the cost of 0 DKK in the comparison of costs for mogamulizumab and alemtuzumab. This assumption has been made based on input from the expert committee, which stated that alemtuzumab is given to the departments free of charge in a compassionate use programme. Further, this assumption implies that the DMC expects the manufacturer of alemtuzumab to continue providing the drug free of charge for the foreseeable future. These assumptions are without precedence and not in compliance with DMC

methods and we ask the DMC to apply the Amgros price (AMKP/SAIP) in the base case analysis, in accordance with their guidelines.

We hope our comments will be considered by the DMC and expert committee in the assessment for treating MF and SS patients with mogamulizumab. These CTCL diseases today have minimal licensed and effective therapies that positively improve patient lives in Denmark.

We look forward to hearing back on items raised in this letter and thank yourselves for the time to do so.

Kind regards

[redacted]

[redacted]

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The Danish Medicines Council
Attn.: [redacted]
Dampfærgevej 27-29, 3.
2100 Copenhagen

17 March 2021

Dear [redacted],

Follow-up: Meeting with the DMC on 12 March 2021

We thank you for the opportunity to elaborate and discuss why the zero-cost approach regarding alemtuzumab as the comparator used in the health economic model is not relevant to our medicinal product. We agreed that we would follow up with a short letter setting out the factual and legal rationales for this position. Below, please find our brief outline.

As you will appreciate, the general rule set out in Article 6(1) Directive 2001/83/EC (the "Directive") is that a human medical product should be issued by an authority either via the central regulatory procedure or de-centralized via a member states authority. The medicinal product shall be used as authorized, e.g., within the authorized indication. However, some exceptions do exist, for example if a non-licensed product is used in a clinical trial in the country or is subject to an early access regime before its medical license/approval.

In the EU, early access schemes may be run either as compassionate use (Article 83 of Regulation 726/2004 (the "Regulation")) or named patient use (Article 5(1) of the Directive).

Based on information from the Danish Medicines Agency ("Lægemiddelstyrelsen") only the later exists in Denmark - named patient use schemes. The named patient use may either be under a general permission ("generel udleveringstilladelse") or an individual permission ("enkelt udleveringstilladelse").

In discussions with the Danish Medicines Agency only the individual permission route ("enkelt udlevering-stilladelse") exists for alemtuzumab in Denmark. There is no documentation showing that alemtuzumab has obtained any general permission under a named patient use either in the past or present within EU.

Under the named patient use (Article 5(1) of the Directive), physicians may request for the supply of a medicine for one specific individual patient under the responsibility of the physician.

> *"A Member State may, in accordance with legislation in force and to fulfil special needs, exclude from the provisions of this Directive medicinal products supplied in response to a bona fide unsolicited order, formulated in accordance with the specifications of an authorised health-care professional and for use by an individual patient under his direct personal responsibility."*

Obviously, the HCP requesting and obtaining the permission retains full responsibility and hence liability for any prescribing decisions.

We agree that story of MabCampath (alemtuzumab) is special as the marketing authorization holder, Genzyme Europe B.V. (acquired by Sanofi), decided to withdraw the indication for B-CLL (B-cell Chronic lymphocytic leukemia) at the same time as Genzyme was granted a new indication for MS (Multiple Sclerosis).

According to our information, Genzyme Corporation (a Sanofi company) has agreed to donate US labelled MabCampath products to the Sanofi Foundation and make MabCampath available to eligible patients through the MabCampath Access Program. The physicians need to sign that they will follow the laws in the country.

Please find the Patient Access and Monitoring document enclosed. A short highlight of the content in the document:

- To request supply of the product under the MabCampath Access Program, a Patient Access and Monitoring Form must be read, completed, and signed by the prescribing physician and where necessary the hospital/pharmacist.

- Informed consent must be obtained from the patient before any treatment is started. The patient should be supplied with all relevant product information, informed that the product is not licensed, and is supplied to meet a special need identified by the patient's physician with the approval, as appropriate, of the national regulatory authority.

- Genzyme (Sanofi) and Clinigen will comply with pharmacovigilance legislation which includes the collection and reporting of adverse drug reactions (ADR's) and other relevant safety information to all relevant regulatory authorities (where required). To comply with this legislation: The prescribing physician must follow all applicable national pharmacovigilance regulations.

- In every patient specific case, the physician shall sign this statement: **"*I have requested, in accordance with the laws in my country, supply of the Product for the above mentioned patient who cannot be adequately treated with medications approved or available through clinical trials in my country at this time. I will only prescribe and use this supply for the above-mentioned patient.*"**

- The physician shall confirm that the patient has a condition for which conventional therapies have failed, are unsuitable or are unavailable either as marketed products or through enrolment into clinical trials. Patients not meeting these criteria may not be eligible for access to MabCampath.

- Supply of the Product is subject to applicable national regulatory requirements, which may include direct approval from your national regulatory authority, and compliance with the requirements described in the "Declaration by the Prescribing Physician".

In contact with the Danish Medicines Agency, it is stated that alemtuzumab named patient use has followed Danish regulation (the Danish Medicines Act, Section 29) and that physicians have requested named patient usage ("enkelt udleveringstilladelse") for treatment for CTCL. The Danish Medicines Agency has approved alemtuzumab according to the named patient scheme to treat CTCL patients, but this was prior to the marketing of Poteligeo in October 2020 and no new applications have been granted after that date as this would be a violation of the Danish Medicines Act, Section 29.

Conclusion:
As highlighted above and during our meeting, the Danish Medicines Agency has made it clear that named patient use program for MabCampath (alemtuzumab) has followed Danish regulation (the Danish Medicines Act, Section 29) and stopped for CTCL patients immediately after Poteligeo being commercially available in Denmark.

Consequently, the zero-cost used in the health economic model is not relevant as physicians are not allowed to request alemtuzumab under any named patient scheme. This follows from the clear and specific rules of the Genzyme MabCampath patient access program and the Danish Medicines Act, Section 29. The physician shall prescribe alemtuzumab according to the normal pathway to grant access for patients and according to the commercial price in Denmark, which shall be used in the health economic model.

We appreciate that we are all eager to move forward with the process at the Danish Medicines Council and we encourage you to swiftly revert to us if you have any queries and to discuss internally with you colleagues in the legal and regulatory department.

As discussed on 12 March 2021, we have attached the link available in the public domain to the Patient Access and Monitoring form (make it available to eligible patients through the MabCampath Access Program: https://hematologiegroningen.nl/protocollen/download/?id=4306).

Looking forward to receiving an updated health economic model that we may all use as a common basis for the next steps.

Kind regards

[redacted]
[redacted]
Kyowa Kirin Ltd.
M: [redacted]
E: [redacted]

Medicinrådet

Medicinrådets vurdering vedrørende mogamulizumab til behandling af voksne patienter med mycosis fungoides eller Sézarys syndrom, der har fået mindst to tidligere systemiske behandlinger

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.

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Godkendelsesdato	27. januar 2021
Dokumentnummer	100868
Versionsnummer	1.0

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1. Medicinrådets konklusion

MF-patienter – sammenligning med kemoterapi

Medicinrådet finder, at den samlede værdi af mogamulizumab sammenlignet med kemoterapi ikke kan kategoriseres i henhold til Medicinrådets metoder. Der er tale om evidens af meget lav kvalitet, hvor dårligt datagrundlag og forskelle i studiepopulationerne vanskeliggør en sammenligning. Rådet vurderer på baggrund af fagudvalgets kliniske vurdering, at der ikke er anledning til at skelne mellem effekten af mogamulizumab og kemoterapi.

MF-patienter – sammenligning med targeteret behandling

Medicinrådet finder, at den samlede værdi af mogamulizumab sammenlignet med targeteret behandling ikke kan kategoriseres i henhold til Medicinrådets metoder. Vurderingen er baseret på evidens af meget lav kvalitet. Baseret på fagudvalgets kliniske vurdering af data for PFS vurderer Rådet, at mogamulizumab muligvis er mindre effektivt end brentuximab vedotin. Datagrundlaget er dog meget usikkert, da data for de øvrige effektmål ikke er sammenligneligt.

SS-patienter – sammenligning med targeteret behandling

Medicinrådet finder, at den samlede værdi af mogamulizumab sammenlignet med targeteret behandling ikke kan kategoriseres i henhold til Medicinrådets metoder. Vurderingen er baseret på evidens af meget lav kvalitet. Datagrundlaget tillader ikke en sammenligning med targeteret behandling, fordi der mangler dokumentation for komparatorerne i en population af SS-patienter. Medicinrådet vurderer, at mogamulizumab er mest effektivt til patienter, hvor der som hos SS-patienter er blodinvolvering, og hvor der i dag er få effektive behandlingsmuligheder.

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

AE: *Adverse event*, uønsket hændelse

CCR4: C-C kemokinreceptor type 4

CI: Konfidensinterval

ECOG: *Eastern Cooperative Oncology Group*

ECP: Ekstrakorporal fotoferese

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

EORTC: *European Organisation for Research and Treatment of Cancer*

EPAR: *European Public Assessment Report*

ESMO: *European Society for Medical Oncology*

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

HDAC: Histondeacetylase

ITT: *Intention to treat*

KTCL: Kutant T-cellelymfom

MF: Mycosis fungoides

OS: Samlet overlevelse

pcALCL Primær kutant anaplastisk storcellet lymfom

PS: *Progressionsfri overlevelse*

PP: *Per Protocol*

PUVA: Psoralen og ultraviolet A-lys

SAE: *Serious Adverse event,* alvorlig uønsket hændelse

SS: Sézarys syndrome

UVB: Ultraviolet B-lys

3. Introduktion

Formålet med Medicinrådets vurdering af mogamulizumab til mycosis fungoides (MF) eller Sézarys syndrom (SS) er at vurdere den værdi, lægemidlet har sammenlignet med dansk standardbehandling.

Vurderingen er udarbejdet, fordi Medicinrådet har modtaget en endelig ansøgning fra Kyowa Kirin Holdings B.V. Medicinrådet modtog ansøgningen den 12. november 2020.

Det kliniske spørgsmål er:

Hvilken værdi har mogamulizumab sammenlignet med nuværende behandling for patienter med mycosis fungoides eller Sézarys syndrom, der har fået mindst to tidligere systemiske behandlinger?

3.1 Mycosis fungoides og Sézarys syndrom

Kutane T-cellelymfomer (KTCL) er en heterogen gruppe af sjældne non-Hodgkin-lymfomer. Mycosis fungoides (MF) er den hyppigste form og udgør omkring 50-60 % af alle KTCL. Sézarys syndrom (SS) er den næstmest almindelige form for KTCL og udgør ca. 3-5 % af alle KTCL [1].

MF viser sig hyppigst i form af erythematøse patches og plaques, i sjældnere tilfælde ved tumorer i huden, og ses meget sjældent med blodinvolvering. Sygdommen er almindeligvis langsomt progredierende [2]. SS er, sammenlignet med MF, en mere aggressiv leukæmisk variant, der primært adskiller sig fra MF ved tilstedeværelsen af høje niveauer af cirkulerende atypiske T-celler (Sézary-celler). Ved SS har patienten omfattende erytem og svær kløe. Patienterne er plaget af deres hudsymptomer, som har stor indflydelse på deres livskvalitet. For både MF og SS gælder, at forandringerne i huden og den medfølgende immunsuppression gør patienterne udsatte for infektioner, der kan udvikle sig til blodforgiftning (sepsis). Ved SS og de mere avancerede stadier af MF er sygdommen dødelig.

MF inddeles efter et tumor-, node-, metastase (TNM)-system i stadier fra I-IV efter International Society for Cutaneous Lymphomas/European Organisation for Research and Treatment of Cancer's reviderede kriterier [3]. Stadieinddelingen omfatter normalt blodprøver, en PET-/CT-skanning og en knoglemarvsundersøgelse. Stadierne er forklaret i Tabel 1.

Tabel 1. Stadieinddeling for MF

Stadie	Beskrivelse af stadie	Udbredelse
IA	Mindre end 10 % af huden er involveret.	Lymfomet er begrænset til huden (patches eller plaque).
IB	10 % eller mere af huden er involveret.	
IIA	Der er patches eller plaques på huden, og lymfeknuderne er forstørrede, men de indeholder ikke unormale lymfomceller.	
IIB	Der er en eller flere forhøjede tumorer i huden. Lymfeknuderne er enten forstørrede eller ikke forstørrede, men indeholder ikke lymfomceller.	
IIIA	Der er få eller ingen lymfomceller i blodbanen (erythrodermisk mycosis fungoides).	80 % eller mere af huden er involveret med erythrodermi (diffus rødme, fortykkelse og eventuelt sprækker i huden), hævelse, kløe og undertiden smerte. Lymfeknuderne kan være forstørrede, men indeholder ikke lymfomceller.
IIIB	Et moderat antal lymfomceller findes i blodbanen.	
IVA	Der er talrige unormale lymfomceller i blodbanen (Sézarys syndrom), eller lymfeknuderne indeholder lymfomceller. Der er lymfom i huden i form af patches, plaques og/eller erythrodermi.	
IVB	Lymfomet er spredt til andre organer.	

3.2 Mogamulizumab

Mogamulizumab er et humaniseret IgG1 kappa-antistof, der selektivt binder sig til C-C kemokinreceptor type 4 (CCR4). Ved at binde til CCR4-antigener på overfladen af T-cellerne induceres en antistofafhængig cellulær cytotoksicitet.

Målet med behandling med mogamulizumab er sygdomskontrol og symptomlindring.

Mogamulizumab blev i 2016 betegnet som orphan drug til følgende tilstand: Behandling af kutant T-cellelymfom.
Mogamulizumab har indikation til voksne patienter med MF eller SS, som har modtaget mindst én tidligere systemisk behandling.

Fagudvalget vurderer, at mogamulizumab vil være et relevant behandlingsalternativ til patienter med fremskreden sygdom (MF, stadie II-IV og SS), der i dansk klinisk praksis har været i behandling med mindst to systemiske behandlinger (fx methotrexat, retinoider og interferon-α) eller har kontraindikation for et eller flere af disse systemiske

behandlinger. Mogamulizumab bør derfor anvendes på linje med de targeterede behandlinger og pathway-inhibitorer, som er beskrevet i afsnit 2.3.

Den anbefalede dosis for mogamulizumab er 1 mg/kg som intravenøs infusion over mindst 60 minutter. Administrationen er ugentlig på dag 1, 8, 15 og 22 i den første 28-dages cyklus, efterfulgt af infusioner hver anden uge på dag 1 og 15 i hver af de efterfølgende 28-dages cykler. Behandlingen fortsættes indtil sygdomsprogression eller uacceptabel toksicitet.

3.3 Nuværende behandling

Behandlingen af kutant T-cellelymfom i Danmark varetages af de dermatologiske afdelinger i samarbejde med hæmatologiske og onkologiske afdelinger. Behandlingen følger internationale guidelines fra ESMO (*European Society for Medical Oncology*) og EORTC (*European Organisation for Research and Treatment of Cancer*) [4,5]. Der er ingen defineret standardbehandling, da behandlingen individualiseres ud fra det kutane lymfoms karakteristika, sygdommens sværhedsgrad, patientens performancestatus, komorbiditeter, tidligere behandlinger, patientens præferencer mv.

Målet med behandlingen er sygdomskontrol og symptomlindring, idet behandlingen, på nær allogen stamcelletransplantation, ikke er kurativ. Først forsøges tumorbyrden nedbragt, hvorefter sygdommen kontrolleres og følges. Den palliative strategi går således ud på at lindre symptomer, forbedre livskvalitet, inducere remissioner, udskyde progression og undgå betydelig behandlingsrelateret toksicitet. Behandlingsforløbene er oftest af længere varighed (år).

I tidlige stadier af MF (IA-IIA) anvendes topikal behandling i form af fx kortikosteroider i kombination med ultraviolet lysbehandling (smalspektret UVB eller 8-Methoxypsoralen + UV-A (PUVA)) eller mustargenpenslinger (kvælstof-sennepsgas).

I senere, mere fremskredne stadier (IIB-IV) af MF anvendes lavdosis elektronvolts helkropsbestråling, lokal strålebehandling mod tumor eller systemisk medicinsk behandling i form af interferon-α, retinoider (fx acitretin og bexaroten) eller lavdosis methotrexat. Til udvalgte patienter kan anvendes knoglemarvstransplantation, som gives med kurativ intention. De forskellige former for systemisk behandling kombineres ofte og anvendes ofte også i kombination med topikale behandlinger og/eller ultraviolet lysbehandling. Behandlingen, der følger efter de første systemiske behandlinger (interferon-α, retinoider, lavdosis methotrexat), planlægges ved multidisciplinær konference med hæmatologisk afdeling, og der anvendes targeterede behandlinger, pathway-inhibitorer eller kemoterapi (fx højdosis methotrexat, gemcitabin eller doxorubicin).

De targeterede behandlinger omfatter brentuximab vedotin (anti CD30), alemtuzumab (anti CD52) og pembrolizumab (PD-1-hæmmer). Pathway-inhibitorer omfatter histone deacetylase (HDAC)-hæmmeren romidepsin. Disse lægemidler betragtes af fagudvalget som ligeværdige behandlingsalternativer til Mogamulizumab. Behandlingsvalget er

individualiseret og guides af patientens markørudtryk på lymfomcellerne. Ingen af de targeterede behandlinger/pathway-hæmmere kan betragtes som standardbehandlinger i Danmark, og kun brentuximab vedotin har indikation til behandling af KTCL, herunder MF/SS. Behandlingen med disse alternativer er derfor afhængig af individuelle ansøgninger til lægemiddelkomitéerne. EMA har tidligere afvist at give markedsføringstilladelse til romidepsin til KTCL. Behandling med pembrolizumab, alemtuzumab og romidepsin er derfor uden for godkendt indikation (off-label).

I dermatologien anvendes off-label-behandling i ganske stort omfang pga. manglende evidens for behandling til givne hudsygdomme.

SS betragtes pr. definition som en systemisk sygdom og kræver derfor systemisk behandling. Ekstrakorporal fotoferese (ECP), enten alene eller i kombination med fx interferon-α og/eller retinoider, elektronvolts helkropsbestråling og PUVA, er foreslået som initiale behandlingsvalg til SS. Som andenlinjebehandling anvendes targeterede behandlinger/pathway-hæmmere som beskrevet ovenfor og sjældnere allogen stamcelletransplantation.

Ofte anvendes systemiske behandlinger i kombination med lokalbehandling med fx PUVA eller potente topikale steroider som supplerende behandling.

4. Metode

Medicinrådets protokol for vurdering af mogamulizumab til behandling af voksne med mycosis fungoides eller Sézarys syndrom, der har fået mindst to tidligere systemiske Behandlinger, 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

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 fra protokollen. I alt 356 publikationer blev screenet baseret på titel og abstract, og 41 publikationer blev screenet baseret på fuldtekstsartikler. Ansøger har udvalgt 6 fuldtekstartikler, som indeholder data fra 5 studier. Tabel 2 indeholder en oversigt over de inkluderede studier.

Tabel 2. Oversigt over inkluderede studier og artikler

Publikationer	Klinisk forsøg	NCT-nummer	Population
Mogamulizumab versus vorinostat in previously treated cutaneous T-cell lymphoma (MAVORIC): an international, open-label, randomised, controlled phase 3 trial [6]	MAVORIC	NCT01728805	MF og SS
Brentuximab vedotin or physician's choice in CD30-positive cutaneous T-cell lymphoma (ALCANZA): an international, open-label, randomised, phase 3, multicentre trial [7]	ALCANZA	NCT01578499	MF og pcALCL
Patient-reported quality of life in patients with relapsed/refractory cutaneous T-cell lymphoma: Results from the randomised phase III ALCANZA study [8]			
Prospective international multicenter phase II trial of intravenous pegylated liposomal doxorubicin monochemotherapy in patients with stage IIB, IVA, or IVB advanced mycosis fungoides: final results from EORTC 21012 [9]	EORTC 21012	NCT00074087	MF
Pegylated liposomal doxorubicin in the treatment of primary cutaneous T-cell lymphomas [10]	Pulini et al.	-	MF, SS og PTCL-U
Phase II evaluation of gemcitabine monotherapy for cutaneous T-cell lymphoma [11]	Duvic et al.	-	MF, SS og pcALCL

MF: Mucosis fungoides, SS: Sézarys syndrom, pcALCL: Primær kutant anaplastisk storcellet lymfom, PTCL-U: Uspecificeret perifært T-cellelymfom.

Ingen af de identificerede studier sammenligner mogamulizumab med de definerede komparatorer (brentuximab vedotin, alemtuzumab, pembrolizumab, romidepsin, højdosis methotrexat, doxorubicin eller gemcitabin) i *head-to-head*-studier. Der er heller ikke identificeret studier, som muliggør en indirekte sammenligning, da der ikke findes en fælles komparator mellem mogamulizumab-studiet og komparatorstudierne. Ansøger har derfor anvendt en narrativ tilgang til de sammenlignende analyser.

5.1.2 Databehandling og analyse

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

På grund af det begrænsede evidensgrundlag har ansøger anvendt en 'basket' tilgang forstået på den måde, at ansøger ikke har valgt én bestemt komparator, men i stedet præsenteret alt tilgængeligt data fra de identificerede studier. Denne fremgangsmåde er brugt for begge sammenligninger, dvs. i sammenligning med kemoterapi og i sammenligning med targeteret behandling.

Gennemgang af studier
MAVORIC-studiet er et fase 3-, multinationalt, open-label-forsøg, der sammenligner mogamulizumab med vorinostat (randomiseret 1:1) hos 372 voksne patienter. Patienterne havde enten MF (n = 204) eller SS (n = 168) bekræftet ved histologi og havde modtaget mindst én tidligere systemisk behandling. Studiet tillod, at patienter krydsede over fra vorinostat til mogamulizumab, idet patienter med sygdomsprogression efter mindst to fulde behandlingscyklusser med vorinostat, eller som ikke var i stand til at tolerere vorinostat på trods af dosisreduktion, overgik til behandling med mogamulizumab (n = 136). Det primære endepunkt er PFS.

ALCANZA er et internationalt, open-label, randomiseret, fase 3-studie. Studiet inkluderede 128 patienter med MF (n = 97) eller pcALCL (n = 31) randomiseret 1:1 til enten brentuximab vedotin eller komparator (peroral methotrexat 5-50 mg ugentligt eller daglig administration af peroral bexaroten 300 mg/m2). Afhængig af baseline-diagnose skulle patienterne have modtaget mindst én forudgående systemisk behandling (MF) eller forudgående strålebehandling eller mindst én forudgående systemisk behandling (pcALCL). Inklusionskriterierne omfattede desuden CD30-positivitet bekræftet ved histologisk undersøgelse. Eksklusionskriterierne var bl.a. samtidig SS-diagnose eller udbredt blodinvolvering (B2-sygdom). Det primære endepunkt er ORR4, som er andelen af patienter, der opnåede en objektiv respons (komplet eller partiel respons), der varede mindst 4 måneder.

EORTC 21012 er en enkelt-armet fase II-undersøgelse af behandling med intravenøs pegyleret liposomal doxorubicin hos 49 patienter med stadie IIB, IVA eller IVB avanceret MF. Patienterne er rekrutteret mellem november 2003 og juli 2009 og skulle have oplevet utilstrækkelig respons eller tilbagefald efter mindst to foregående systemiske behandlinger. Det primære endepunkt er responsrate.X

Pulini et al. er et enkelt-armet fase II-forsøg med pegyleret liposomalt doxorubicin til behandling af patienter med avanceret, tilbagevendende og refraktære kutant t-cellelymfom. Der blev inkluderet 19 patienter rekrutteret fra maj 2002 til maj 2005. Studiets endepunkter var responsrate, OS, PFS og sikkerhed.

Duvic et al. er et prospektivt, enkelt-center-, enkelt-armet fase II-, *open-label*-studie af behandling med gemcitabin. Patienter med stadie IB eller IIA ved baseline skulle have oplevet behandlingssvigt med én tidligere systemisk behandling, mens patienter med

tumorer (T3), erythroderma (T4) eller knoglesygdom kunne inkluderes uafhængigt af dette. 33 patienter (heraf 8 uden for protokol) indgik i studiet. Patienterne er rekrutteret mellem juni 1999 og maj 2003. Studiets endepunkter er responsrate, OS og sikkerhed.

En oversigt over studiekarakteristika og inkluderede effektmål af relevans for denne vurdering findes i Tabel 3.

Tabel 3. Studiekarakteristika

Studie	MAVORIC	ALCANZA	EORTC 21012	Pulini et al.	Duvic et al.
Design	Open-label, randomiseret, fase 3	Open-label, randomiseret, fase 3	Enkelt-arm, fase 2, multicenter	Enkelt-arm, fase 2, multicenter	Enkelt-arm, fase 2, enkelt-center
Antal deltagere	372	128	49	19	33
Population	MF og SS	MF og pcALCL	MF	MF, SS og PTCL-U	MF, SS og pcALCL
Intervention	Mogamulizumab	Brentuximab vedotin	Doxorubicin	Doxorubicin	Gemcitabin
Komparator	Vorinostat	Bexaroten eller lav dosis methotrexat	-	-	-
Opfølgningstid (median, min.-maks.)	17,0 måneder (IQR 11,6 – 26,9)*	22,9 måneder (95 % CI 18,4 – 26,1)	10,6 måneder	22,6 måneder (3,4 – 45,9)	36 måneder
Tilgængeligt data					
Median OS	√	-	-	√	√
Median PFS	√	√	(√)	√	-
Livskvalitet, Skindex-29	√	√	-	-	-
Uønskede hændelser grad ¾ / SAE	√ / √	√ / √	√ / -	√ / -	- / √

*Opfølningtid i publikationen (cut-off 31. december 2016). Ansøgningen indeholder også data fra en længere opfølgningstid (cut-off marts 2019). MF: Mucosis fungoides, SS: Sézarys syndrom, pcALCL: Primær kutant anaplastisk storcellet lymfom, PTCL-U: Uspecificeret perifært T-cellelymfom.

Sammenligning med kemoterapi

På grund af manglende komparativt effektdata for kemoterapi antager ansøger, at effekten af komparatoren i MAVORIC-studiet, vorinostat, er en passende tilnærmelse til effekten af kemoterapi. Ansøger argumenterer med, at PFS-kurverne for vorinostat-

armen i MAVORIC-studiet og for bexaroten-/methotrexat-armen i ALCANZA-studiet har ens forløb.

Fagudvalget er ikke enig i denne antagelse. Dette skyldes studiernes begrænsede sammenlignelighed, og at komparator i ALCANZA-studiet (bexaroten/lav dosis methotrexat) ikke svarer til nogle af de ønskede komparatorer. På grund af de begrænsninger anser fagudvalget en narrativ sammenligning af effektdata fra mogamulizumab-armen i MAVORIC-studiet mod effektdata fra kemoterapistudierne (EORTC, Pulini og Duvic) som den mest relevante fremgangsmåde. Studiernes sammenlignelighed er diskuteret nedenfor.

Sammenligning med targeteret behandling
Af de i protokollen definerede targeterede behandlinger findes der kun data fra ALCANZA-studiet, hvor brentuximab vedotin sammenlignes med bexaroten eller lav dosis methotrexat i en population af patienter med enten MF eller pcALCL. Ansøger fremhæver en række forskelle mellem populationerne i MAVORIC og ALCANZA, som udfordrer sammenligneligheden. Ansøger fremhæver følgende:

- Patienter i ALCANZA-studiet er gennemsnitligt i et mindre avanceret sygdomsstadie.
- ALCANZA-populationen er en selektiv population af CD30+ positive patienter.
- Der er ikke inkluderet SS-patienter eller MF-patienter med udbredt blodinvolvering (B2).
- Der indgår en andel af pcALCL-patienter i ALCANZA-studiet.

Fagudvalget er enig i, at sammenligneligheden mellem de to *intention-to-treat* (ITT)-populationer er begrænset og vanskeliggør en klinisk vurdering af forskellen mellem mogamulizumab og brentuximab vedotin. Sammenligneligheden af studierne er diskuteret yderligere nedenfor. Derudover er der ikke identificeret data, der kan bruges til sammenligning med alemtuzumab eller pembrolizumab.

Sammenlignelighed af de inkluderede studier
Da studiernes ITT-populationer er så forskellige, har fagudvalget fundet det relevant at opdele vurderingen af mogamulizumab efter sygdomstype. For de effektmål, hvor det er muligt, giver det et bedre sammenligningsgrundlag, fordi populationerne bliver mere sammenlignelige. MF- og SS-subpopulationerne var præspecificerede i MAVORIC. Til patienter med MF finder fagudvalget det relevant at sammenligne med både kemoterapi og targeteret behandling. Den eneste targeterede behandling, der er repræsenteret i de inkluderede studier, er brentuximab vedotin. Til patienter med SS finder fagudvalget det kun relevant at sammenligne med targeteret behandling, fordi disse patienter kun i ringe omfang behandles med og har gavn af kemoterapi.

MAVORIC sammenlignet med kemoterapistudier
I MAVORIC er 56 % af patienterne MF-patienter, og ansøger har leveret særskilt baseline karakteristik herfor. Studierne er forskudt i tid, hvilket betyder, at der er forskelle på den kliniske praksis udenom studierne, herunder fx prognose, understøttende behandling, diagnostiske metoder og monitorering af effekt, hvilket bidrager til usikkerhed ved

sammenligningerne på tværs af studierne. Særligt responsvurderinger har ændret sig over den pågældende tidsperiode. EORTC 21012 inkluderer udelukkende patienter med MF, mens Pulini et al. og Duvic et al. inkluderer henholdsvis 16 og 33 % SS-patienter foruden 16 % patienter med PTCL-U (uspecificeret perifært T-cellelymfom) i Pulini et al. og 6 % pcALCL i Duvic et al. Andelene af SS, PTCL-U og pcALCL har betydning for effektestimaterne, og forskellene mellem studierne vanskeliggør en sammenligning, hvorfor EORTC 21012 udgør det bedste sammenligningsgrundlag af de tre studier. EORTC 21012 er samtidig det største og seneste af de tre kemoterapistudier. De fleste patienter i MAVORIC og EORTC 21012 er i ECOG performance status 0 eller 1. Pulini et al. og Duvic et al. rapporterer ikke patienternes ECOG-status. Patienternes ECOG-status bliver først afgørende for behandlingsvalg ved ECOG = 2, så fordelingen af patienter i ECOG 0 og 1 er ikke betydende for vurderingen. Det er ikke angivet, hvor mange tidligere behandlinger patienterne i EORTC 21012 har modtaget, men fagudvalget vurderer, at det ikke påvirker sammenligneligheden af data fra de to studier, idet antallet af tidligere systemiske behandlinger ikke nødvendigvis korrelerer med respons på behandling [12]. Samlet set kan de inkluderede studier anvendes til en sammenligning af mogamulizumab med kemoterapi i MF-patienter, når der tages forbehold for forskelle i studiepopulationer og den kliniske kontekst, herunder praksis på det tidspunkt, studiet er udført.

MAVORIC sammenlignet med ALCANZA (targeteret behandling)

Sammenligningen med targeteret behandling er relevant for både MF- og SS-patienter.

MF-patienter

Studiepopulationen i ALCANZA inkluderer 25 % med pcALCL, hvilket fagudvalget vurderer er af væsentlig betydning for studiernes sammenlignelighed. Patienter med pcALCL er karakteriseret ved en bedre prognose end MF-patienter. Derfor vil effektestimaterne fra ALCANZAs ITT-population sandsynligvis være overestimerede i en sammenligning med en 'ren' MF-population fra MAVORIC. Der er ikke væsentlige forskelle i studiernes fordeling af ECOG-status. Fagudvalget vurderer, at studiernes MF-populationer og fordeling på sygdomsstadier er mere sammenlignelige end studiernes ITT-populationer. Dog bemærker fagudvalget en forskel i fordeling mellem stadierne IVA og IVB. MAVORICs MF-population ser ud til at inkludere en højere andel af patienter med blodinvolvering end ALCANZAs MF-population. Fagudvalget vurderer, at det påvirker sammenligneligheden af effektestimaterne for mogamulizumab og brentuximab vedotin. Den store variation inden for begge studier i antallet af tidligere systemiske behandlinger skal ses som et udtryk for variationen i behandlingspraksis mellem centre, hvilket ikke påvirker sammenligneligheden af effektestimaterne. Samlet set er sammenligningen med targeteret behandling dog alvorligt udfordret af studiernes forskellige populationer. Derfor vurderer fagudvalget, at det kun er meningsfuldt at sammenligne effektestimater fra studiernes MF-populationer.

SS-patienter

ALCANZA, som er det eneste studie med targeteret behandling, inkluderer ikke patienter med SS. Det er derfor ikke muligt at sammenligne effektestimater for mogamulizumab med targeteret behandling (brentuximab vedotin eller andre) hos SS-patienter.

Tabel 4. Baselinekarakteristika pr. relevant studiearm

	MAVORIC ITT	MAVORIC MF-ptt	ALCANZA ITT	EORTC 21012	Pulini et al.	Duvic et al.
Alder (IQR)	64 år (54-73)	[redacted]	62 år (51-70)	59 år (27-84)*	67 år (29-84)*	62 år (22-83)*
Køn % (n), mænd	59 % (109)	[redacted]	52 % (33)	67 % (33)	74 % (14)	58 % (19)
ECOG-status, % (n)						
0	57 % (106)	[redacted]	67 % (43)	43 % (21)	-	-
1	42 % (78)	[redacted]	28 % (18)	53 % (26)	-	-
2	1 % (2)	[redacted]	5 % (3)	4 % (2)	-	-
Sygdomstype, % (n)						
MF	56 % (105)	[redacted]	75 % (48)	100 % (49)	68 % (13)	61 % (20)
SS	44 % (81)	[redacted]	0	0	16 % (3)	33 % (11)
Anden (angiv)	0	[redacted]	pcALCL 25 % (16)	0	PTCL-U 16 % (3)	pcALCL 6 % (2)
Sygdomsstadie, % (n)						
IA-IIA	19 % (36)	[redacted]	31 % (15)	0	21 % (4)	10 % (3)
IIB	17 % (32)	[redacted]	40 % (19)	63 % (31)	26 % (5)	42 % (13)
IIIA-IIIB	12 % (22)	[redacted]	8 % (4)	0	5 % (1)	0
IVA	49 % (92)	[redacted]	4 % (2)	37 % (18)	47 % (9)	23 % (7)
IVB	2 % (4)	[redacted]	15 % (7)			26 % (8)
Antal tidligere behandlinger, median (range)						
Systemisk	3 (2 – 5)#	[redacted]	2 (0 – 11)	-	1 (0 – 4)^	5 (2 – 13)
Topikal	IA	[redacted]	1 (0 – 6)	-	1 (0 – 3)^	-
Tidligere behandlinger, % (n)						
Retinoid	58 % (107)	[redacted]	49 % (31)	-	21 % (4)	-
Interferon	44 % (81)	[redacted]	-	-	42 % (8)	-
Kemoterapi	58 % (108)	[redacted]	71 % (45)	37 % (18)	42 % (8)	-

	MAVORIC ITT	MAVORIC MF-ptt	ALCANZA ITT	EORTC 21012	Pulini et al.	Duvic et al.
HDAC-inhibitor	24 % (45)	[redacted]	21 % (13)	-	-	-
Anden immunterapi	19 % (35)	[redacted]	29 % (18)	6 % (3)	-	-

ITT = Intention-to-treat, *Range, #IQR, ^Beregnet ud fra tabel i publikation, - Ingen information i publikationen/ansøgning

5.1.3 Evidensens kvalitet

Medicinrådet anvender GRADE til at foretage en systematisk og transparent vurdering af kvaliteten af evidensen, når der er direkte sammenligninger mellem intervention og komparator. Da denne vurdering af mogamulizumab er baseret på en narrativ sammenligning, kan GRADE ikke anvendes til at vurdere kvaliteten af evidensen.

Kvaliteten af evidensen, som danner baggrund for vurderingen, er meget lav, når det er naive sammenligninger af studiearme fra forskellige studier. Medicinrådet har anvendt Cochrane risk of bias tool 2.0 til vurdering af risk of bias. Medicinrådet har vurderet det pivotale studie MAVORIC, som udgør evidensgrundlaget for mogamulizumab samt det randomiserede studie ALCANZA, der udgør datagrundlaget for brentuximab vedotin. Da de øvrige studier ikke er randomiserede, er risk of bias ikke vurderet. Medicinrådet vurderer, at MAVORIC samlet set har høj risiko for bias pga. studiets ublindede design og tilladt crossover fra vorinostat-armen til mogamulizumab-armen, hvilket kan påvirke effektforskellene og har betydning for de analyser, der danner grundlag for de rapporterede resultater. For ALCANZA er der forbehold for risiko for bias pga. studiets ublindede design, som særligt påvirker effektmålene *uønskede hændelser* og *livskvalitet*.

Vurdering af risikoen for bias ved de enkelte studier fremgår af bilag 1.

5.1.4 Effektestimater og kategorier

Til denne vurdering har Medicinrådet ikke foretaget en formel kategorisering af mogamulizumabs værdi, idet de narrative sammenligninger ikke kan danne grundlag for en kategorisering jf. Medicinrådets metoder. Effektestimaterne fra de forskellige studier er præsenteret for hvert effektmål, og vurderingerne er foretaget for MF- og SS-patienter hver for sig, hvor datagrundlaget tillader det.

Overlevelse
Overlevelse (OS) er et kritisk effektmål i vurderingen. Fagudvalget inkluderede overlevelse i vurderingen for at sikre, at mogamulizumab ikke har en negativ indflydelse på patienters overlevelse. Med udgangspunkt i mediane overlevelser fra 3-6 år til mindre end 2 år i de seneste sygdomsstadier har fagudvalget fastsat den mindste klinisk relevante forskel på median OS til 6 måneder.

Sammenligning med kemoterapi, MF-patienter

Data for overlevelse er ikke opgjort særskilt for MF- og SS-patienter i MAVORIC. Derfor vurderer fagudvalget her data for ITT-populationen og crossover-justerede analyser fra MAVORICs blandede population af MF- og SS- patienter samt data fra Duvic et al. og Pulini et al., som inkluderede MF-, SS- og pcALCL-populationer. EORTC 21012 rapporterede ikke overlevelsesdata. De mediane overlevelser fra studierne fremgår af Tabel 5.

Tabel 5. Effektestimater for overlevelse

	MAVORIC Mogamulizumab ITT	MAVORIC Mogamulizumab Crossover-justeret	Duvic et al. Gemcitabin	Pulini et al. Doxorubicin (pegyleret liposomal)
Overlevelse (median, mdr.)	57,16 (43,3-n.e.)	51,7 (40,0-n.e.)	20,4	34

n.e. Ikke estimérbart.

Fagudvalget mener med udgangspunkt i studiernes forskellige populationer ikke, at det er relevant at sammenligne effektestimaterne for overlevelse.

Sammenligning med targeteret behandling, MF- og SS-patienter

I subgruppen af MF-patienter i ALCANZA-studiet blev median OS ikke nået i brentuximab vedotin-armen. Der er derfor intet data, der kan belyse en sammenligning mellem mogamulizumab og targeteret behandling i hverken MF-eller SS-patienter.
På baggrund af det sparsomme data har fagudvalget ikke fundet grundlag for at vurdere mogamulizumabs værdi vedr. OS i sammenligning med targeteret behandling.

Livskvalitet

Effektmålet livskvalitet er kritisk for vurderingen af lægemidlets værdi for patienterne, fordi behandlingen er palliativ. Patienternes livskvalitet undervejs i behandlingen er derfor afgørende.

Sammenligning med kemoterapi, MF-patienter

Ingen af de inkluderede studier med kemoterapi rapporterer data for livskvalitet.

Sammenligning med targeteret behandling, MF- og SS-patienter

Data for livskvalitet er opgjort for ITT-populationerne i hhv. MAVORIC og ALCANZA. Data er rapporteret på forskellige måder ved forskellige tidspunkter, og dette udfordrer sammenligneligheden.

Som angivet i Tabel 6 observeres der tilsvarende reduktioner i Skindex-29 totalscore ved både mogamulizumab og brentuximab vedotin, men ved forskellige opfølgningstidspunkter.

Disse data viser, at de to targeterede behandlinger giver klinisk meningsfulde forbedringer i patienternes livskvalitet, mens de er i behandling, hvilket kan indikere, at forbedring i livskvalitet er forbundet til respons på behandling. Da der som tidligere nævnt er betydelige forskelle mellem de to ITT-populationer (se afsnit 5.1.2, s. 14), er det

ikke muligt at vurdere, om der er forskel mellem mogamulizumab og brentuximab vedotin.

Tabel 6. Effektestimater for livskvalitet

	MAVORIC Mogamulizumab ITT	ALCANZA Brentuximab vedotin ITT
Skindex-29 totalscore (gennemsnitlig ændring)	-15,7 point* (95 % CI: -20,96; -10,67)	-14,84 point^ (SD: 22,68)

*Ændring frem til cyklus 11. ^Ændring til *end of treatment.*

Fagudvalget vurderer, at data for livskvalitet ikke giver anledning til at skelne mellem de targeterede behandlinger mogamulizumab og brentuximab vedotin, men fremhæver, at begge behandlinger påvirker livskvaliteten positivt.

Progressionsfri overlevelse

Progressionsfri overlevelse (PFS) er hos MF- og SS-patienter tæt forbundet med livskvalitet og anvendes i vurderingen af mogamulizumab som et udtryk for længden af sygdomskontrol, som opnås under og efter behandling. Fagudvalget vurderer, at PFS er et kritisk effektmål i vurderingen. Længden af den progressionsfri periode for patienter, der behandles med de nuværende behandlingsmuligheder, varierer fra ca. 6-12 måneder. Baseret på fagudvalgets erfaringer med de nuværende behandlingsmuligheder vurderer fagudvalget, at det nye lægemiddel skal tilbyde en forbedring i median PFS på minimum 4 måneder.

Sammenligning med kemoterapi

Ansøger angiver effektestimater for PFS i MAVORIC, EORTC og Pulini et al. I MAVORIC er PFS-estimaterne også opgjort særskilt for MF- og SS-populationerne. Effektestimaterne fremgår af Tabel 7.

Tabel 7. Effektestimater for progressionsfri overlevelse (sammenligning af mogamulizumab og kemoterapi)

	MAVORIC Mogamulizumab ITT	MAVORIC-MF Mogamulizumab	MAVORIC-SS Mogamulizumab	EORTC Doxorubicin (pegyleret liposomal)	Pulini Doxorubicin (pegyleret liposomal)
PFS (median, mdr.)	6,7 (5,7-9,4)*	5,4#	13,3#	6,2	19

*Vurderet af studiets independent-review-committee. #Vurderet af investigatorerne.

Fagudvalget vurderer, at der ikke ser ud til at være længere median PFS ved behandling med mogamulizumab sammenlignet med kemoterapi. Fagudvalget bemærker, at varigheden af PFS ved behandling med mogamulizumab stiger med højere sygdomsstadier af MF og er længere, når der blodinvolvering (Tabel 8).

Tabel 8. Effektestimater for progressionsfri overlevelse i MAVORIC-subpopulationer

PFS (median, mdr.)	Mogamulizumab
MAVORIC-ITT	6,7 (5,-9,4)*
MAVORIC-MF	5,4#
MAVORIC-MF, IB/II	4,7
IB/II uden blodinvolvering	4,7¤
IB/II med blodinvolvering	8,4¤
MAVORIC-MF, III/IV	10,9
III/IV uden blodinvolvering	5,1¤
III/IV med blodinvolvering	11,4¤
MAVORIC-SS	13,1

*Vurderet af studiets independent-review-committee. #Vurderet af investigatorerne. ¤Data i EPAR.

Sammenligning med targeteret behandling, MF-patienter

Sammenligningen med brentuximab vedotin er foretaget med MF-populationen fra MAVORIC, idet denne population bedst matcher populationen i ALCANZA. Den naive sammenligning af effektestimaterne i Tabel 9 viser, at der hos MF-patienter er længere PFS ved behandling med brentuximab vedotin end ved behandling med mogamulizumab. Fagudvalget bemærker, at fordelingen af sygdomsstadier kan have betydning for resultaterne i de enkelte studier. ALCANZA inkluderer primært patienter med tumorer, hvor brentuximab vedotin virker godt. De MF-sygdomsstadier i MAVORIC, hvor mogamulizumab har vist sig at virke bedst (SS eller MF med blodinvolvering), udgør under 50 % af MF-patienterne. Forskellen på PFS mellem brentuximab vedotin og mogamulizumab i de samlede MF-populationer er derfor også drevet af, at de hver især virker bedst på forskellige sygdomsstadier af MF.

Tabel 9. Effektestimater for progressionsfri overlevelse (sammenligning af mogamulizumab og targeteret behandling)

	MAVORIC Mogamulizumab ITT	MAVORIC-MF Mogamulizumab	MAVORIC-SS Mogamulizumab	ALCANZA Brentuximab vedotin ITT	ALCANZA-MF Brentuximab vedotin
PFS (median, mdr.)	6,7 (5,7-9,4)*	5,4#	13,3#	16,7 (14,9-22,8)#	15,9#

*Vurderet af studiets independent-review-committee. #Vurderet af investigatorerne.

Sammenligning med targeteret behandling, SS-patienter

I MAVORIC er PFS længere hos patienter med SS end hos patienter med MF. Fagudvalget bemærker, at resultaterne fra MAVORIC subgruppeanalyser på sygdomsstadier viser, at effekten af mogamulizumab på PFS stiger med øget blodinvolvering og er længst hos patienter med SS. Fagudvalget vurderer, at det gør mogamulizumab til et oplagt behandlingsalternativ til netop SS-patienter, som har et begrænset antal af andre behandlingsmuligheder. For de øvrige targeterede behandlinger findes der ikke tilsvarende dokumentation fra de kliniske studier, og i klinisk praksis har de andre targeterede behandlinger ikke vist samme gode effekt på patienter med blodinvolvering. Der findes ikke data, der kan anvendes i en sammenligning mellem mogamulizumab og anden targeteret behandling i SS-patienter.

Uønskede hændelser

Effektmålet uønskede hændelser er vigtigt for vurderingen af lægemidlets værdi for patienterne, fordi fagudvalget vil sikre, at bivirkningstyngden og bivirkningsprofilen står mål med lægemidlets effekt, især når der er tale om en pallierende behandling. Bivirkningerne har også betydning for den enkelte patients livskvalitet og vilje til at forblive i behandling over en længere periode.

I protokollen er efterspurgt to opgørelser af uønskede hændelser: Uønskede hændelser (AE) grad 3-4 og alvorlige uønskede hændelser (SAE'er). Effektestimaterne er rapporteret i Tabel 10.

Det er ikke meningsfuldt at sammenligne den kvantitative opgørelse af uønskede hændelser på tværs af studier pga. af forskelle i studiepopulationer og opfølgningstid. SS-patienter er mere systemisk påvirket af deres sygdom end MF-patienter, hvilket gør det udfordrende at vurdere, om de uønskede hændelser er relateret til behandlingen eller opstår som en konsekvens af selve sygdommen hos disse patienter.

Vurderinger af bivirkninger og uønskede hændelser er kvalitative og inkluderer fagudvalgets erfaringer med særligt komparatorerne.

Tabel 10. Opgørelse af uønskede hændelser grad 3-4 og alvorlige uønskede hændelser

	MAVORIC Mogamulizumab ITT	ALCANZA Brentuximab vedotin ITT	EORTC 21012 Doxorubicin (pegyleret, liposomal) ITT	Pulini Doxorubicin (pegyleret, liposomal) ITT
Opfølgningstid, mdr.	17	22,9	10,6	22,6
Grad 3-4 AE (%)	41	41	20	11
SAE (%)	38	29	-	-

Mogamulizumab

Ansøger har inkluderet en opgørelse af uønskede hændelser fra MAVORIC. Her hæfter fagudvalget sig især ved frekvensen af infektioner (64 %) – særligt øvre luftvejsinfektioner på 10 %. På grund af den øgede forekomst af infektioner vil det sandsynligvis være rationelt at opstarte en forebyggende antibiotisk behandling i forbindelse med mogamulizumab-behandling. Da patienterne i forvejen følges tæt hver anden uge, medfører det ikke et øget behov for monitorering.

Kemoterapi

Gemcitabin opleves i klinikken som relativt atoksisk, mens fagudvalget fremhæver, at pegyleret doxorubicin er forbundet med perifer neuropati efter 12-18 behandlinger, som ofte er irreversibel. Det er en bivirkning, der knytter sig til det pegylerede doxorubicin, og som først indtræder relativt sent i behandlingen, men som ofte er årsag til, at patienten må stoppe behandling.

Targeteret behandling

Behandling med brentuximab vedotin er som pegyleret doxorubicin forbundet med perifer neuropati. Neuropatien indtræder ofte efter 12-18 behandlinger (eller flere), men er ofte reversibel. Brentuximab vedotin giver også ofte forbigående træthed. Alemtuzumab og pembrolizumab gives i lavere dosis (ca. 1/3) end dem, der anvendes i onkologien, hvorfor de bivirkninger, der opleves her og er rapporteret i de kliniske studier (bl.a. infektioner og nerveforstyrrelser), ikke opleves i samme grad ved behandling af MF og SS.

5.1.5 Fagudvalgets konklusion

MF-patienter, sammenligning med kemoterapi

Den samlede værdi kan ikke kategoriseres. Evidensens kvalitet er meget lav. Fagudvalget vurderer, at der ikke er anledning til at skelne mellem effekten af mogamulizumab og kemoterapi i til behandling af MF-patienter. Fagudvalget lægger vægt på det dårlige datagrundlag og forskelle i studiepopulationer, der vanskeliggør sammenligningen.

MF-patienter, sammenligning med targeteret behandling

Den samlede værdi kan ikke kategoriseres. Evidensens kvalitet er meget lav. Baseret på data for PFS vurderer fagudvalget, at mogamulizumab er mindre effektivt end brentuximab vedotin. Fagudvalget lægger vægt på resultaterne for PFS, hvor der er data for MF-subpopulationerne. Fagudvalget anser PFS som kritisk for patienten og et udtryk for sygdomskontrol. Fagudvalget lægger vægt på, at datagrundlaget for de øvrige effektmål ikke er sammenligneligt.

SS-patienter, sammenligning med targeteret behandling

Den samlede værdi kan ikke kategoriseres. Evidensens kvalitet er meget lav. Baseret på data for PFS vurderer fagudvalget, at mogamulizumab er mest effektivt til patienter, hvor der som hos SS-patienter er blodinvolvering, og hvor der i dag er få effektive behandlingsmuligheder. Fagudvalget lægger vægt på resultaterne for PFS, som anses som kritiske for patienten, da behandlingen har pallierende sigte, og PFS er et udtryk for

sygdomskontrol. Baseret på erfaring med de øvrige targeterede behandlinger (brentuximab vedotin, alemtuzumab og pembrolizumab) og den begrænsede dokumentation for deres anvendelse i patienter med SS, vurderer fagudvalget, at behandling med mogamulizumab er særligt relevant for denne patientgruppe. Fagudvalget fremhæver, at der ikke er datagrundlag til en sammenligning med targeteret behandling.

Samlet set vurderer fagudvalget, at mogamulizumab vil være en behandlingsmulighed til patienter med SS eller MF med blodinvolvering, som tidligere har modtaget mindst to systemiske behandlinger.

6. Andre overvejelser

6.1 Komparator

Ansøgers redegørelse for vorinostats sammenlignelighed med dansk behandlingspraksis samt fagudvalgets vurdering heraf er beskrevet i afsnit 5.1.2.

6.2 Differentiering af effekt i MF- og SS-patienter

Ansøger har leveret effektestimater for MF- og SS-patienter hvor muligt.

6.3 Behandlingsvarighed

Behandlingsvarigheden for mogamulizumab og komparatorerne er beskrevet i den sundhedsøkonomiske afrapportering.

6.4 Efterfølgende behandling

I den sundhedsøkonomiske ansøgning har ansøger angivet den efterfølgende behandling. Fagudvalgets vurdering heraf fremgår af den sundhedsøkonomiske afrapportering.

7. Relation til behandlingsvejledning

Der findes ikke en relevant behandlingsvejledning.

8. Referencer

1. European Medical Agency (EMA). Assessment report - Poteligeo [internet]. 2018. Tilgængelig fra: https://www.ema.europa.eu/en/documents/assessment-report/poteligeo-epar-public-assessment-report_en.pdf
2. Trautinger F, Eder J, Assaf C, Bagot M, Cozzio A, Dummer R, et al. European Organisation for Research and Treatment of Cancer consensus recommendations for the treatment of mycosis fungoides/Sézary syndrome - Update 2017. Eur J Cancer [internet]. 2017;77:57–74. Tilgængelig fra: http://www.ncbi.nlm.nih.gov/pubmed/28365528
3. Olsen E, Vonderheid E, Pimpinelli N, Willemze R, Kim Y, Knobler R, et al. Revisions to the staging and classification of mycosis fungoides and Sezary syndrome: a proposal of the International Society for Cutaneous Lymphomas (ISCL) and the cutaneous lymphoma task force of the European Organization of Research and Treatment of Ca. Blood [internet]. 2007;110(6):1713–22. Tilgængelig fra: http://www.ncbi.nlm.nih.gov/pubmed/17540844
4. Kempf W, Pfaltz K, Vermeer MH, Cozzio A, Ortiz-Romero PL, Bagot M, et al. EORTC, ISCL, and USCLC consensus recommendations for the treatment of primary cutaneous CD30-positive lymphoproliferative disorders: lymphomatoid papulosis and primary cutaneous anaplastic large-cell lymphoma. Blood [internet]. 2011;118(15):4024–35. Tilgængelig fra: http://www.ncbi.nlm.nih.gov/pubmed/21841159
5. Willemze R, Hodak E, Zinzani PL, Specht L, Ladetto M. Primary cutaneous lymphomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol [internet]. 2018;29:iv30-iv40. Tilgængelig fra: https://linkinghub.elsevier.com/retrieve/pii/S092375341931693X
6. Kim YH, Bagot M, Pinter-Brown L, Rook AH, Porcu P, Horwitz SM, et al. Mogamulizumab versus vorinostat in previously treated cutaneous T-cell lymphoma (MAVORIC): an international, open-label, randomised, controlled phase 3 trial. Lancet Oncol [internet]. 2018;19(9):1192–204. Tilgængelig fra: https://linkinghub.elsevier.com/retrieve/pii/S1470204518303796
7. Prince HM, Kim YH, Horwitz SM, Dummer R, Scarisbrick J, Quaglino P, et al. Brentuximab vedotin or physician's choice in CD30-positive cutaneous T-cell lymphoma (ALCANZA): an international, open-label, randomised, phase 3, multicentre trial. Lancet [internet]. 2017;390(10094):555–66. Tilgængelig fra: https://linkinghub.elsevier.com/retrieve/pii/S0140673617312667
8. Dummer R, Prince HM, Whittaker S, Horwitz SM, Kim YH, Scarisbrick J, et al. Patient-reported quality of life in patients with relapsed/refractory cutaneous T-cell lymphoma: Results from the randomised phase III ALCANZA study. Eur J Cancer [internet]. 2020;133:120–30. Tilgængelig fra: https://linkinghub.elsevier.com/retrieve/pii/S0959804920302082
9. Dummer R, Quaglino P, Becker JC, Hasan B, Karrasch M, Whittaker S, et al. Prospective International Multicenter Phase II Trial of Intravenous Pegylated Liposomal Doxorubicin Monochemotherapy in Patients With Stage IIB, IVA, or IVB Advanced Mycosis Fungoides: Final Results From EORTC 21012. J Clin Oncol [internet]. 2012;30(33):4091–7. Tilgængelig fra: http://ascopubs.org/doi/10.1200/JCO.2011.39.8065
10. Pulini S, Rupoli S, Goteri G, Pimpinelli N, Alterini R, Tassetti A, et al. Pegylated liposomal doxorubicin in the treatment of primary cutaneous T-cell lymphomas. Haematologica [internet]. 2007;92(5):686–9. Tilgængelig fra: http://www.haematologica.org/cgi/doi/10.3324/haematol.10879

11. Duvic M, Talpur R, Wen S, Kurzrock R, David CL, Apisarnthanarax N. Phase II Evaluation of Gemcitabine Monotherapy for Cutaneous T-Cell Lymphoma. Clin Lymphoma Myeloma [internet]. 2006;7(1):51–8. Tilgængelig fra: https://linkinghub.elsevier.com/retrieve/pii/S1557919011702931
12. Hanel W, Briski R, Ross CW, Anderson TF, Kaminski MS, Hristov AC, et al. A retrospective comparative outcome analysis following systemic therapy in <scp>M</scp> ycosis fungoides and <scp>S</scp> ezary syndrome. Am J Hematol [internet]. 2016;91(12):E491–5. Tilgængelig fra: https://onlinelibrary.wiley.com/doi/abs/10.1002/ajh.24564

9. Sammensætning af fagudvalg og kontaktinformation til Medicinrådet

Medicinrådets fagudvalg vedrørende lymfekræft (lymfomer)

Forvaltningslovens § 4, stk. 2, har været anvendt i forbindelse med udpegning af medlemmer til dette fagudvalg.

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
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Kathrine Bruun Svan *Farmaceut*	Dansk Selskab for Sygehusapoteksledelse
Kenneth Skov *Afdelingslæge*	Dansk Selskab for Klinisk Farmakologi
Rikke Bech *Afdelingslæge*	Dansk Dermatologisk Selskab
Maria Kamstrup *Afdelingslæge*	Dansk Dermatologisk Selskab
Jørn Søllingvrå *Patient/patientrepræsentant*	Danske Patienter
En patient/patientrepræsentant	Danske Patienter

Sammensætning af fagudvalg	
Tidligere medlemmer, som har bidraget til arbejdet	**Udpeget af**
Peter Kamper *Overlæge, ph.d.*	Region Midtjylland
Øvrige medlemmer, som ikke har bidraget til arbejdet	**Udpeget af**
Torsten Holm Nielsen *Speciallæge i hæmatologi, afdelingslæge*	Region Hovedstaden

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10. Versionslog

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

Bilag 1: Evidensens kvalitet

Cochrane – risiko for bias

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

Tabel 1. Vurdering af risiko for bias, Kim et al. 2018, MAVORIC, NCT01728805

Bias	Risiko for bias	Uddybning
Risiko for bias i randomiserings-processen	**Lav**	Der anvendes central randomisering med brug af *interactive voice web response system*. De to arme virker velbalancerede mht. baselinekarakteristika.
Effekt af tildeling til intervention	**Høj**	Studiet er open-label. Patienter i vorinostat-armen, der havde modtaget mindst to behandlingsserier, som progredierede eller havde intolerabel toksicitet, kunne krydse over til mogamulizumab-armen. Den vurdering kan påvirkes af kendskab til behandlingen. Cross-over påvirker effektestimaterne. Der er flere behandlingsophør i mogamulizumab-armen, hvilket også kan være påvirket af kendskab til behandlingen
Manglende data for effektmål	**Lav**	Data er tilgængeligt for næsten alle patienter for de fleste effektmål.
Risiko for bias ved indsamlingen af data	**Forbehold**	Der er tale om et 'open-label'-studie, hvor patient og investigator kender til behandlingen. Uønskede hændelser og livskvalitet må formodes at kunne være påvirket heraf.
Risiko for bias ved udvælgelse af resultater, der rapporteres	**Lav**	Der findes en offentligt tilgængelig protokol og statistisk analyseplan. De planlagte analyser er rapporteret.
Overordnet risiko for bias	**Høj**	

Tabel 2. Vurdering af risiko for bias, Prince et al. 2017, ALCANZA, NCT01578499

Bias	Risiko for bias	Uddybning
Risiko for bias i randomiserings-processen	**Lav**	Der anvendes central randomisering med brug af *interactive voice web response system*. De to arme virker velbalancerede mht. baselinekarakteristika.
Effekt af tildeling til intervention	**Forbehold**	Der er en andel af patienterne (45 %) i komparator-armen, som efterfølgende modtager brentuximab vedotin. Det vil påvirke data for overlevelse.
Manglende data for effektmål	**Lav**	Data er tilgængeligt for næsten alle patienter for de fleste effektmål.
Risiko for bias ved indsamlingen af data	**Forbehold**	Der er tale om et 'open-label'-studie, hvor patient og investigator kender til behandlingen. Uønskede hændelser og livskvalitet må formodes at kunne være påvirket heraf.
Risiko for bias ved udvælgelse af resultater, der rapporteres	**Lav**	Der findes en offentligt tilgængelig protokol og statistisk analyseplan. De planlagte analyser er rapporteret.
Overordnet risiko for bias	**Forbehold**	

Medicinrådet

Application for the assessment of Poteligeo® (mogamulizumab) for treatment of patients with mycosis fungoides or Sézary syndrome, who have received at least two prior systemic treatments

Clinical application for the Danish Medicines Council

25-09-2020

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1 Basic information

Table 1 Contact information

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Table 2 Overview of the pharmaceutical

Proprietary name	**Poteligeo®**
Generic name	Mogamulizumab
Marketing authorization holder in Denmark	Kyowa Kirin Holdings B.V. Bloemlaan 2 2132 NP Hoofddorp Holland
ATC code	L01XC25
Pharmacotherapeutic group	Poteligeo® (mogamulizumab) is a defucosylated, humanised IgG1 kappa immunoglobulin.
Active substance(s)	Mogamulizumab
Pharmaceutical form(s)	Intravenous infusion
Mechanism of action	Poteligeo® (mogamulizumab) is a defucosylated, humanised IgG1 kappa immunoglobulin that selectively binds to CCR4 resulting in depletion of the target cells. CCR4 is a G protein-coupled receptor for CC chemokines that is involved in the trafficking of lymphocytes to various organs including the skin. CCR4 is expressed on the surface of some cancer cells including T cell malignancies, such as MF and SS in which CCR4 expression is inherent.
Dosage regimen	The recommended dose is 1 mg/kg mogamulizumab administered as an intravenous infusion over at least 60 minutes. Administration is weekly on days 1, 8, 15 and 22 of the first 28-day cycle, followed by infusions every two weeks on Days 1 and 15 of each subsequent 28-day cycle until disease progression or unacceptable toxicity
Therapeutic indication relevant for assessment (as defined by the European Medicines Agency, EMA)	Poteligeo® (mogamulizumab) is indicated for the treatment of adult patients with mycosis fungoides (MF) or Sézary syndrome (SS) who have received at least one prior systemic therapy.
Other approved therapeutic indications	No
Will dispensing be restricted to hospitals?	Yes

Combination therapy and/or co-medication	N/A
Packaging – types, sizes/number of units, and concentrations	20mg vials of mogamulizumab in 5ml, corresponding to 4mg/mL
Orphan drug designation	Yes, Poteligeo® (mogamulizumab) received orphan drug designation by the EMA 14 October 2016

2 Abbreviations

MF	Mycosis fungoides
SS	Sézary syndrome
CTCL	Cutaneous T-cell lymphomas
RCT	Randomized controlled trial
DMC	Danish Medicines Council
EMA	European Medicines Agency
PFS	Progression-free survival
KOL	Key opinion leader
ITT	intention-to-treat population
OS	Overall survival
TTNT	Time to next treatment
HR	Hazard ratio
CI	Confidence interval
CFB	change from baseline
MCID	Minimal clinical important difference
AEs	Adverse events
SAE	Serious adverse events
TEAEs	Treatment-emergent adverse events
QoL	Quality of life
ECP	Extracorporeal photopheresis
EPAR	European Public Assessment Report
IQR	Interquartile range
pcALCL	Primary cutaneous anaplastic large cell lymphoma
TBI	Tumour burden index
NE	Not estimated

KM	Kaplan-Meier
aSCT	Autologous stem cell transplant
IPCW	Inverse probability of censoring weights
TSE	Two-stage estimation
HRQoL	Health-related quality of life

3 Summary

On 15 June 2020, the Danish Medicine Council published the protocol for the evaluation of mogamulizumab for the treatment of adults with mycosis fungoides (MF) or Sézary syndrome (SS) who have received at least two previous systemic treatments. The protocol included the following clinical questions:

1. What value does mogamulizumab have compared to current treatment for patients with mycosis fungoides or Sézary syndrome who have received at least two previous systemic treatments?

Both chemotherapy and targeted treatments are considered to be relevant comparators for mogamulizumab by the specialist committee of the Danish Medicine Council. Chemotherapy and targeted treatments are therefore, included as comparators in this analysis.

This document describes the clinical application as part of the application to the Danish Medicine Council for the clinical question. The purpose of this document is to describe the clinical studies, study results and comparative analyses relevant to answer the clinical question.

Patients with mycosis fungoides (MF) and Sézary syndrome (SS) represent an orphan population with very limited treatment options. As a result of these few effective available treatment options, patients can cycle through multiple treatments that have either previously failed, or are off label, imposing a substantial burden on individuals and health care systems[1]. As MF and SS are orphan disease populations, very limited data exists for the treatment of MF and SS patients with the regimens listed in the DMC protocol. As the majority of the treatments listed in the protocol are used off-label, no efficacy data is available to support the use of the included treatment alternatives in the protocol for the defined MF/SS population. This is supported by the clinical expert committee, which were not able to make a prioritized treatment choice for the patient population considered in the application. Given the lack of data for the relevant comparators, no comparative studies for the stated comparators allowed for direct or indirect statistical comparisons.

The efficacy and safety of mogamulizumab was assessed in the MAVORIC pivotal phase 3 trial, where it was compared to vorinostat in patients with stage IB to IVB MF or SS, who have failed at least one prior therapy[2]. Patients were aged at least 18 years (in Japan, ≥20 years), and had an ECOG performance score of 1 or less and adequate haematological, hepatic, and renal function. For the MAVORIC trial, vorinostat was chosen as the comparator, as an alternative to other current standard of care that patients were already refractory to. The choosing of vorinostat enabled high recruitment of patients where re-challenge with previously tried treatments would have been inappropriate and unethical in a clinical trial setting and also to ensure a robust sample size for the MAVORIC study.

MAVORIC is the largest randomized Phase III study conducted in any CTCL subgroup to date, with 372 patients enrolled[2]. Approximately 80% of patients had advanced disease (i.e. stage ≥IIB MF and all SS patients) and 45% of all patients recruited had SS; this is the largest number of SS patients to ever be recruited to a randomized trial. Patients were also heavily pre-treated with a median of 3 previous systemic treatments received including 58% of patients previously treated with bexarotene, 47% with interferon-alpha and 66% with chemotherapy; 5% of patients previously received brentuximab vedotin.

In the ITT population mogamulizumab resulted in:

- Significantly better progression-free survival (PFS) with a HR of 0,53 (95% CI 0,41-0,69) (median 7,7 vs. 3,1 months for mogamulizumab vs. vorinostat respectively)
- Significantly better quality of life change from baseline using the Skindex-29 total score
- A tolerable and manageable safety profile in patients with MF and SS, and despite the duration of mogamulizumab therapy being double that of vorinostat.

The MAVORIC trial provides comparative data versus vorinostat in MF and SS patients with at least one prior systemic treatment irrespective of CD30 status, whereas the treatments defined in the protocol lack data for the specific protocol populations of MF and SS or have data only in specific subgroups. Due to the

lack of data and clinical evidence for the other targeted therapies, defined in the DMC protocol, no relevant comparison can be made with the targeted therapies. Vorinostat is considered standard of care in the US, Canada, Australia and Japan, although it is not currently licensed in Europe, it is assumed to be an appropriate proxy for the effectiveness of chemotherapy.

There is a clear unmet need for new licensed treatment options for advanced MF and SS patients who require a systemic therapy that can target all four disease compartments (skin, blood, lymph nodes and viscera) and provide a durable response in order to extend patients' disease-free interval and, subsequently, time to receiving next therapy, as well as a meaningful survival benefit.

Mogamulizumab addresses this unmet need by providing a novel immune-modulatory oncology agent which has provided improved efficacy and HRQoL compared to an active comparator in both advanced MF and SS patients.

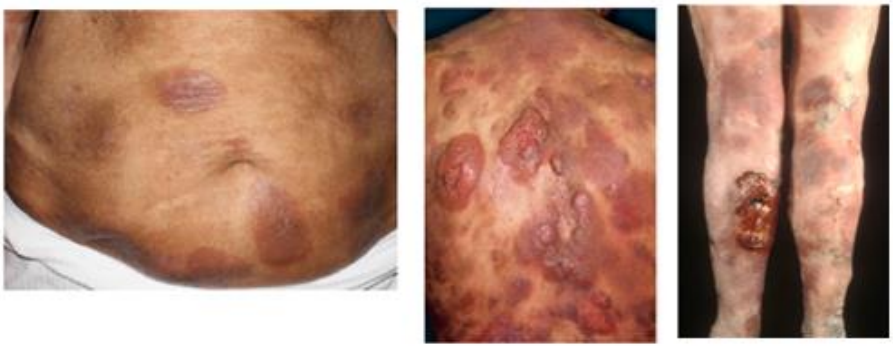
Mogamulizumab is the only treatment available, which specifically targets the malignant T cells in all four disease compartments; in particular the blood compartment. Blood involvement (B1 and B2) is a prognostic indicator[3], thus mogamulizumab is offering the potential for significant improvements in life expectancy for these patients. It should be noted that treatment of CTCL patients with all comparators listed, except brentuximab vedotin, are used off-label. EMA has previously rejected marketing authorization for romidepsin in CTCL.

4 Introduction

4.1 Background

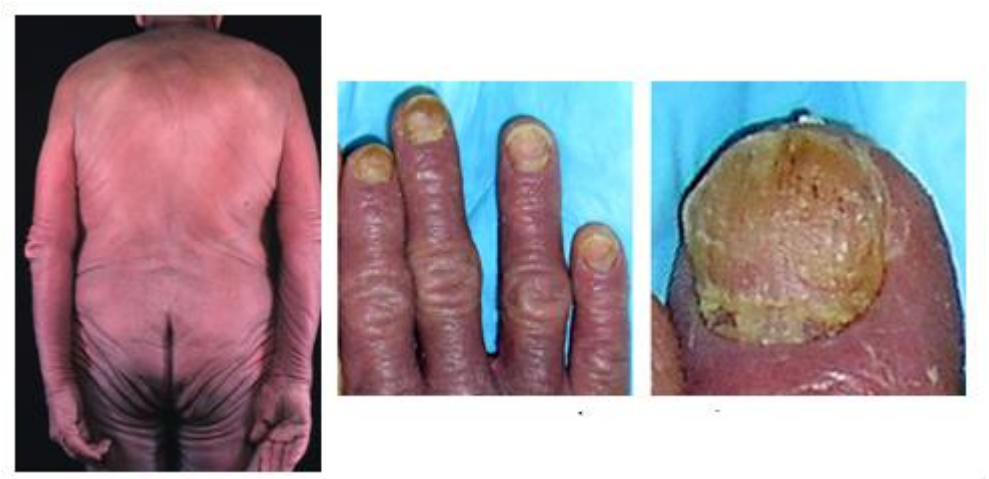
The submission focuses on adults with advanced mycosis fungoides (MF) or Sézary syndrome (SS) cutaneous T-cell lymphoma (CTCL). CTCL is a subset of non-Hodgkin's lymphoma that manifests in the skin, leading to rash-like skin redness, slightly raised or scaly patches on the skin and skin tumours[4], which account for about 4 percent of all cases of NHL[5]. Patients with MF and SS represent an orphan population, as MF accounts for 55% of all CTCLs and is characterized by patches and plaques in the early stages[6]. Around 30% of patients develop advanced disease, characterized by tumours, ulceration, systemic involvement with lymph node or visceral spread, and is therefore linked with significant morbidity and mortality[7]. SS accounts for 2,5% of all CTCLs and is a more aggressive, leukemic form of CTCL characterized by the presence of malignant lymphocytes called 'Sézary cells' in the peripheral blood[7,8]. SS are also characterized by erythroderma and lymphadenopathy, they also experience thickened scaly and fissured skin on their palms and soles leading to opportunistic infections, sepsis and death[9,10]. MF and SS are not skin-only diseases, making them distinct from other CTCLs[7]. Instead, there are four potentially involved 'compartments': skin, blood, lymph nodes and viscera. All four compartments have prognostic significance in this disease[2].

Figure 1 Visual representation of more advanced mycosis fungoides disease



Source: Fujii, 2018[11].

Figure 2 Visual representation of Sézary syndrome disease



Source: Prince et al. 2009[12]; Damasco et al. 2018[13]

Staging of MF and SS was initially dependent on the type and extent of skin lesions and extracutaneous disease, first captured in the tumour, node, metastasis (TNM) classification published for CTCL in 1979. Suggested modifications published in 2007 for MF/SS revised the nodal classification, added blood involvement and removed the ambiguity surrounding variables critical to standardized staging and classification[14], resulting in the adapted version of the TNM staging system (TNMB) which takes into account concurrent disease involvement of all four compartments: skin, lymph nodes, blood and viscera[6]. Advanced disease is defined as Stage IIB or above; as such, by definition, all SS patients are considered advanced[15].

While patients in early stages of the disease have a median survival of 21,5 years (stage IB), this is dramatically reduced to under 5 years for patients with advanced disease (stage IIB onwards); for patients with stage IVB disease, the median survival is under 2 years[3]. MF patients that have extensive blood involvement and SS patients also have reduced survival. One-year survival reduced from 67% and 75% in patients with little or no detectable blood involvement (with 0% circulating Sézary cells) to 21% and 25% in patients with the highest levels of involvement[16]. In the MAVORIC trial, the patients that are ≥2 line were around ≥40 months from diagnosis, so these OS estimates may overestimate the survival estimate for patients indicated for mogamulizumab[2].

Alongside the psychological distress of living with an incurable cancer, patients face a significant, disfiguring physical burden with the skin often oozing and infected; patients report discomfort, cracking and bleeding and skin 'like tin foil'[17]. Importantly, the skin manifestations from CTCL have a significant impact on quality of life (QoL) with one patient quoted as saying 'you want to scratch yourself to pieces. You'd like to just rip your skin off'. Another major impact of CTCL is that of role function, as CTCL causes significant disruption in the lives of patients e.g. the disease significantly affects their sleep[18].

The disease also has a serious impact on patient's family life, causes the patients to miss work and due to its physical manifestation, has a significant impact on social interactions, such as participation in sports or hobbies[17,18]. Caregivers face a substantial burden with psychologically and emotionally demanding responsibilities. In particular, the physical burden of practical care, such as regular changing of dressings, which is often time consuming and overwhelming[19], resulting in a more intensive caregiver burden compared with other cancer indications.

As a result of the few treatment options available, patients can cycle through multiple treatments that have previously failed, imposing a substantial burden on individuals and health care systems[1].

There is a clear unmet need for new treatment options for advanced MF and SS patients who require systemic therapy that can target all disease compartments (skin, blood, lymph nodes and viscera) and provide a durable response in order to extend patients' disease-free interval and, subsequently, time to receiving next therapy, as well as a meaningful survival benefit.

In Denmark, approximately 400-500 patients live with treatment intensive CTCL[20]. The DMC estimates that there are approximately 15 patients who are candidates for mogamulizumab (prevalence) and that there will be an incidence of approximately 5 new patients per year[20].

4.2 Standard treatment

The treatment of CTCL in Denmark is carried out by the dermatological departments in cooperation with haematological and oncology departments. The treatment follows international guidelines from ESMO and EORTC[21,22]. There is no defined standard treatment as treatment is individualized based on the characteristics of the cutaneous lymphoma, the severity of the disease, the patient's performance status, comorbidities, previous treatments, patient preferences, etc.[20]

The aim of the treatment is to prevent disease progression and symptom relief, since the available treatments, excluding allogeneic stem cell transplantation, are not curative. The aim is to reduce tumor

burden followed by disease control. The disease management is therefore, to relieve symptoms, improve QoL, induce remissions, delay progression, and avoid significant treatment-related toxicity. The courses of treatment in the early stages are usually of a longer duration (years), and the patients are treated depending on response and remission status. However, most therapies have response rates that are less than 50% and a PFS usually less than 6 months, so patients are likely to require multiple therapies[23].

In early stages of MF (stage IA-IIA), topical therapy is used in the form of e.g. corticosteroids in combination with ultraviolet phototherapy (narrow spectrum UVB or 8-Methoxypsoralen + UV-A (PUVA)) or chlormethine (nitrogen-mustard). In later, more advanced stages (stage IIB-IV) of MF, total skin electron beam therapy (TSEBT), local radiotherapy are used against the tumour or first-line systemic medical treatment in the form of interferon-α, retinoids (e.g. acitretin and bexarotene) or low-dose methotrexate.[20]

The treatment following the first line of systemic treatments is planned at the multidisciplinary conference with the haematology department and targeted treatments, pathway inhibitors or chemotherapy (e.g. high-dose methotrexate, gemcitabine, or doxorubicin) are used.[20]

The targeted treatments include brentuximab vedotin (anti-CD30), alemtuzumab (anti-CD52), and pembrolizumab (PD-1 inhibitor). The pathway inhibitor includes a histone deacetylase (HDAC) inhibitor, romidepsin. These treatment regimens are considered equal treatment alternatives by the clinical expert committee. The choice of treatment is individualized and is guided by the patient's biomarker expression and previous treatments[20,24,25]. None of the targeted treatments/pathway inhibitors can be considered standard treatments in Denmark, and only brentuximab vedotin is indicated for the treatment of CD30 positive CTCL, including MF/SS. The pivotal trial for brentuximab vedotin did not include SS patients, hence no data is available for brentuximab vedotin in SS patients or patients with B2 blood involvement[26]. Treatment with these alternatives is therefore dependent on individual applications to the pharmaceutical committees. The EMA has previously refused to grant marketing authorisation for romidepsin for this indication[27]. Treatment with pembrolizumab, alemtuzumab and romidepsin are therefore used outside the approved indication (off-label). Alemtuzumab received an EMA warning in November 2019 due to risk of serious side effects[28].

SS and advanced MF is by definition a systemic disease and therefore, requires systemic treatment. Extracorporeal photopheresis (ECP), either alone or in combination with e.g. interferon-α and/or retinoids, TSEBT and PUVA have been proposed as initial treatment options for SS. Targeted treatments/pathway inhibitors are used as second-line treatments as described above.

In addition, reduced intensity allogenic stem cell transplant (aSCT) is noted as a treatment option for SS patients or advanced stage MF patients after first-line therapy. Although aSCT is potentially curative. Because of its safety profile is only offered to certain patients, that are, young, well-performing patients with a low tumour burden at the time of transplant.[6]

4.3 Intervention treatment

Mogamulizumab (Poteligeo®) is a humanised IgG1 kappa immunoglobulin that selectively binds to CCR4, a G-protein-coupled-receptor involved in trafficking of lymphocytes to various organs including the skin[29]. CCR4 is expressed in high concentrations on the surface of some cancer cells including T cell malignancies, such as MF and SS in which CCR4 expression is inherent.

Mogamulizumab is indicated for adult patients with MF or SS, who have received at least one previous systemic treatment. Mogamulizumab was designated an orphan drug in 2016 for the following condition: Treatment of cutaneous T-cell lymphoma.

The DMC considers that mogamulizumab will be a relevant treatment alternative for patients with advanced disease (MF, stage II-IV and SS) who have been treated in Danish clinical practice with at least two systemic treatments (e.g. methotrexate, retinoids and interferon-α) or have a contraindication for one or more of these

systemic treatments. Mogamulizumab should therefore, be used in line with the targeted treatments and pathway inhibitors described in the DMC protocol.

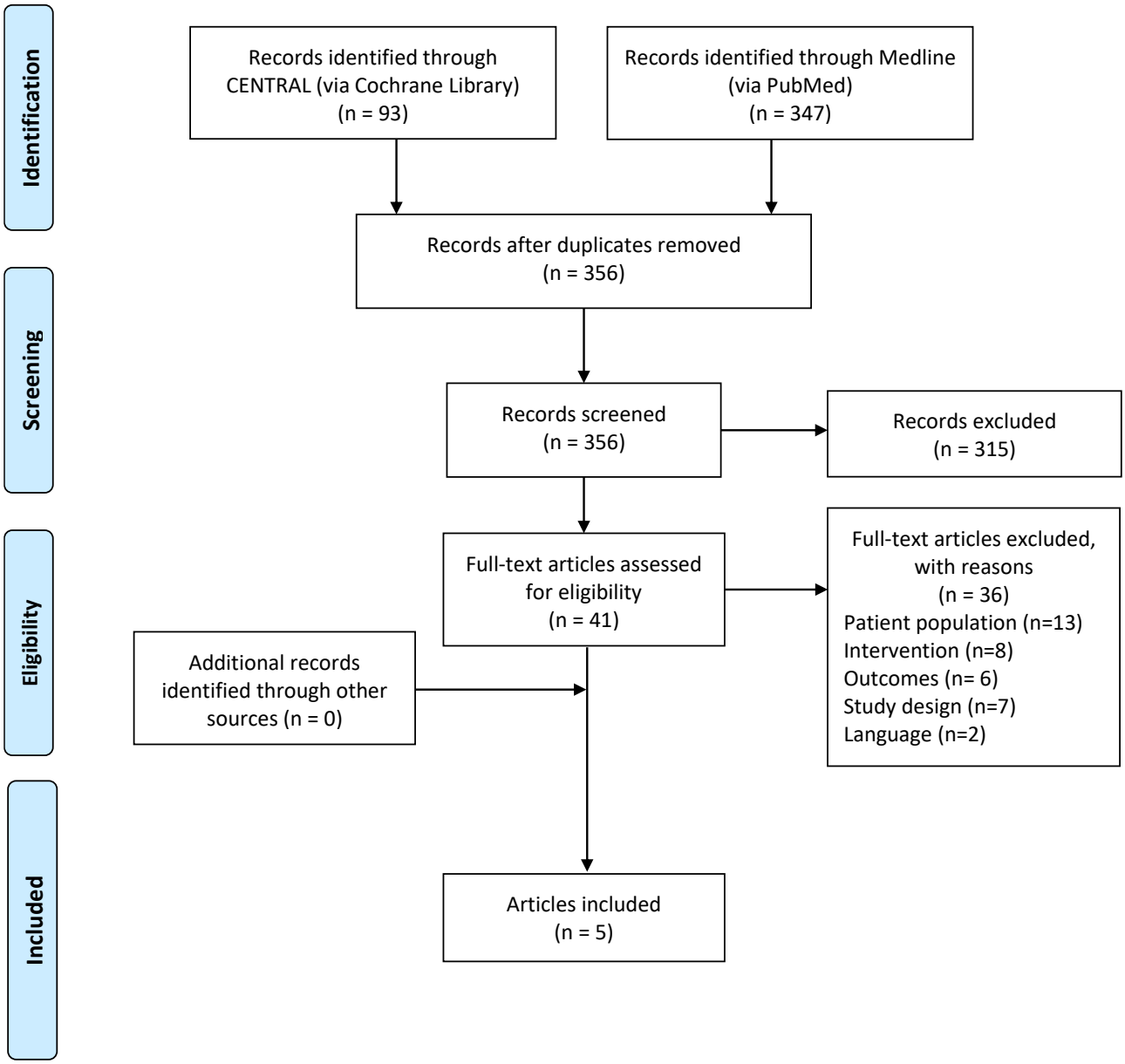
5 Literature search

The following electronic databases were searched on 15.07.2020 for randomised and non-randomised controlled trials (RCT): MEDLINE via PubMed and CENTRAL via Cochrane Library. The search strategy was carried out as defined in the protocol and no date limit was applied to the electronic searches. Due to the definition of two prior systemic treatments the search only identified one study and excluded the pivotal MAVORIC trial for mogamulizumab, as most trials included ≥1 prior treatment. Based on dialogue with the DMC secretariat the inclusion criteria were broadened to include at least one prior systemic treatment. Results of the searches are illustrated in section 10.1.

Primary screening was performed by two reviewers who independently reviewed each reference (title and abstract) identified by the literature search, applied study selection criteria, and decided on whether to include or exclude the reference at that stage. Secondary screening included obtaining the full-text articles for potentially relevant studies identified by primary screening of titles and abstracts. These were independently reviewed by two reviewers against each eligibility criterion.

The systematic database searches identified 440 records. A de-duplication step was performed to remove studies that overlapped across the databases; 84 of the studies were identified as duplicates and excluded. The remaining 356 studies were screened based on the information reported in their titles and/or abstracts. Of these, 315 records were excluded, and 41 records were included. The 41 records were further assessed for eligibility for review by full-text screening, which resulted in the exclusion of 36 publications and inclusion of 5 publications. No additional records were identified through other sources. Thus, a total of 5 articles were included in this review. Relevant data were then extracted from 2 RCTs reported in 3 publications and from 2 single-arm studies reported in 2 publications. Figure 3 presents the PRISMA flow diagram of studies identified for clinical review.

Figure 3 PRISMA diagram



5.1 Relevant studies

The four relevant studies, covering five publications, identified through the SLR included two phase III trials and two phase II trials. The identified phase III trials include the phase III trial (MAVORIC) from the mogamulizumab clinical trial program comparing mogamulizumab and vorinostat, and the brentuximab vedotin phase III trial (ALCANZA) comparing brentuximab vedotin and physician's choice of methotrexate or bexarotene. The two phase II trials include single-arm studies of liposomal doxorubicin and gemcitabine, respectively. In addition, the European Public Assessment Reports (EPAR) of mogamulizumab and brentuximab vedotin were reviewed as requested in the protocol.

None of the identified studies included a direct comparison between the intervention and the comparator regimes defined in the protocol (brentuximab vedotin, alemtuzumab, pembrolizumab, romidepsin, high dose methotrexate, doxorubicin or gemcitabine). Additionally, no common comparator for indirect comparison

between the intervention and comparator regimes was available. In the absence of a direct and indirect common comparator, it is not possible to conduct a statistical comparison between mogamulizumab and the specified comparators. Therefore, a narrative approach has been adopted for the comparative analyses.

Table 3 Relevant studies included in the assessment

Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)
Mogamulizumab versus vorinostat in previously treated cutaneous T-cell lymphoma (MAVORIC): an international, open-label, randomised, controlled phase 3 trial, Kim, Lancet Oncol, 2018[2]	*MAVORIC*	*NCT01728805*	Actual Study Start Date: November 2012 Estimated Study Completion Date: December 2020
Brentuximab vedotin or physician's choice in CD30-positive cutaneous T-cell lymphoma (ALCANZA): an international, open-label, randomised, phase 3, multicentre trial, Prince, Lancet, 2017[26]	*ALCANZA*	*NCT01578499*	Actual Study Start Date: June 11, 2012 Actual Study Completion Date: July 6, 2018
Patient-reported quality of life in patients with relapsed/refractory cutaneous T-cell lymphoma: Results from the randomised phase III ALCANZA study, Dummer, Eur J Cancer, 2020[30]			
Prospective international multicenter phase II trial of intravenous pegylated liposomal doxorubicin monochemotherapy in patients with stage IIB, IVA, or IVB advanced mycosis fungoides: final results from EORTC 21012, Dummer, J Clin Oncol, 2012[31]	EORTC 21012	*NCT00074087*	Study Start Date: October 2003 Actual Study Completion Date: September 2010
Phase II evaluation of gemcitabine monotherapy for cutaneous T-cell lymphoma, Duvic, Clin Lymphoma Myeloma, 2006[32]	*NA*	*NR*	Actual Study Start Date: June 1999 Actual Study Completion Date: May 2003

5.2 Main characteristics of included studies

The main characteristics of all studies included in the assessment of the clinical questions defined in the protocol are presented in the following section. For a complete overview of the included studies please see section 10.2.1.

5.2.1 MAVORIC

Clinical efficacy of mogamulizumab in the treatment of patients with MF or SS has been investigated in the MAVORIC trial, a Phase 3, multinational, open-label trial of anti-CCR4 monoclonal antibody mogamulizumab versus vorinostat in 372 adult patients randomised 1:1 to treatment with either mogamulizumab or vorinostat.

Each arm enrolled 186 patients. Mogamulizumab infusion was administered at a dose of 1 mg/kg once weekly for the first 28-day cycle (on Days 1, 8, 15 and 22), and on days 1 and 15 of subsequent 28-day cycles. Vorinostat was administered at a starting dose of 400 mg orally, once daily beginning on day 1 for 28-day cycles. Vorinostat patients with disease progression after at least two full treatment cycles of vorinostat, or who were unable to tolerate vorinostat despite dose reduction, to cross over to treatment with mogamulizumab. Treatment with mogamulizumab continued until disease progression or unacceptable toxicity. The trial excluded patients with active autoimmune diseases, central nervous system metastasis,

and medical conditions that required systemic corticosteroids or other immunosuppressive medicinal products, or an active infection requiring therapy, including HIV, or hepatitis B or C. Patients with ECOG performance status ≥2 were also excluded. At study baseline, 38% had stage IB-II disease, 10% stage III, 52% stage IV. This study included patients regardless of their baseline level of CCR4 expression in skin biopsy.[2]

All patients had a histologically confirmed diagnosis of either MF, 56,5%, 53,2%, or SS, 43,5%, 46,8%, in the mogamulizumab and vorinostat groups, respectively, and had received at least one prior systemic therapy[2].

Patient demographic and disease characteristics were generally well balanced between treatment arms, as were the distributions in previous CTCL therapies. In total, 58% of patients were male and 70% were white. The median time from initial diagnosis was 37,6 months (3,1 years; range: 1–362 months)[33]. Patients with advanced disease (Stage ≥IIB) accounted for 77% of the population and measurable blood involvement (defined as stage B1 or B2, based on central flow cytometry) was present in 66% of patients. It should also be noted that almost half (45,2%) of the total population were SS patients. Patients were a median age of 64 years at the time of screening (range 25 to 101 years) and 49,5% were 65 years or older.[2]

Patients in the MAVORIC trial were heavily pre-treated before enrolment. All randomized patients had received prior CTCL therapies including topical or systemic, with the majority of patients having received three or more prior systemic therapies (median: 3; interquartile range [IQR]: 2-5). All except one patient (in the vorinostat arm) had failed at least one prior systemic therapy (the patient was included following a protocol deviation), and the majority of randomised patients (66,8%) did not respond to their most immediate prior therapy.[2]

The primary efficacy endpoint was progression-free survival (PFS) based on investigator assessment using a global composite response criteria that took into account all potentially affected disease compartments (skin, blood, lymph nodes and viscera). The global composite response criteria is seen as the most appropriate way to assess clinical trials in CTCL in published consensus criteria[14]. PFS is considered an acceptable primary endpoint in particular as CTCL is characterized by frequent recurrences and an indolent course in early stages reflected by the relatively long OS. However, the clinical relevance of the observed effect should be reinforced by supportive secondary endpoints, such as ORR and QoL assessments using relevant tools i.e. Skindex-29. The primary endpoint is based on investigator assessment, which is acceptable as it is more representative of clinical practice in this disease, where visual skin inspection is an important part of response assessment. Moreover, investigator-assessed PFS provided a more consistent application of the Olsen et al. guidelines[14] compared to an independent review PFS as photos can't distinguish between drug rash and progression, and can be considered, therefore, more reliable in terms of diagnosis of progression and response data. Response in skin and blood was evaluated every 4 weeks. Response in lymph nodes and viscera were evaluated at week 4, then every 8 weeks in the first year, and then every 16 weeks thereafter. It should also be noted that MAVORIC is the first pivotal trial in CTCL to compare systemic therapies using PFS as a primary endpoint.[2]

The median duration of exposure with mogamulizumab was 5,6 months (range: <1 to 45,3 months). 56% of patients received mogamulizumab for at least 6 cycles, and 25% of patients received mogamulizumab for at least 12 cycles.[2]

Of the patients randomized to vorinostat, 135 patients (72,6%) crossed over to mogamulizumab during the study. The number of infusions of mogamulizumab administered to crossover patients ranged from 1 to 94 (up to 46 months of treatment) as of the December 2016 data-cut.[2]

5.2.2 ALCANZA

ALCANZA was a randomized, open-label, phase III trial of brentuximab vedotin versus physician's choice (methotrexate or bexarotene) in patients with CD30-positive cutaneous T-cell lymphoma. The trial included patient populations of primary cutaneous anaplastic large cell lymphoma (pcALCL) and MF.[26]

Adult patients (aged ≥18 years) with CD30-positive MF who had received at least one previous systemic therapy, or adult patients with CD30-positive primary cutaneous anaplastic large cell lymphoma (pcALCL) who had received at least one previous systemic therapy or radiotherapy (ECOG PS 0 to 2) were eligible for study enrolment. Patients were randomized 1:1 to either receive brentuximab vedotin or to receive the physician's choice of either bexarotene or methotrexate using an interactive voice response system, stratified by baseline disease diagnosis (MF or pcALCL). Demographic data and baseline clinical data are balanced between the two arms with the exception of more severe pcALCL and more time since initial diagnosis in the brentuximab vedotin arm compared to the treatment arm. A high proportion of the MF patients did not have advanced stage disease (≥stage II) and most pcALCL patients had stage 3 disease (generalized skin involvement) at study entry. In both arms, MF patients received a median of two systemic therapies. The median follow-up was 22,9 months (95% CI 18,4–26,1).[26]

The primary endpoint was ORR4, which is the proportion of patients who achieved an objective response (CR or PR) that lasted at least 4 months, as determined by an independent review facility (IRF). Key secondary endpoints were PFS and changes in symptom domain (7 items) according to Skindex-29 questionnaire and safety.[26]

In total, 128 patients were included in the intention-to-treat population (64 in each group). 97 (76%) patients had mycosis fungoides and 31 had pcALCL in the overall intention-to-treat population. No SS patients were included in the study or MF patients with high blood involvement (B2). 34% of the patient were in disease stage IA-IIA, 39% in IIB, 6% in IIIA-IIIB, 1% in IVA[1], 10% in IVA[2] and 7% in IVB. Patients had received a median of 2,0 (95% CI: 1,0-4,0) previous systemic therapies.[26]

5.2.3 EORTC 21012

This was a single-arm phase II study of intravenous pegylated liposomal doxorubicin (PLD) in patients with stage IIA, IVA, or IVB advanced MF. Eligible patients were registered to receive PLD as monotherapy at a dose of 20 mg/m^2 on days 1 and 15, every 28 days (one cycle). A minimum washout period of 2 weeks, during which patients were not allowed to receive any therapy, was required before starting treatment. The disease was assessed every two cycles until documented progression, and adverse effects of treatment were assessed for each cycle of therapy. Evaluation of the extent of cutaneous involvement with the disease was performed by assessing the tumour burden index (TBI) based on the modified severity-weighted assessment tool. Patients eligibility criteria were histopathologically confirmed diagnosis of stage IIB, IVA[1/2], or IVBMF, no CNS involvement or erythroderma (T4), refractory or recurrent disease after two or more previous therapies, no systemic treatment with steroids at the time of study entry; and age ≥18 years. Prior systemic chemotherapy was allowed if all of the following conditions were met: anthracycline cumulative dose <200 mg/m^2, no allergy to anthracyclines, and low-dose methotrexate (weekly dose >30mg). Patients requiring systemic treatment with steroids for any reason at the time of study entry were excluded. Patients had to have an ECOG performance status (PS) of 0 to 2; no other prior or concurrent primary malignant tumour; no active infection requiring specific therapy (e.g. antibiotics, anti-HIV therapy); adequate hematologic function; adequate renal and liver functions.[31]

A total of 49 patients received 20 mg/m^2 PLD. Most patients had a PS of 0 or 1 (96%), had refractory disease (71%), were men (67%), and were between the ages of 56 and 75 years (63%). Prior therapies included combination therapy with or without chemotherapy (22% and 41%, respectively), chemotherapy alone, and topical treatment with or without chemotherapy (14% and 12%, respectively).[31]

The primary endpoint was response rate by Tumor Burden Index for cutaneous disease and appearance or disappearance of lesions for non-cutaneous disease every 8 weeks during treatment and then every 12 weeks until progression. Time to progression measured by Tumor Burden Index for cutaneous disease and appearance or disappearance of lesions for non-cutaneous disease every 8 weeks during treatment and safety. All analyses were carried according to the per-protocol population.[31]

5.2.4 Duvic et al. 2006

This was a single-center open-label phase II trial of gemcitabine monotherapy in cutaneous T-cell lymphoma (CTCL), which is a wider inclusion criterion than defined in the DMC protocol. Patients were aged >16 years with biopsy-proven CTCL. No exposure to fludarabine was allowed within 6 months. Life expectancy was >12 weeks, and patients with active infections, cancer, or central nervous system disease were excluded. Mycosis fungoides was staged by the TNM system. Patients with stage IB or IIA disease at baseline must have experienced treatment failure with another systemic therapy, whereas those with tumours (T3), erythroderma (T4), or nodal disease were eligible for treatment.[32]

Thirty-three patients with CTCL were treated with gemcitabine (1000 mg/m^2) on protocol, and 8 were treated off protocol. Two patients were classified as primary cutaneous CD30+ anaplastic large T-cell lymphoma and 20 were classified as MF and 11 with SS. Thirteen patients with cutaneous tumours had large-cell transformation, and 6 patients also had nodal involvement. All had been previously heavily treated with a median of 5 previous therapies (range, 2-13 therapies). The median follow-up time for the combined group of patients (protocol and treated off protocol) was 36 months.[32]

Endpoints were response rate in the skin, OS and safety. The publication does not report primary and secondary endpoints.[32]

6 Clinical questions

6.1 What value does mogamulizumab have compared to current treatment for patients with mycosis fungoides or Sézary syndrome who have received at least two prior systemic treatments?

The clinical question specified in the DMC protocol states that the value of mogamulizumab should be investigated in patients who have received at least two prior systemic treatments contrary to the EMA approved indication of one prior systemic treatment and compared to one of the following protocol-specified comparators:

- *Targeted therapies:*
  - brentuximab vedotin
  - alemtuzumab
  - pembrolizumab

  Pathway inhibitor: romidepsin

  Or

- *Chemotherapy:*
  - high dose methotrexate
  - doxorubicin
  - gemcitabine.

It should be noted that treatment of CTCL patients with all comparators listed, except brentuximab vedotin, are used off-label. EMA has previously rejected marketing authorization for romidepsin in CTCL.

The protocol requests a comparison with at least one of the comparators within each of the two groups. The clinical expert committee states that the choice of therapy will depend on the individual patient characteristics, and consequently, selecting one specific comparator is not clinically meaningful. This is further substantiated by KOL input from two clinicians, a dermatologist and an oncologist[24,25]. Both clinicians stated that the choice of treatment would be based on the assessment of each individual patient, and no specific treatment could therefore be considered standard treatment. For the chemotherapy regimens, the oncologist preferred the use of gemcitabine, while the dermatologist mentioned the use of methotrexate and doxorubicin in their practice.[24,25] For the targeted therapy regimens, the dermatologist primarily uses brentuximab vedotin for CD30+ patients and alemtuzumab for CD52+ patients[25]. The oncologist primarily uses brentuximab vedotin for CD30+ patients, and noted that pembrolizumab might be used for some patients, however, she had the most experience with brentuximab[24].

As MF and SS are orphan disease populations, and given the high off-label use, very limited data exists for the treatment of MF and SS patients with the regimens listed in the DMC protocol. As no comparative efficacy data is available to differentiate the treatments from each other in the patient population relevant for mogamulizumab, the underlying assumption of the grouping of comparators in the DMC protocol is that the treatment regimens are considered equal alternatives. No studies for the stated comparators were identified which allowed for direct or indirect statistical comparison.

In this application, a basket approach has been applied for both the chemotherapy comparison and the targeted therapy comparison. This approach was adopted to allow for incorporation of the potential evidence available for the clinical question, given the limited evidence available. In addition, this approach is in line with the statements made in the protocol and KOL inputs[24,25], i.e. choosing one single comparator is not clinically meaningful, and all comparators in each basket are considered clinically equal.

Chemotherapy

Given the lack of available efficacy data for chemotherapy, vorinostat is assumed to be an appropriate proxy for the effectiveness of chemotherapy. This is assumed, as PFS outcomes with vorinostat in the MAVORIC study were similar to PFS outcomes observed in the physician's choice arm (i.e. bexarotene and methotrexate) in the ALCANZA study, the pivotal trial for brentuximab vedotin for the treatment of CTCL. The PFS curves from the ITT population of the vorinostat arm in the MAVORIC study and the physicians choice arm in the ALCANZA study overlap, as illustrated in Figure 16. This indicates that there is no statistical difference between efficacy of vorinostat and bexarotene/methotrexate for PFS. The ALCANZA study only included CD30+ positive patients, to match the mode of action of brentuximab vedotin, which challenges the comparison of the brentuximab vedotin arm, but clinically does not affect the use of the physicians choice arm (bexarotene and MTX), as these are not sensitive to CD30 status.

Due to the high effectiveness, safety, and ease of use, bexarotene is preferred to chemotherapies in Denmark, and is therefore used as first-line systemic treatment for MF and SS. Therefore, the use of vorinostat as a proxy for chemotherapy might overestimate the efficacy of chemotherapy especially given the differences in disease severity between the trial populations as explained above. Consequently, the observed efficacy difference between mogamulizumab and chemotherapy might be underestimated by this approach. Therefore, this approach is considered conservative.

The two Danish clinicians stated that vorinostat could be considered an appropriate proxy for chemotherapy[24,25].

Based on this, the vorinostat data from the MAVORIC trial is used as a proxy for the effectiveness of the chemotherapy arm, and the data has been used to capture PFS, OS, TTNT, and adverse events of the chemotherapy group.

Targeted therapy

The DMC committee considers all treatments in the targeted therapy basket as equal treatment options for the patient population. No efficacy data are available for the use of pembrolizumab, alemtuzumab and romidepsin for the full population of scope for this application. Brentuximab vedotin was investigated in the ALCANZA study, which reports data for CD30+ positive CTCL patients (MF and primary cutaneous anaplastic large cell lymphoma (pcALCL)), but due to significant differences in baseline characteristics and inclusion criteria, it is not possible to directly compare ALCANZA study results with MAVORIC study results.

6.1.1 Presentation of relevant studies

Two RCTs were included in the analysis together with two single-arm studies. All studies assessed patients diagnosed with MF[2,26,31,32], but only two included SS patients (MAVORIC[2] and Duvic et al. 2006[32]). MAVORIC compared mogamulizumab to vorinostat, ALCANZA compared brentuximab vedotin to methotrexate or bexarotene. EORTC 21012 and Duvic et al. 2006 were single-arm studies of doxorubicin and gemcitabine, respectively[31,32]. In all studies patients had received at least one prior systemic treatment, the median number of prior systemic treatments ranged from two in ALCANZA[26] to five in Duvic et al. 2006[32]. The proportion of patients in disease stage IIB or above ranged from 66% in ALCANZA[26] to 87% in EORTC 21012[31]. The median age ranged from 60 years in ALCANZA[26] to 64 years in MAVORIC[2].

OS was reported in MAVORIC, ALCANZA and Duvic et al. 2006. It is important to note that for both MAVORIC and ALCANZA crossover was allowed from the control arms (vorinostat and physicians choice, respectively), which significantly affected the OS results. Two trials reported PFS[2,26], and an additional trial reported time to progression (TTP)[32]. Only MAVORIC and ALCANZA reported estimates for Skindex-29. All studies reported on safety.

The proportion of patients with ECOG PS 0 ranged across the four trials from 43% in EORTC 21012 to 70% in ALCANZA. ECOG PS 1 ranged from 27% in ALCANZA to 53% in EORTC 21012. ECOG PS 2 ranged from 1% in MAVORIC to 4% in EORTC 21012.

6.1.2 Results per study

6.1.2.1 MAVORIC

To investigate whether using the ITT population would be appropriate to answer the clinical question, a subgroup analysis was conducted comparing the ITT population with the subgroup of patients from the MAVORIC trial, who had received at least two prior systemic treatments. The analysis showed that the Kaplan-Meier (KM) data for the two populations overlapped for both PFS and overall survival (OS) (included in section 10.5). No significant difference in OS, PFS and overall response rate (ORR) was observed between the ITT population and the subgroup, who had received at least two prior systemic treatments. It was therefore, concluded that it was appropriate to use the ITT population as the data analysis set. The median number of prior systemic treatment in the MAVORIC trial was 3, which supports the findings of the subgroup analysis. By using the ITT population, we avoid breaking the randomization and reducing the sample size. This approach was also approach considered appropriate by the DMC secretariat in dialogue leading up to the submission.

6.1.2.1.1 Overall survival (OS)

The MAVORIC trial was not powered to detect OS differences between the treatment arms. Furthermore, treatment switching, or crossover, from vorinostat to mogamulizumab was allowed for patients if they had received at least two cycles of treatment and showed confirmed disease progression or had intolerable toxicity (grade ≥3 adverse events, excluding inadequately treated nausea, vomiting, diarrhoea, and

alopecia), despite dose reduction and appropriate management of side-effects. Therefore, the unadjusted OS data are heavily confounded by consequence of the one-way crossover design: 135 patients (72,6% of patients) switched to mogamulizumab from the vorinostat arm. Consequently, the unadjusted OS data are not appropriate to use to assess the efficacy on OS of mogamulizumab compared to vorinostat. Results for both the unadjusted and crossover adjusted OS are explored in the following section.[2,33]

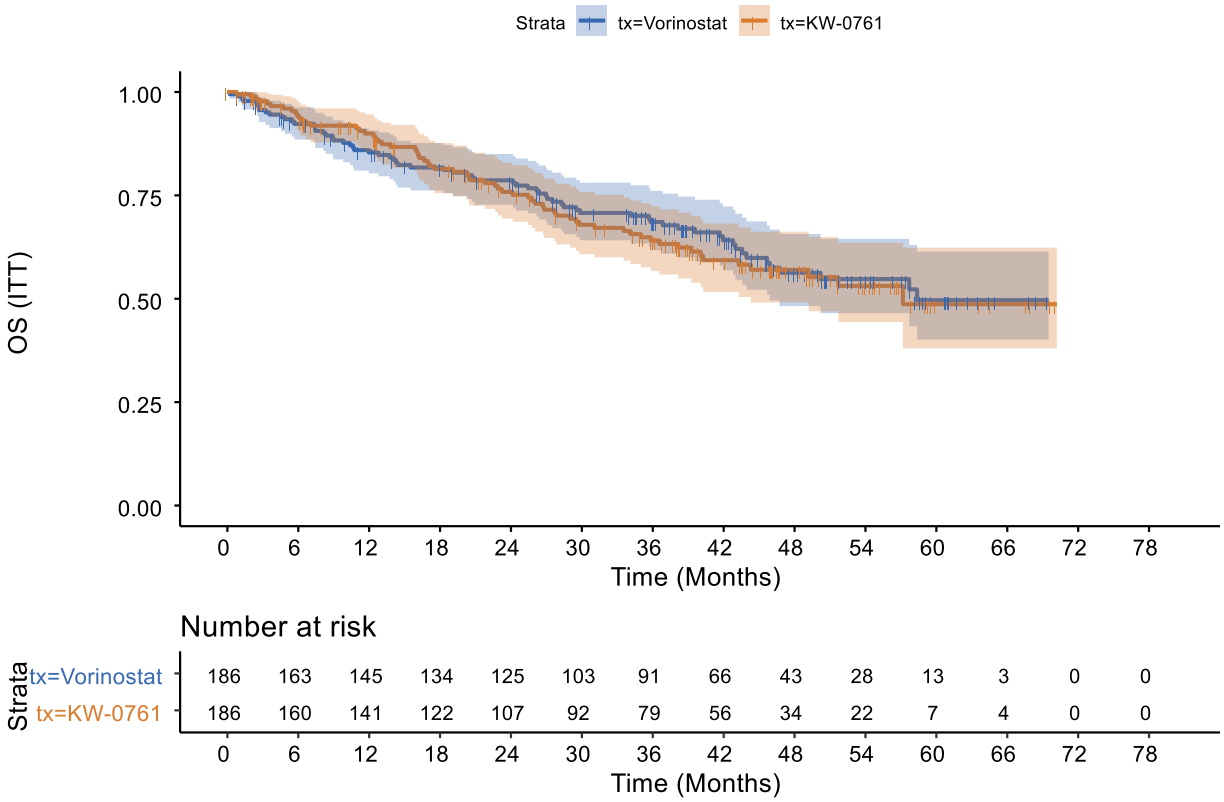
The median OS in the ITT population was not reached with mogamulizumab and was 43,9 months with vorinostat resulting in a HR of 0,93 (95% CI: 0,6-1,4; p-value: 0,94) in the unadjusted ITT analysis at the data cut-off, 31 December 2016. This data should be interpreted with caution, due to the immaturity of the data (only 23% of patients have experienced an OS event) and the confounding, due to high rate of crossover (72,6% of patients switched to mogamulizumab from the vorinostat arm), makes the interpretation of the results difficult without additional adjustment.[2,33] At the data cut-off 2 March 2019, the median OS in the ITT population was 57,16 months (95% CI: 43,26-NE) with mogamulizumab and was 58,37 months (95% CI: 45,9-NE) with vorinostat resulting in a HR of 1,057 (95% CI: 0,751-1,489; p-value: 0,75).

A summary of unadjusted OS is presented in Table 4, and a KM plot for unadjusted OS is presented in Figure 4.

Table 4: Summary of overall survival: ITT population, data cut-off 31 December 2016

Data cut-off	31 December 2016		2 March 2019	
	Mogamulizumab (n=186)	Vorinostat (n=186)	Mogamulizumab (n=186)	Vorinostat (n=186)
OS (months), median (95% CI)	NE (NE-NE)	43,93 (43,57-NE)	57,16 (43,26-NE)	58,37 (45,9-NE)
Hazard ratio (95% CI)	0,93 (0,61-1,43)		1,057 (0,75-1,49)	
Log rank p-value	0,94		0,75	
CI, confidence interval; ITT, intention-to-treat; NE, not estimable; OS, overall survival.				

Figure 4: MAVORIC unadjusted OS KM data, ITT population, data cut-off 2 March 2019

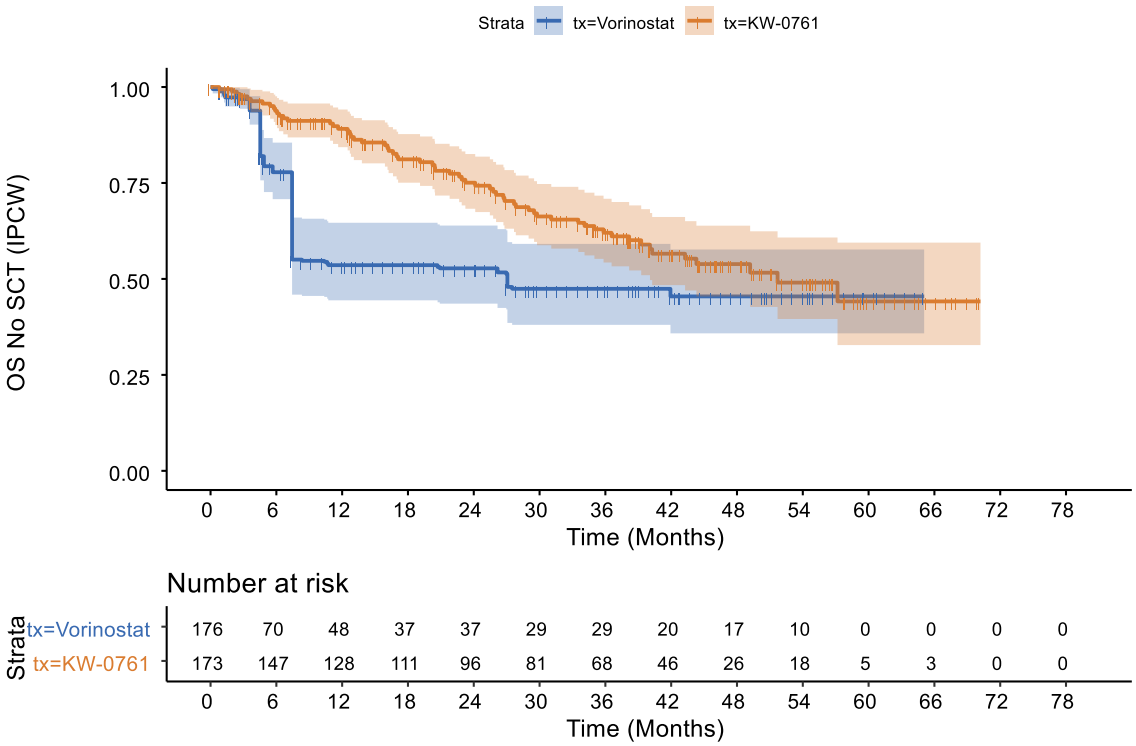


To adjust for the effect of patients crossing over to the mogamulizumab arm, a crossover adjusted OS data set have been included. According to the NICE DSU TSD 16, both simple and complex methods are available for crossover adjustment[34]. Simple methods such as censoring or excluding patients who crossover would remove prognostically worse patients from the comparator arm, and as such likely artificially inflate the treatment effect. Therefore, two complex methods were considered: the inverse probability of censoring weights (IPCW) and the two-stage estimation method (TSE). Both crossover adjusted analyses below have excluded patients receiving aSCT, as the OS of the MAVORIC trial could not take into account the survival of these patients due to their longer survival.

The IPCW method weights patients in the control arm according to their probability of switching treatment. This method increases weights for patients with a low probability of treatment switch and decreases weights for patients with a high probability of treatment switch. Patients who switch are censored at the time of cross-over. A key assumption of this method is no unmeasured confounders. If there are any baseline or time-dependent prognostic factor data for mortality that independently predict informative censoring (switching) which were not collected, then the results could be biased. The analysis considered the following characteristics: Progression status, ECOG, Histology (MF/SS), Disease Stage, age > 65 years, adverse events, and region.

Figure 5 presents the IPCW adjusted KM curves by randomised treatment arm for OS in the ITT population, with the patients receiving aSCT excluded. A large drop in risk at six months with the IPCW adjustment is observed in Figure 5. This a statistical artefact of the MAVORIC trial protocol and is due to the MAVORIC trial design, which allows patients to crossover after two full cycle of treatment and an additional minimum of two weeks waiting period.

Figure 5 MAVORIC OS KM data, ITT population with IPCW adjustment, data cut-off 2 March 2019



The median OS in the ITT population with IPCW adjustment was 51,7 months (95% CI: 40,07 - NE) mogamulizumab and was 27,07 months (95% CI: 7,43 - NE) with vorinostat resulting in a HR of 0,57 (95% CI: 0,26, 1,25; p-value: 0,16) in the ITT analysis with IPCW adjustment. A summary of OS is presented in Table 5.

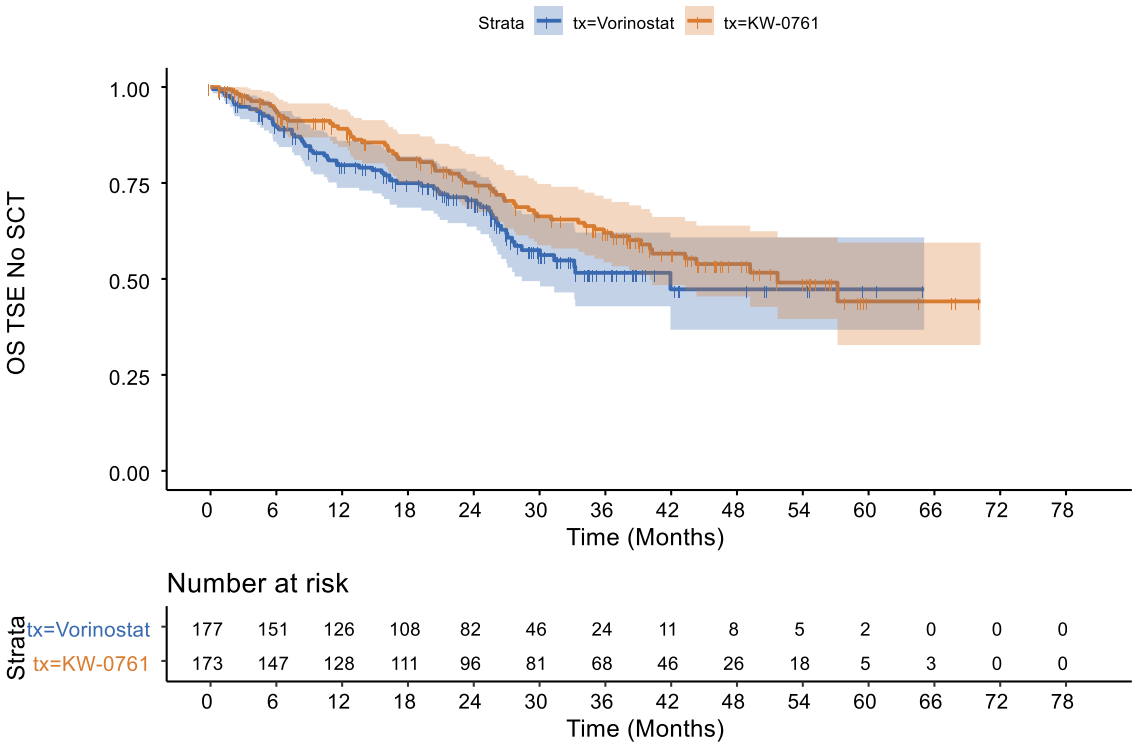
Table 5: Summary of overall survival: ITT population with IPCW adjustment excl. aSCT, data cut-off 2 March 2019

	Mogamulizumab (n=173)	Vorinostat (n=176)
OS (months), median (95% CI)	51,7 (40,07 - NE)	27,07 (7,43 - NE)
Hazard ratio (95% CI)	0,57 (0,26-1,25)	
Log rank p-value	0,16	
CI, confidence interval; ITT, intention-to-treat; NE, not estimable; OS, overall survival.		

The TSE method models the potentially different treatment effects at the beginning versus in the later course of a trial, then estimate the treatment effect using the counterfactual survival time as if no treatment switch had occurred after the pre-specified secondary baseline.

Figure 6 presents TSE adjusted KM curves by randomised treatment arm for OS in the ITT population, with patients receiving aSCT excluded.

Figure 6. MAVORIC OS KM data, ITT population with TSE adjustment, data cut-off 2 March 2019



The median OS in the ITT population with TSE adjustment was 51,7 months (95% CI: 40,07-NE) mogamulizumab and was 41,9 months (95% CI: 28,37-NE) with vorinostat resulting in a HR of 0,75 (95% CI: 0,53-1,07; p-value: 0,116) in the ITT analysis with TSE adjustment. A summary of OS is presented in Table 6.

Table 6: Summary of overall survival: ITT population with TSE adjustment excl. aSCT, data cut-off 2 March 2019

	Mogamulizumab (n=173)	Vorinostat (n=177)
OS (months), median (95% CI)	51,7 (40,07-NE)	41,93 (28,37-NE)
Hazard ratio (95% CI)	0,75 (0,53-1,07)	
Log rank p-value	0,116	
CI, confidence interval; ITT, intention-to-treat; NE, not estimable; OS, overall survival.		

The findings presented above for OS are expected, as the study was not powered to detect differences in OS i.e. OS data from MAVORIC is not appropriate to make conclusions on the statistical significance of the OS differences. Even though MAVORIC was not powered to detect differences in OS, the results show a trend of an OS improvement in the ITT and crossover adjusted analyses, which is remarkable within the limited study time frame.

6.1.2.1.1.1 Validation crossover adjusted analyses

Methodologically, neither the IPCW or TSE crossover adjustment method is preferred to the other. To determine the appropriate crossover adjustment method, validation with external data have been conducted. Survival data was identified for MF and SS patients after one prior systemic treatment in published data and in the UK HES database. When comparing to this data, the IPCW method results are in line with the prognosis of these patients in the database and did not exceed the prognosis of the patients in the publications. The TSE method were likely to overestimate overall survival prognosis compared to the HES

data and the published data. For statistical comparison, see section 3.3.3 in the health economic technical document.

6.1.2.1.2 Progression-free survival (PFS)

Mogamulizumab treatment resulted in a statistically significant improvement in investigator-based PFS.[2,33]

At 6, 12, 18 and 24 months after the start of randomised treatment, the percent of subjects alive without disease progression was higher for mogamulizumab (55,3%, 38,3%, 28,0%, and 14,1%, respectively) compared to vorinostat (28,8%, 15,3%, 7,2%, and 7,2%, respectively). Median PFS for the mogamulizumab group was 7,7 months (95% CI: 5,67-10,33) and 3,1 months (95% CI: 2,87-4,07) for the vorinostat group, which resulted in a HR of 0,53 (95% CI: 0,41-0,69), p<0,0001 (2-sided, stratified log rank test) according to the investigator-assessed analysis. According to independent review, median progression-free survival was 6,7 months (95% CI: 5,6-9,4) in the mogamulizumab group and 3,8 months (95 CI: 3,0-4,7) in the vorinostat group resulting a HR of 0,64 (95% CI: 0,49-0,84; p<0,0007).[2,33]

The PFS effect size was not consistent across subgroups; subgroup analyses indicate that the effect size of PFS depends on the stage of the disease. The available data demonstrate a clinically relevant PFS advantage with mogamulizumab compared to vorinostat in subjects with SS (median PFS 13,3 vs. 3,13 months, respectively, HR 0,32, p<0,0001) and MF patients with advanced disease (stage III/IV, median PFS 10,9 vs. 3,0 months, HR 0,36, p<0,0001). In the less advanced patients (stage IB/II), a limited 0,8 months advantage in PFS was observed with mogamulizumab vs. vorinostat (median PFS 4,7 vs. 3,9 months, HR 0,88, p=0,7166). In the MF patients, a moderate 2,3 months advantage was observed with mogamulizumab vs. vorinostat (median PFS 5,4 vs. 3,1 months, HR 0,72, p=0,0675).[2,33]

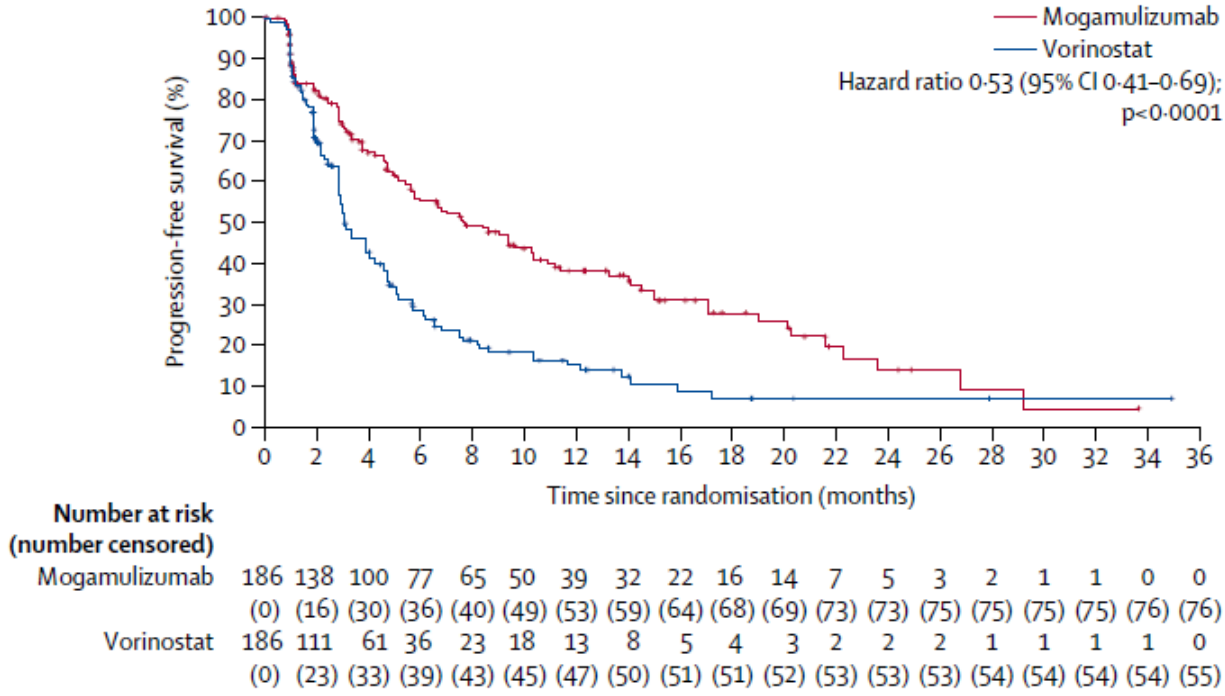
Table 7 Summary of PFS in ITT population and pre-specified subgroups, data cut-off 31 December 2016

	Mogamulizumab (n=173)	Vorinostat (n=177)
PFS (months) ITT, median (95% CI)	7,70 (5,67-10,33)	3,10 (2,87-4,07)
Hazard ratio (95% CI)	0,53 (0,41-0,69)	
Log rank p-value	0,0001	
PFS (months) SS, median (95% CI)	13,3 (7,70-17,07)	3,13 (2,83-3,87)
Hazard ratio (95% CI)	0,32 (0,21-0,49)	
Log rank p-value	0,0001	
PFS (months) MF, median (95% CI)	5,40 (3,97-7,57)	3,10 (2,87-4,70)
Hazard ratio (95% CI)	0,72 (0,51-1,01)	
Log rank p-value	0,0675	
PFS (months) III/IV, median (95% CI)	10,90 (7,03-15,03)	3,00 (2,83-3,87)
Hazard ratio (95% CI)	0,36 (0,26-0,51)	
Log rank p-value	0,0001	
PFS (months) IB/II, median (95% CI)	4,70 (2,90-7,47)	3,90 (2,87-4,73)
Hazard ratio (95% CI)	0,88 (0,58-1,35)	
Log rank p-value	0,716	

CI, confidence interval; ITT, intention-to-treat; NE, not estimable; OS, overall survival.

Figure 7 presents a Kaplan–Meier (KM) plot of PFS for the ITT population. The curves for the mogamulizumab and vorinostat treatment arms begin to separate within the second cycle of treatment, and the separation is maintained through till approximately month 28.

Figure 7: Kaplan–Meier plot of investigator-assessed progression-free survival: ITT population, data cut-off 31 December 2016



CI, confidence interval; ITT, intention-to-treat.

For the 133 patients who crossed over from vorinostat and received mogamulizumab, median PFS calculated from the first dose of mogamulizumab was 8,87 months (95% CI: 5,37-14,77)[2,33].

The majority of censored observations were due to patients who discontinued randomized treatment without documented disease progression per CTCL response criteria. The percentage of patients who were censored due to discontinuation for AE or intolerance was higher for the vorinostat group than for the mogamulizumab group, while the percentage of patients who were censored due to discontinuation for clinical progression was similar for the two treatment groups.

6.1.2.1.3 Skindex-29

The Skindex-29 is used to measure the effect of skin disease on health-related quality of life (HRQoL); it consists of 29 items assessing three domains: emotions, symptoms, and functioning. Higher scores indicate a higher impact of skin disease.

Skindex-29 results from MAVORIC indicated significant HRQoL improvements following treatment with mogamulizumab compared with vorinostat. The least-square (LS) mean change from baseline (CFB) to cycle 11 of -15,7 (95% CI: -20,96- -10,67) for treatment with mogamulizumab and -3,6 (95%: -9,93-2,7) for treatment with vorinostat, resulted in LS mean CFB difference between mogamulizumab and vorinostat of -12,1 (95%: -19,47- -4,69) p=0,0014.[35]

Figure 8 Skindex-29 Total Score

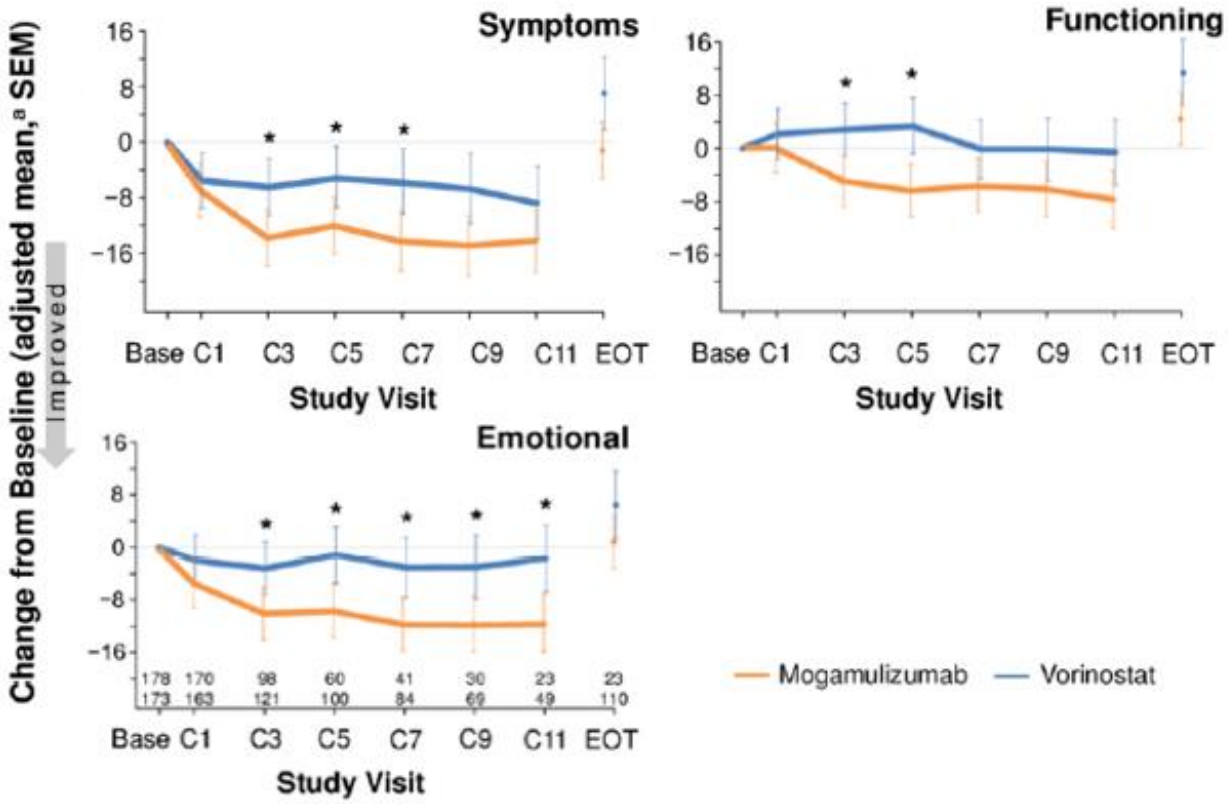
		n	Mean (SD)	LS mean (SD)
Vorinostat	Baseline	164	48,3 (20,06)	-3,6 (-9,93 - 2,7)
	Cycle 11	22	45,3 (19,06)	

Mogamulizumab	Baseline	155	52,3 (21,13)	-15,7 (-20,96 - -10,67)
	Cycle 11	44	54,6 (21,68)	
CFB difference mogamulizumab vs vorinostat (LS mean, 95% CI) p-value			**-12,1 (-19,47- -4,69) p=0,0014**	

Time points beyond Cycle 11 are not included due to the small number of subjects on study after cycle 11.

These findings were further supported by analyses of individual emotional, functional and symptoms domain scores, where mogamulizumab demonstrated significant improvements.[35]

Figure 9 Treatment effects in the Skindex-29



EOT, end of treatment; SEM, standard error of mean. [a]p<0.05.
Source: Quaglino, et al. 2018[36]

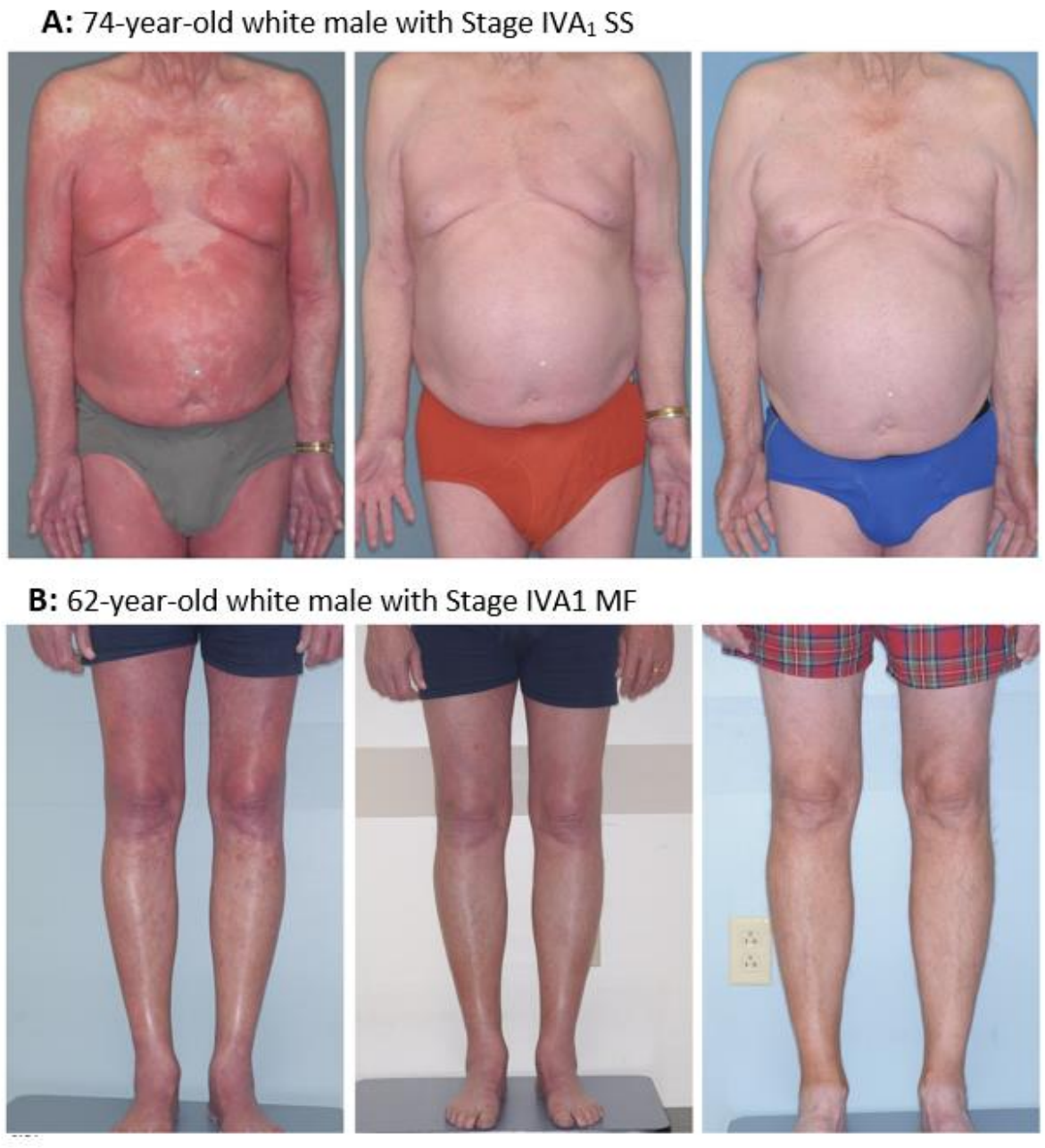
Improvements in all three domains were seen in patients in both treatment arms, however, greater improvements were observed with mogamulizumab treatment compared with vorinostat.[35]

When assessing the proportion of patients reporting clinically meaningful improvements in the individual Skindex-29 domains, statistically significant differences in favour of mogamulizumab were observed at cycle 5 for the functioning domain (54,3% vs. 28,8%; p=0,0068), and at cycles 3, 5, 7 and 11 for the symptoms domain. At least 60% of patients randomised to mogamulizumab reported clinically meaningful improvements in symptoms beginning at cycle 3 and lasting throughout treatment.[35]

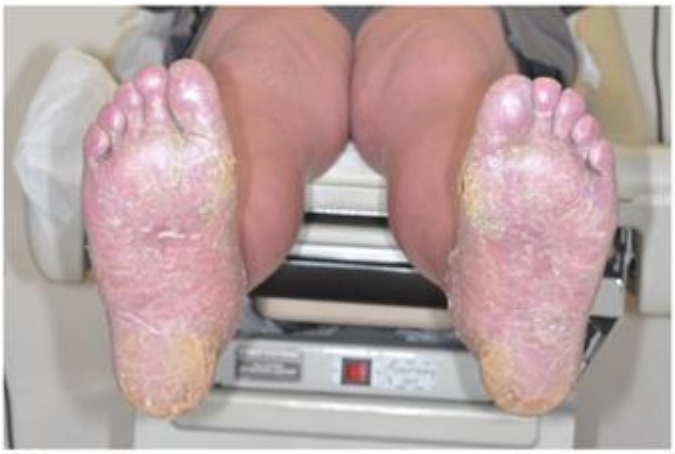
Treatment with mogamulizumab also resulted in numerically longer times to clinically meaningful worsening in Skindex-29 domains compared with vorinostat. The median time to worsening of symptoms was significantly longer for patients treated with mogamulizumab compared to those treated with vorinostat (27,4 vs. 6,6 months; p=0,08).[35]

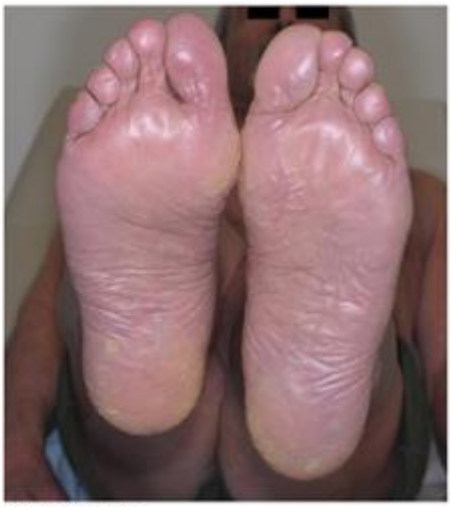
These data indicate that mogamulizumab improves both disease-specific symptoms (e.g. skin pain, burning, stinging, bleeding and itching) and patient functioning (e.g. fatigue, ability to work and sex-life) in addition to preserving HRQoL for a substantial period of time compared to vorinostat.[35]

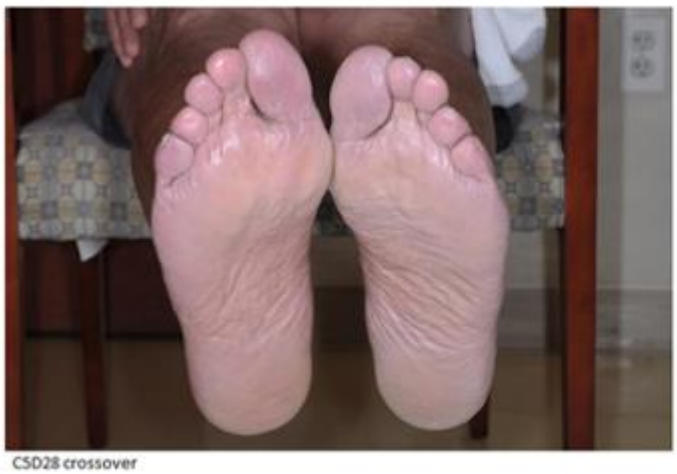
Figure 10 Images of response to mogamulizumab in advanced MF and SS patients (movement over time from left to right)

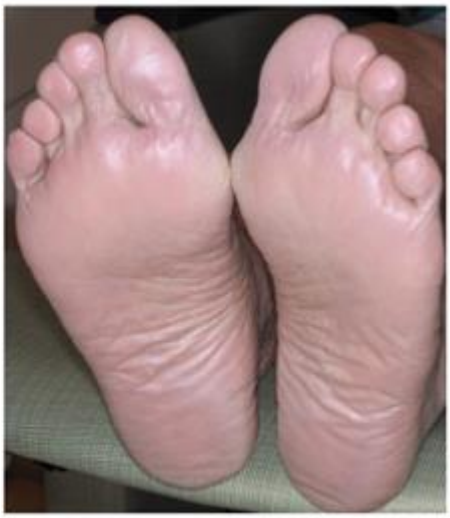


C: 68-year old white male with Stage IIIA MF


C1D1 crossover


C2D28 crossover


C5D28 crossover


C10D28 crossover

C, cycle; D, day; MF, mycosis fungoides; SS, Sézary syndrome.
Notes: A, progression of response through 51 cycles of mogamulizumab from 3 December 2014 to December 2016; B, progression of response through 36 cycles of mogamulizumab from 19 Dec 2013 to 20 October 2016; C, progression of response through 20 cycles of mogamulizumab from 13 October 2015 to December 2016.
Source: Data on file

6.1.2.1.4 Adverse events

6.1.2.1.4.1 Proportion of patients experiencing adverse events grade 3-4

The MAVORIC trial reported similar rates of Grade 3, 4 or 5 AEs between the mogamulizumab group and the vorinostat group (45,7% and 46,2%, respectively) and Grade 3, 4 or 5 treatment-emergent adverse events (TEAEs) (42,4% and 45.7, respectively), while the incidence of drug-related Grade 3, 4 or 5 TEAEs was lower for mogamulizumab (25,5%) compared to vorinostat (34,9%). Of note, the incidence of TEAEs observed for patients receiving mogamulizumab after crossover was similar to that observed for patients randomised to mogamulizumab. During the randomised treatment period, the incidence of TEAEs were very similar between the mogamulizumab and vorinostat treatment groups (97,3% and 99,5%, respectively), while

the incidence of drug-related TEAEs was somewhat lower for mogamulizumab (84,8%) compared with vorinostat (95,7%).[2,33]

6.1.2.1.4.2 Proportion of patients experiencing serious adverse events

The incidence of serious adverse events (SAEs) was higher in the mogamulizumab group (39,7%) than the vorinostat group (24,7%). Treatment-emergent serious adverse events (SAEs) was higher in the mogamulizumab group (37,5%) than the vorinostat group (24,7%); the incidence of drug-related SAEs was 19,6% in the mogamulizumab group compared with 16,1% in the vorinostat group. In the mogamulizumab arm, the most frequently reported SAEs of any cause were pyrexia in eight (4%) and cellulitis in five (3%) patients. In the vorinostat arm, the most frequently reported SAEs were cellulitis in six (3%), pulmonary embolism in six (3%), and sepsis in five (3%) patients.[2,33]

For mogamulizumab, the most common treatment-related SAEs were pneumonia in four (2%) patients and pyrexia in four (2%) patients and for vorinostat pulmonary embolism in five (3%) patients and thrombocytopenia in three (2%) patients.[2,33]

Table 8 Overview of adverse events: Safety population

	Pre-treatment and randomised treatment period		Crossover portion
	Mogamulizumab (n=184)	Vorinostat (n=186)	Mogamulizumab (n=136)
Adverse Events (AEs), n (%)			
Any AEs	180 (97,8)	185 (99,5)	127 (93,4)
Any TEAEs	179 (97,3)	185 (99,5)	127 (93,4)
Drug-related TEAEs	156 (84,8)	178 (95,7)	99 (72,8)
NCI/CTCAE Grade 3, 4, 5 AEs, n (%)			
Any Grade 3, 4, 5 AEs	84 (45,7)	86 (46,2)	48 (35,3)
Any Grade 3, 4, 5 TEAEs	78 (42,4)	85 (45,7)	47 (34,6)
Drug-related Grade 3, 4, 5 TEAEs	47 (25,5)	65 (34,9)	21 (15,4)
AEs with Outcome of Death	5 (2,7)[b]	9 (4,8)[a]	4 (2,9)[a]
Serious Adverse Events, n (%)			
Any SAEs	73 (39,7)	46 (24,7)	38 (27,9)
Treatment-emergent SAEs	69 (37,5)	46 (24,7)	36 (26,5)
Drug-related Treatment-emergent SAEs	36 (19,6)	30 (16,1)	14 (10,3)
Discontinuation due to AEs, n (%)			
Any AEs	35 (19,0)	43 (23,1)	30 (22,1)
Any TEAEs	35 (19,0)	43 (23,1)	30 (22,1)
Drug-related TEAEs	25 (13,6)	40 (21,5)	23 (16,9)

AE, adverse event; SAE, serious adverse event; TEAE, treatment-emergent adverse event;
Notes: [a], includes one patient with TEAE with outcome of death that occurred during crossover and >30 days after the last dose of vorinostat, but was related to vorinostat; [b], includes two patients with non-TEAEs with outcome of death.

6.1.2.1.4.3 Exposure Adjusted Incidence of Selected AEs

During the randomized treatment period, the median duration of exposure was approximately twice as long for mogamulizumab compared to vorinostat (170 and 84 days, respectively). In order to determine the effect that length of treatment might have on the incidence of AEs, exposure-adjusted analyses of incidence rates were examined for pre-selected system organ classes (SOCs) including Infections and Infestations;

Respiratory, Thoracic and Mediastinal Disorders; Musculoskeletal and Connective Tissue Disorders; and Renal and Urinary Disorders. Although there was a higher percentage of subjects with TEAEs in the Infections and Infestations SOC in the mogamulizumab group (64,1%) versus the vorinostat group (50,0%), the exposure-adjusted TEAE incidence rate was lower for the mogamulizumab group (0,058 events per patient-months of exposure) compared to the vorinostat group (0,091 events per patient-months of exposure). For individual TEAEs that occurred more frequently in the mogamulizumab group than in the vorinostat group, including upper respiratory tract infection, folliculitis, and oral candidiasis, the exposure adjusted incidence was similar for the treatment groups, suggesting that these events were due to underlying conditions in this subject population.

Exposure-adjusted incidence rates are presented for all TEAEs in the Infections and Infestations SOC in Table 9.

Table 9 Exposure-adjusted incidence rates for infections and infestations treatment-emergent adverse events reported by ≥ 5% of subjects in either treatment group (safety analysis set)

MedDRA system organ class[b] preferred term	Number (%) of Subjects with TEAE		Incidence rates per subject-months of exposure[a]	
	Vorinostat N=186	Mogamulizumab N=184	Vorinostat	Mogamulizumab
Infections and Infestations	93 (50,0)	118 (64,1)	0,091	0,058
Upper respiratory tract	9 (4,8)	19 (10,3)	0,009	0,009
Skin infection	13 (7,0)	17 (9,2)	0,013	0,008
Folliculitis	4 82,2)	13 (7,1)	0,004	0,006
Nasopharyngitis	15 (8,1)	12 (6,5)	0,015	0,006
Urinary tract infection	15 (8,1)	12 (6,5)	0,015	0,006
Oral candidiasis	1 (0,5)	10 (5,4)	0,001	0,005
Cellulitis	10 (5,4)	6 (3,3)	0,010	0,003

A: Incidence rates per subject-months of exposure = (Number of Subjects with TEAE/ Sum of days at risk for TEAE) × 30.42 days/month B: MedDRA Version 15.1 was used for coding.
MedDRA=Medical Dictionary for Regulatory Activities; TEAE=treatment-emergent adverse event.

6.1.2.2 ALCANZA

6.1.2.2.1 Overall survival (OS)

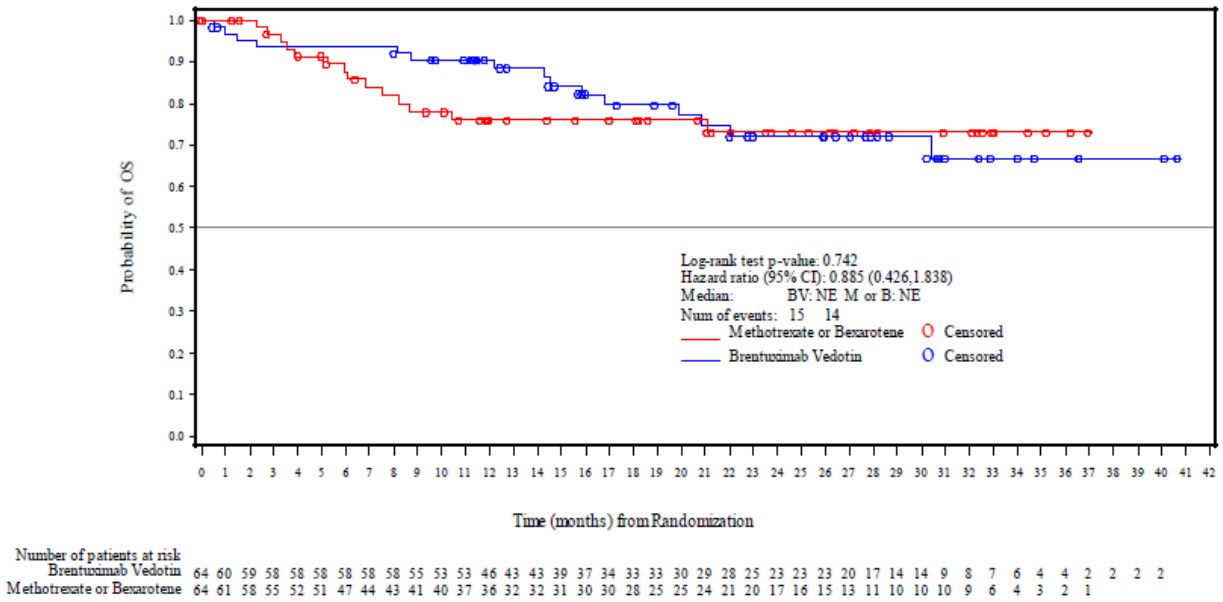
The median OS was not reached in either the brentuximab vedotin or the physician's choice arm. The number of events were 15/64 patients (23%) in the brentuximab vedotin arm and 14/64 patients (22%) in the physician's choice arm resulting a HR of 0,89 (95% CI: 0,43-1,84; p-value: 0,74). This data should be viewed with caution due to the immaturity of the data (only 23% of patients experienced an OS event) and crossover. Table 10 provides an overview of the OS data in the ITT population.[26] A Kaplan-Meier (KM) plot of OS is presented in Figure 11.

Table 10: Summary of overall survival: ITT population

	Brentuximab vedotin (n=64)	MTX or bexarotene (n=64)
OS (months), median (95% CI)	NE (30,4-NE)	NE (NE-NE)
Hazard ratio (95% CI)	0,89 (0,43-1,84)	
Log rank p-value	0,4	

Patients died, n (%)	15 (23)	14 (22)
CI, confidence interval; ITT, intention-to-treat; NE, not estimable; OS, overall survival.		

Figure 11 Kaplan–Meier curve of overall survival: ITT population

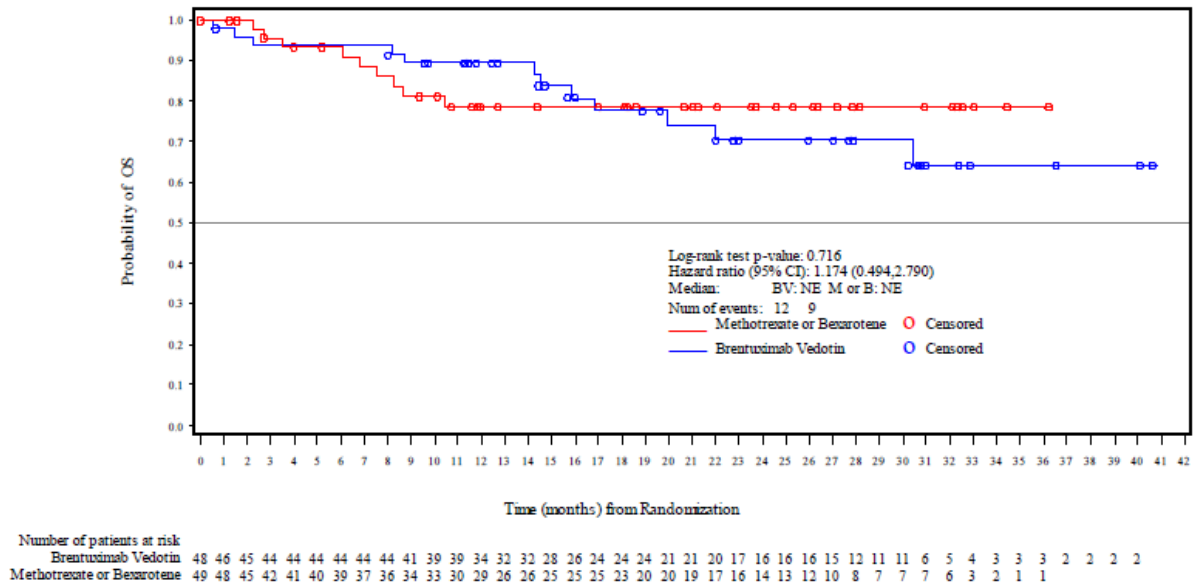


In the MF subgroup analysis, the median OS was not reached in either the brentuximab vedotin or the physician's choice arm. The number of events was 12/48 patients (25%) in the brentuximab vedotin arm and 9/49 patients (18%) in the physician's choice arm resulting in a HR of 1,17 (95% CI: 0,49-2,79; p-value: 0,72). This data should be viewed with caution due to the immaturity of the data and crossover. Table 11 provides an overview of the OS data in the ITT population.[26] A Kaplan-Meier (KM) plot of OS is presented in Figure 12.

Table 11: Summary of overall survival: MF subgroup

	Brentuximab vedotin (n=48)	**MTX or bexarotene (n=49)**
OS (months), median (95% CI)	NE (30,4-NE)	NE (NE-NE)
Hazard ratio (95% CI)	1,17 (0,49-2,79)	
Log rank p-value	0,72	
Patients died, n (%)	12 (25)	9 (18)
CI, confidence interval; ITT, intention-to-treat; NE, not estimable; OS, overall survival.		

Figure 12 Kaplan–Meier curve of overall survival: MF population



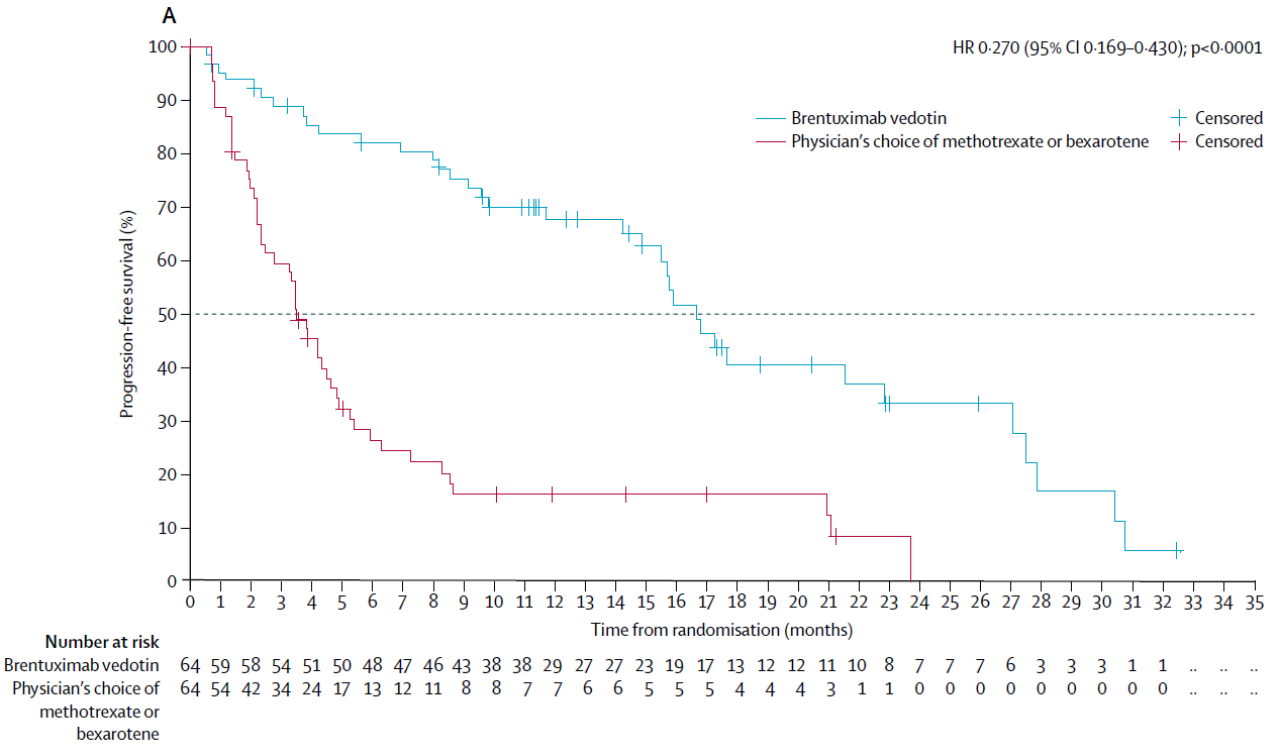
6.1.2.2.2 Progression-free survival (PFS)

The PFS analyses were performed with a median PFS follow-up of 17,5 months. At the time of data cut-off, 86 (67%) patients had experienced a PFS event: progressive disease per IRF in 74 patients (30 patients (47%) in the brentuximab vedotin arm and 44 patients (69%) in the physician's choice arm and death in 12 patients (6 patients (9%) in the brentuximab vedotin arm and 6 patients (9%) in the physician's choice arm. Median progression-free survival was 16,7 months in the brentuximab vedotin group versus 3,5 months in the physician's choice group (HR 0,27 (95% CI: 0,17-0,43; p<0,0001)). Table 12 provides an overview of the PFS data in the ITT population.[26] A Kaplan-Meier (KM) plot of PFS is presented in Figure 13.

Table 12: Summary of PFS: ITT population

	Brentuximab vedotin (n=64)	MTX or bexarotene (n=64)
PFS (months), median (95% CI)	16,7 (14,9-22,8)	3,5 (2,4-4,6)
Hazard ratio (95% CI)	0,27 (0,17-0,43)	
Log rank p-value	<0,01	
CI, confidence interval; ITT, intention-to-treat; NE, not estimable; PFS, progression-free survival.		

Figure 13 Kaplan–Meier curve of PFS: ITT population



In the MF subgroup analysis, the median PFS was 15,9 months in the brentuximab vedotin group versus 3,5 months in the physician's choice group (HR 0,273 (95% CI: 0,164-0,455)).[26]

6.1.2.2.3 Skindex-29

The ALCANZA trial measured the following Skindex-29 domains: symptoms, emotions, functioning and total score. The mean changes from baseline to end of treatment Skindex-29 composite total score were -14,84 (SD: 22,68) with brentuximab vedotin and -0,96 (SD: 18,97) with physician's choice, resulting in a difference of 13,88 points.[30]

6.1.2.2.4 Adverse events

6.1.2.2.4.1 Proportion of patients experiencing adverse events grade 3-4

Grade 3–4 adverse events were reported in 27 (41%) of 66 patients in the brentuximab vedotin group and 29 (47%) of 62 patients in the physician's choice group. Grade 3 TEAEs were reported with similar frequency in both arms (32%). Grade 4 TEAEs were reported in 5% of brentuximab vedotin treated patients and 15% of patients in the physician's choice arm. The most frequent Grade 3-4 TEAEs in the brentuximab vedotin arm were infections and infestations, and nervous system disorders.[26]

6.1.2.2.4.2 Proportion of patients experiencing serious adverse events

Serious adverse events were similar between groups, occurring in 19 (29%) of 66 patients in the brentuximab vedotin group versus 18 (29%) of 62 patients in the physician's choice group. Nine patients (14%) in the brentuximab vedotin arm and 3 patients (5%) in the physician's choice arm experienced a combined total of 20 SAEs that were assessed as related to study drug. Discontinuation due to adverse events occurred in 16 (24%) patients in the brentuximab vedotin group versus five (8%) in the physician's choice group.[26]

Considering all adverse events, peripheral neuropathy, a known toxicity with brentuximab vedotin, was reported in 44 (67%) of 66 patients in the brentuximab vedotin group (n=17 grade 1, n=21 grade 2, n=6 grade 3) and four (6%) of 62 patients in the physician's choice group (n=1 grade 1, n=3 grade 2). Nine patients discontinued assigned treatment due to peripheral neuropathy in the brentuximab vedotin group (none in the physician's choice group). At the last follow-up (median 22,9 months), 36 (82%) of 44 patients in the brentuximab vedotin group had improvement (≥1 grade) or resolution of peripheral neuropathy. Elevated serum transaminase concentrations, a known toxicity for methotrexate, were not frequently seen in either group. Elevated triglycerides, a known toxicity with bexarotene, were reported in one (2%) of 66 patients receiving brentuximab vedotin (grade 1) versus 11 (30%) of 37 patients receiving bexarotene (n=1 grade 1, n=2 grade 2, n=5 grade 3, n=3 grade 4).[26]

6.1.2.3 EORTC 21012

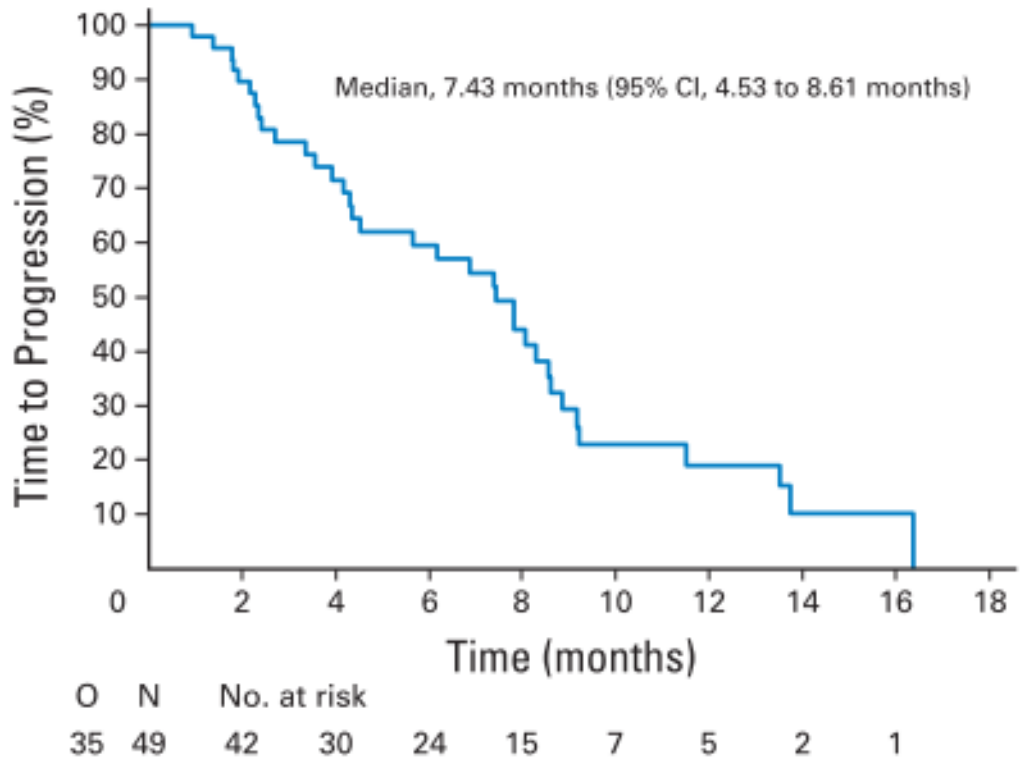
6.1.2.3.1 Overall survival (OS)

EORTC 21012 did not report data for OS.

6.1.2.3.2 Progression-free survival (PFS)

EORTC 21012 reported time to progression (TTP) based on skin assessment alone but not PFS. As PFS and TTP are similar, with the difference being TTP do not count patients who die from other causes but is otherwise a close equivalent to PFS, TTP estimates were included as a close proxy for PFS. TTP was defined as the interval of time between the date of registration and the date of first documentation of disease progression. Patients who died without progressive disease were censored at the date of death. Patients alive without progressive disease were censored at the last date they were known to be alive. Of 49 patients, 35 progressions were observed. The median TTP was 7,4 months (95% CI: 4,5-8,6 months).[31]

Figure 14 Kaplan–Meier curve of TTP



6.1.2.3.3 Skindex-29

EORTC 21012 did not report data for QoL or Skindex-29.

6.1.2.3.4 Adverse events

6.1.2.3.4.1 Proportion of patients experiencing adverse events grade 3-4

Grade 3–4 adverse events were reported in 20 (41%) of 49 patients. There were no grade 3 to 4 hematologic toxicities. Grade 3 to 4 nonhematologic or nonbiochemical toxicities included cardiac symptom (n=1), allergy/hyper- sensitivity (n=1), constitutional symptom (n= 2), hand and foot reaction (n=1), other dermatologic toxicity (n=3), GI toxicity (n= 2), and infection (n=2). One patient experienced grade 4 pulmonary embolism, one experienced grade 4 cardiac ischemia, and two experienced grade 3 middle-ear inflammation.[31]

6.1.2.3.4.2 Proportion of patients experiencing serious adverse events

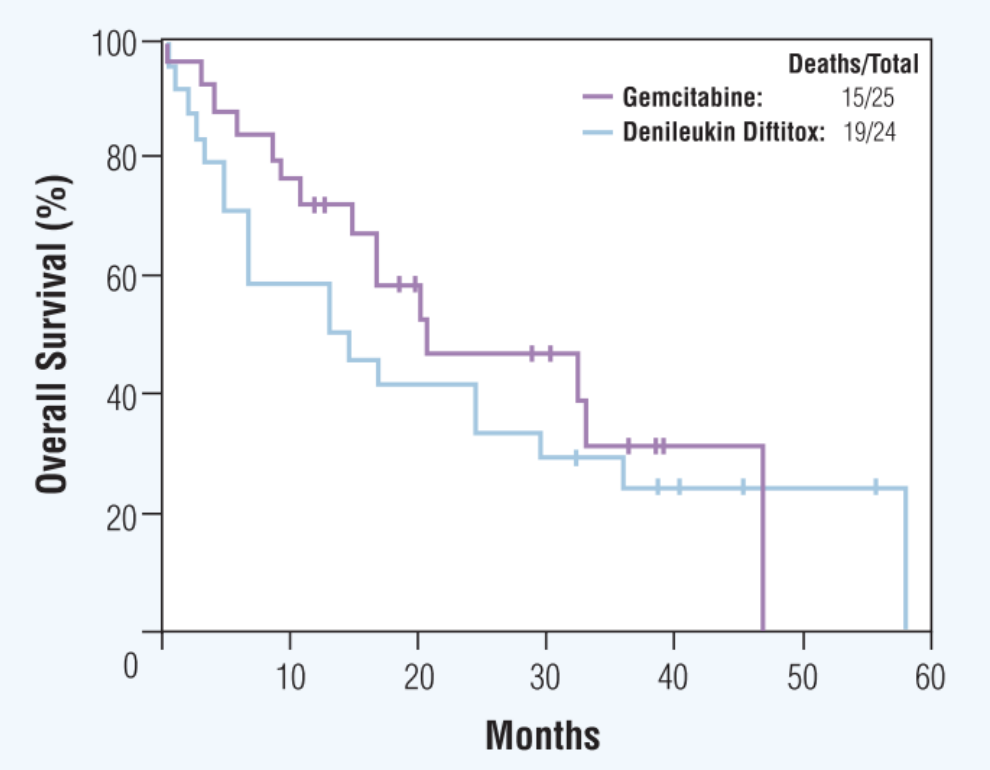
Serious adverse events were not reported in EORTC 21012[31].

6.1.2.4 Duvic et al. 2006

6.1.2.4.1 Overall survival (OS)

Overall survival of all patients treated with gemcitabine was compared retrospectively, with OS among 24 patients treated with denileukin diftitox. Twenty-five patients were followed for a median of 38,5 months, with 15 deaths occurring. The estimated median OS was 20,4 months, and the estimated 3-year OS was 28% (95% CI, 17%, 46%). Among 8 patients treated with gemcitabine off protocol, 6 have died and 2 were lost to follow-up within 3 years after treatment. These patients had a median OS of 15 months.
Figure 15 shows the KM curve of OS in patients treated with gemcitabine.

Figure 15 Kaplan–Meier curve of OS in patients treated with gemcitabine and denileukin diftitox



6.1.2.4.2 Progression-free survival (PFS)

Duvic et al. 2006 did not report data for PFS.

6.1.2.4.3 Skindex-29

Duvic et al. 2006 did not report data for QoL or Skindex-29.

6.1.2.4.4 Adverse events

6.1.2.4.4.1 Proportion of patients experiencing adverse events grade 3-4

Grade 3–4 adverse events were reported in 22 (41%) of 33 patients. Grade 3 hematologic side effects (anaemia, thrombocytopenia, or leukopenia) were present in 13 patients who required dose reductions of 25%-50% (Table 7). Eight patients developed thrombocytopenia: 3 grade 2, 4 grade 3, and 1 grade 4. Twelve patients had leukopenia, but only 6 had grade 3.[32]

6.1.2.4.4.2 Proportion of patients experiencing serious adverse events

The proportion of patients experiencing SAEs were reported in 12 (36.3%) of 33 patients. One patient (treated off protocol) died of neutropenic sepsis. Two patients with pre-existing deep venous thrombosis experienced pulmonary embolism not attributed to gemcitabine. Anaemia occurred in 7 patients. Two elderly patients with SS and bone marrow involvement developed hemolytic uremic syndrome (HUS).[32]

6.1.3 Comparative analyses

The effect size of mogamulizumab is not compared to any of the treatment regimens used in Denmark or the EU. Vorinostat is not approved in the EU, however, it has been approved in the US for progressive, persistent or recurrent disease on or following two systemic therapies.

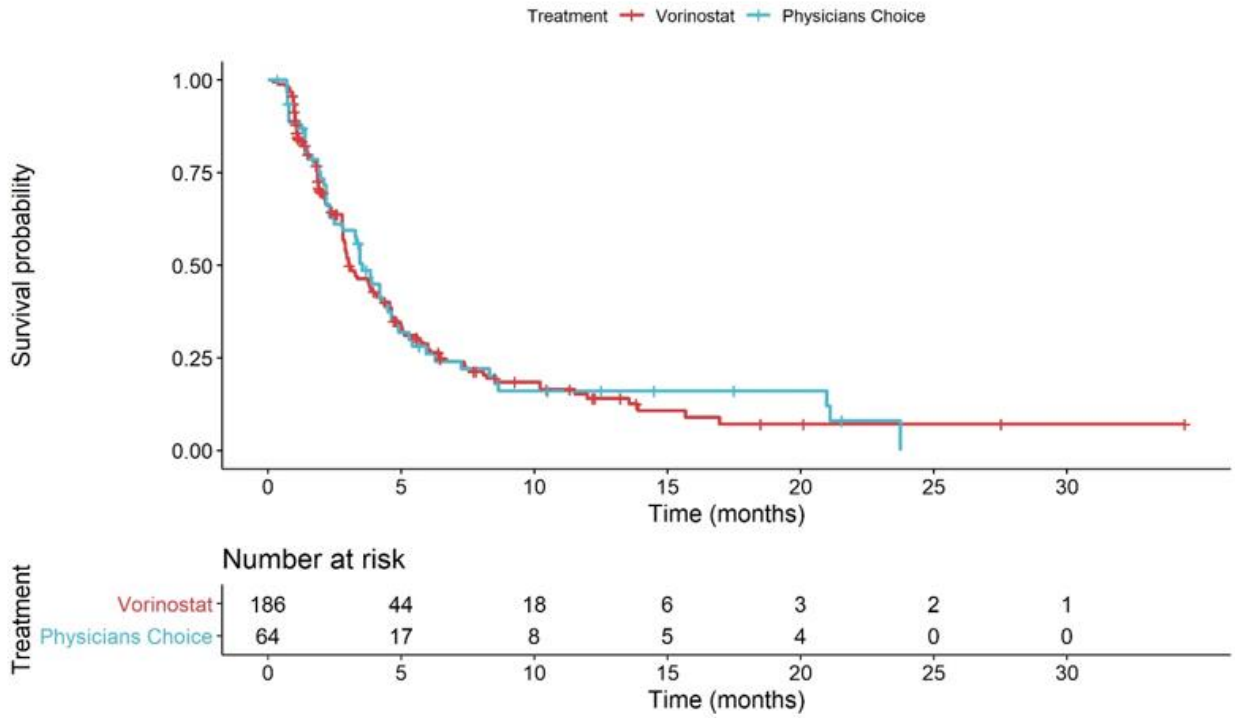
Given the lack of comparative data for the chemotherapies defined in the DMC protocol, vorinostat is assumed to be considered a reasonable proxy for current standard of care in Danish clinical practice. This assumption is based on a naïve comparison of results from the vorinostat arm of the MAVORIC study and the physician's choice arm (methotrexate or bexarotene i.e. Danish standard treatments in first-line) of the ALCANZA study and the similar skin response rate of 29,7% for vorinostat in MAVORIC versus 31% for bexarotene in a Phase II study of 193 CTCL patients[37]. The assumption is also supported by Danish clinical expert opinion[24,25], and the EMA accepted this comparison when granting marketing authorisation for mogamulizumab[33].

The ALCANZA study is the most recent phase III RCT conducted in CTCL and is the second largest study after MAVORIC. As shown in Figure 16, the PFS curves for vorinostat and physician's choice from the ITT population of these studies overlap. This indicates that there is no statistical difference between efficacy of vorinostat and bexarotene/methotrexate for PFS.

The protocol requests a comparison with at least one of the comparators within each of the two groups (chemotherapy and targeted therapies). The only data identified for targeted therapies is the ALCANZA trial, and as previously mentioned the differences in the patient populations between MAVORIC and ALCANZA are significant. The less advanced disease state, highly selective population of CD30+ positive patients, no SS or MF patients with high blood involvement (B2), and inclusion of pcALCL patients in the ALCANZA trial compared to MAVORIC makes it impossible to conduct any meaningful comparison between mogamulizumab and brentuximab vedotin.

As such, the key strength for mogamulizumab in this population is the evidence base with a phase III active controlled RCT, MAVORIC; the largest trial in CTCL and the most robust study resulting in the least uncertainty, which provides the best evidence on the clinical benefits of mogamulizumab compared to Danish chemotherapy comparators given the paucity of comparative data on chemotherapy within MF and SS.

Figure 16 KM investigator assessed PFS curves for vorinostat (MAVORIC, ITT) and physician's choice (ALCANZA, ITT)



ITT, intent-to-treat; KM, Kaplan–Meier; PFS, progression-free survival.

6.1.3.1 Overall survival

OS was not pre-specified as a primary objective within the MAVORIC trial and thus the study was not powered to detect differences in OS. This is due to several factors confounding the assessment of OS, notably the one-way crossover, and the relatively long overall life span of the patient population, during which many events unrelated to CTCL disease can occur. As such, OS was pre-specified as an exploratory endpoint only. Nevertheless, due to the highly positive results seen for PFS, and as previously noted, a survival benefit seen after cross-over adjustment with mogamulizumab is logical.

In the MAVORIC trial, the median OS in the crossover adjusted analysis (inverse probability of censoring weights (IPCW)) excluding patients receiving aSCT, was 51,7 months (95% CI: 40,07 - NE) with mogamulizumab and was 27,07 months (95% CI: 7,43 - NE) with vorinostat resulting in a HR of 0,57 (95% CI: 0,26 - 1,25; p-value: 0,16). In the ITT population, the median OS was not reached with mogamulizumab and was 43,9 months with vorinostat resulting in a hazard ratio (HR) of 0,93 (95% CI: 0,6 - 1,4; p-value: 0,94) in the ITT analysis. Even though MAVORIC was not powered to detect differences in OS, the results show a trend of an OS improvement in the ITT and crossover adjusted analyses, which is remarkable within the limited study time frame. The absolute difference in median OS between mogamulizumab and vorinostat is 9,77 months, which exceeds the minimum clinically important difference of 6 months as defined in the DMC protocol[20].

In the MF subgroup analysis of the ALCANZA trial, which is the most representative analysis for the clinical question, the median OS was not reached in neither the brentuximab vedotin nor the physician's choice arm. The number of events was 12/48 patients (25%) in the brentuximab vedotin arm and 9/49 patients (18%) in the physician's choice arm resulting in a HR of 1,17 (95% CI: 0,49-2,79; p-value: 0,72). It is important to note

that the ALCANZA trial only investigated CD-30 positive patients and is not comparable with the MAVORIC study[26].

EORTC 21012 did not report any data for overall survival.

Duvic et al. 2006 reported a median survival of 20,4 months for gemcitabine treatment. No confidence intervals were reported, and the trial was a single-arm design[32].

Table 13 OS results per study

	Intervention	Median (95% CI)	HR
MAVORIC (crossover adjusted IPCW excl. aSCT)	Mogamulizumab	51,7 (40,07-NE)	0,57 (0,26-1,25)
	Vorinostat	27,07 (7,43-NE)	
ALCANZA (only CD-30+, MF subgroup)	Brentuximab vedotin	NE (30,4-NE)	1,17 (0,49-2,79)
	MTX/bexarotene	NE (NE-NE)	
EORTC 21012	Doxorubicin	NR	NA
Duvic 2006	Gemcitabine	20,4 (NR-NR)	NA

NE, not estimated; MF, mycosis fungoides; MTX, methotrexate; NR, not reported; NA, not appliable

The trial designs, populations and limited data reported of the included studies makes it impossible to apply any statistical comparison of the interventions, but based on the available point estimates and the lower limit confidence intervals, an overall survival advantage is observed for treatment with mogamulizumab compared to chemotherapy by the proxy of vorinostat.

6.1.3.2 Progression-free survival

Progression-free survival was the primary outcome in the MAVORIC trial, as the first trial in CTCL, whereas the ALCANZA trial investigated PFS as a secondary outcome. As previously described were the patients enrolled in the MAVORIC trial in a more advanced disease state at baseline compared to the patients in the ALCANZA trial. Further, the ALCANZA trial only included CD 30 positive patients and no SS patients. Due to the high effectiveness, safety, and ease of use, bexarotene is preferred to chemotherapies in Denmark and is therefore used as first-line systemic treatment for MF and SS. Therefore, the use of vorinostat as a proxy for chemotherapy might overestimate the efficacy of chemotherapy. Consequently, the observed efficacy difference between mogamulizumab and chemotherapy might be underestimated by this approach. Therefore, this approach is considered conservative. The newer trials (MAVORIC and ALCANZA) used a global composite response criteria in the assessment of PFS, that accounted for all potential affected disease compartments (skin, blood, lymph nodes and viscera). The global composite response criteria perceived as the most appropriate way to assess clinical trials in CTCL in published consensus criteria[14]. Whereas the elder trials (EORTC & Duvic et al. 2012) used skin only response criteria in the assessment. This difference further challenges the comparison of PFS between mogamulizumab and the older chemotherapy regimens.

Mogamulizumab treatment resulted in a statistically significant improvement in investigator-based PFS in the ITT analysis, with a median improvement of 4,6 months with mogamulizumab compared to vorinostat (7,7 vs. 3,1 months, respectively) resulting in a HR of 0,53 (95% CI: 0,41-0,69), p<0,0001[2,33]. The median improvement of 4,6 months meets the minimally clinical important difference (MCID) of 4 months defined in the DMC protocol. According to the DMC methods guideline, the confidence interval of the ITT analysis indicates a large added value for PFS.

The PFS effect size was not consistent across subgroups; subgroup analyses indicate that the effect size of PFS depends on the stage of the disease. The available data demonstrate a clinically relevant PFS advantage with mogamulizumab compared to vorinostat in subjects with SS (median PFS 13,3 vs. 3,13 months, respectively, HR 0,32, p<0,0001) and with advanced disease (stage III/IV, median PFS 10,9 vs. 3,0 months, HR 0,36, p<0,0001). In the less advanced patients (stage IB/IIA), a limited 0,8 months advantage in PFS was observed with mogamulizumab vs. vorinostat (median PFS 4,7 vs. 3,9 months, HR 0,88, p=0,7166). In the MF whole patient population, a moderate 2,3 months advantage was observed with mogamulizumab vs. vorinostat (median PFS 5,4 vs. 3,1 months, HR 0,72, p=0,0675).[2,33]

In the ALCANZA trial, the median progression-free survival was 16,7 months in the brentuximab vedotin group versus 3,5 months in the physician's choice group (HR: 0,27 (95% CI: 0,169-0,430; p<0,0001)) in the ITT analysis. In the MF subgroup analysis, the median PFS was 15,9 months in the brentuximab vedotin group versus 3,5 months in the physician's choice group (HR: 0,27 (95% CI: 0,16-0,46)). Due to the reasons mentioned above the results for the ALCANZA trial are not comparable to the results from the MAVORIC trial.[26]

EORTC 21012 reported time to progression (TTP) in skin only defined as the interval of time between the date of registration and the date of first documentation of disease progression. The median TTP was 7,4 months (95% CI: 4,5-8,6).[31]

Duvic et al. 2006 did not report data for PFS.

An overview of the PFS estimates across the trials is provided in Table 14.

Table 14 PFS analyses per study

Trial	Intervention	Median, 95% CI	HR
MAVORIC ITT	Mogamulizumab	7,7 (5,67-10,33)	0,53 (0,41-0,69)
	Vorinostat	3,1 (2,87-4,07)	
MAVORIC (SS population)	Mogamulizumab	13,3 (7,70-17,07)	0,32 (0,21-0,49)
	Vorinostat	3,13 (2,83-3,87)	
MAVORIC (MF population)	Mogamulizumab	5,4 (3,97-7,57)	0,72 (0,51-1,01)
	Vorinostat	3,1 (2,87-4,70)	
MAVORIC (≥IIB population)	Mogamulizumab	9,40 (5,73-14,03)	0,43 (0,31-0,58)
	Vorinostat	3,07 (2,87-3,90)	
MAVORIC (III/IV population)	Mogamulizumab	10,90 (7,03-15,03)	0,36 (0,26-0,51)
	Vorinostat	3,00 (2,83-3,87)	
ALCANZA ITT (only CD-30+)	Brentuximab vedotin	16,7 (NR)	0,27 (0,17-0,43)
	MTX/bexarotene	3,5 (NR)	
ALCANZA (only CD-30+, MF subgroup)	Brentuximab vedotin	15,9 (NR)	0,27 (0,16–0,46)
	MTX/bexarotene	3,5 (NR)	
EORTC 21012*	Doxorubicin	7,4 (4,5-8,6)	NA

Duvic 2006	Gemcitabine	NR	NA

MF, mycosis fungoides; MTX, methotrexate; NR, not reported; NA, not appliable
*EORTC 21012 only reported time to progression (TTP).

The PFS estimates for mogamulizumab treatment versus chemotherapy, based on vorinostat as a proxy for the chemotherapy basket, indicates statistically significant improvements in the ITT population, SS patients and patients with advanced disease.

6.1.3.3 Skindex-29

The Skindex-29 results from MAVORIC indicated significant HRQoL improvements following treatment with mogamulizumab compared with vorinostat. The least-square mean change from baseline (CFB) to cycle 11 of -15,7 (95% CI: -20,96 - -10,67) for treatment with mogamulizumab and -3,6 (95%: -9,93-2,7) for treatment with vorinostat on Skindex-29 total score, resulting in LS mean CFB difference between mogamulizumab and vorinostat of -12,1 (95%: -19,47 - -4,69) p=0,0014.[35] The change from baseline exceeds the MCID of 10 points as defined in DMC protocol[20].

The ALCANZA trial reported mean changes from baseline to end of treatment Skindex-29 composite total score of -14,84 (SD: 22,68) with brentuximab vedotin and -0,96 (SD: 18,97) with physician's choice, resulting in a difference of 13,88 points.[30]

The similarities in differences between the control arms in the MAVORIC and ALCANZA trials further highlights that vorinostat can be used as a proxy for Danish clinical practice, especially given that MTX and bexarotene are used in an earlier treatment line. Mogamulizumab displays a clinically significant difference in Skindex-29 total score when assuming that vorinostat is a proxy for chemotherapy. The patient population enrolled in the MAVORIC trial had more advanced disease (i.e. stage ≥IIB) and included a large proportion of SS patient (45%) compared to the ALCANZA trial.

None of the remaining trials reports the mean change from baseline in the Skindex-29 total score.

6.1.3.4 Adverse events

6.1.3.4.1 Proportion of patients with adverse events grade 3-4

The MAVORIC trial reported similar rates of Grade 3, 4 or 5 AEs between the mogamulizumab group and the vorinostat group (45,7% and 46,2%, respectively) and Grade 3, 4 or 5 TEAEs (42,4% and 45,7, respectively), while the incidence of drug-related Grade 3, 4 or 5 TEAEs was lower for mogamulizumab (25,5%) compared to vorinostat (34,9%). Of note, the incidence of TEAEs observed for patients receiving mogamulizumab after crossover was similar to that observed for patients randomised to mogamulizumab.[2,33]

Based on the difference in drug-related Grade 3, 4 or 5 TEAEs treatment with mogamulizumab exceeds the MCID of 5% change as defined by DMC protocol.

The ALCANZA trial reports an incidence rate of Grade 3–4 AEs to be 41% in the brentuximab vedotin group and 47% in the physician's choice group.[26]

In the EORTC 21012 trial and Duvic et al. 2006 reported similar incidences of Grade 3–4 AEs with 41% in both trials.[31,32]

Table 15 Proportion of patients with Grade 3-4 adverse events across trials

Trial	Intervention	Grade 3-4 AEs %	Difference
MAVORIC (Grade 3-5)	Mogamulizumab	45,7%	0,5%

	Vorinostat	46,2%	
MAVORIC (drug-related Grade 3-5 TEAEs)	Mogamulizumab	25,5%	9,4%
	Vorinostat	34,9%	
ALCANZA (Grade 3-4)	Brentuximab vedotin	41%	6%
	MTX/bexarotene	47%	
EORTC 21012	Doxorubicin	41%	NA
Duvic 2006	Gemcitabine	41%	NA

TEAE, treatment-emergent adverse event; NA, not appliable

The incidence of Grade 3-4 AEs in the control arms, i.e. vorinostat and MTX/bexarotene in the MAVORIC trial and ALCANZA trial are comparable, which further emphasizes that vorinostat is a suitable proxy for Danish standard chemotherapy treatment. The MAVORIC trial reported Grade 3-5 AEs, whereas the remaining trials reported Grade 3-4. This difference should be taken into consideration when interpreting the results.

The estimates for mogamulizumab treatment versus chemotherapy, based on vorinostat as a proxy for the chemotherapy basket, indicates no difference in the incidence of Grade 3-5 AEs and significant improvements in the incidence of drug-related Grade 3-5 TEAEs. The Grade 3-4 estimates for doxorubicin and gemcitabine are not directly comparable to the Grade 3-5 estimates from the MAVORIC trial but does indicate that mogamulizumab is at least as equally tolerable as doxorubicin or gemcitabine. The drug-related TEAEs show that mogamulizumab is associated with fewer events compared to vorinostat.

6.1.3.4.2 Proportion of patients with serious adverse events (SAEs)

In the MAVORIC trial, the incidence of drug-related SAEs was similar between mogamulizumab and vorinostat with 19,6% in the mogamulizumab group compared with 16,1% in the vorinostat group. The trial reported a higher incidence of serious adverse events (SAEs) in the mogamulizumab group (39,7%) than the vorinostat group (24,7%). The incidence of treatment-emergent SAEs in the mogamulizumab group (37,5%) was higher than the vorinostat group (24,7%).[2,33]

In the ALCANZA trial, SAEs were similar between groups, occurring in 29% of patients in the brentuximab vedotin group versus 29% of patients in the physician's choice group. [26]

Duvic et al 2006 reported an incidence of 36,3% patients experiencing SAEs[32] and the EORTC 21012 trial did not report SAEs.

Table 16 Proportion of patients with serious adverse events across trials

Trial	Intervention	SAEs %	Difference
MAVORIC (SAEs)	Mogamulizumab	39,7%	15,0%
	Vorinostat	24,7%	
MAVORIC (drug-related SAEs)	Mogamulizumab	19,6%	3,5%
	Vorinostat	16,1%	
ALCANZA	Brentuximab vedotin	29%	0%
	MTX/bexarotene	29%	

EORTC 21012	Doxorubicin	NR	NA
Duvic 2006	Gemcitabine	36,3%	NA

TEAE, treatment-emergent adverse event; SAEs, serious adverse events; NA, not appliable; NR, not reported

The estimates for mogamulizumab treatment versus chemotherapy, based on vorinostat as a proxy for the chemotherapy basket, indicates no difference in the incidence of Grade 3-5 AEs and significant improvements in the incidence of drug-related Grade 3-5 TEAEs. The Grade 3-4 estimate for gemcitabine is not directly comparable to the Grade 3-5 estimates from the MAVORIC trial but does not indicate that mogamulizumab should be less tolerable than gemcitabine.

As treatment options for MF and SS patients are limited patients are treated with off-label treatments, such as pembrolizumab and alemtuzumab. No comparative data is available for the targeted therapies on Grade 3-4 AEs but based on the EMA EPARs for pembrolizumab and alemtuzumab both treatments indicates to have a profound impact on immune function with a high incidence of severe auto-immune AEs. Alemtuzumab received an EMA warning in November 2019 due to risk of serious side effects[28]. Treatment with brentuximab vedotin is associated with high incidence rates of peripheral neuropathy that limits its use to 16 cycles max as per SmPC administration[38].

Table 17 Incidence of AEs by SOC

	Mogamulizumab(n=186)*	Pembrolizumab (n=1012)**	Alemtuzumab (n=1188)***
Blood and lymphatic system disorders	47 (25,5)	203 (20,1)	172 (14,5)
Cardiac disorders	29 (15,8)	88 (8,7)	189 (15,9)
Endocrine disorders	-	109 (10,8)	148 (12,5)
Eye disorders	34 (18,5)	157 (15,5)	205 (17,3)
Gastrointestinal disorders	93 (50,5)	671 (66,3)	626 (52,7)
General disorders and administration site conditions	106 (57,6)	733 (72,4)	798 (67,2)
Infections and infestations	118 (64,1)	411 (40,6)	848 (71,4)
Injury, poisoning and procedural complications	81 (44,0)	145 (14,3)	331 (27,9)
Investigations	65 (35,3)	322 (31,8)	349 (29,4)
Metabolism and nutrition disorders	59 (32,1)	395 (39,0)	85 (7,2)
Musculoskeletal and connective tissue disorders	67 (36,4)	559 (55,2)	579 (48,7)
Neoplasms benign, malignant and unspecified (incl. cyst and polyps)	-	102 (10,1)	45 (3,8)
Nervous system disorders	65 (35,3)	415 (41,0)	889 (74,89)
Psychiatric disorders	32 (17,4)	192 (19,0)	388 (32,7)
Renal and urinary disorders	-	114 (11,3)	197 (16,6)
Respiratory, thoracic and mediastinal disorders	56 (30,4)	476 (47,0)	478 (40,2)
Skin and subcutaneous tissue disorders	97 (52,7)	583 (57,6)	965 (81,2)
Vascular disorders	29 (15,8)	148 (14,6)	238 (20,0)

* TEAEs reported by ≥5% of subjects in either treatment group during randomisation (Safety Population). ** Subjects with adverse events (incidence ≥ 10% in one or more treatment group). *** Incidence of TEAEs by MedDRA SOC

7 Other considerations

7.1 Differentiation of effect in MF and SS patients

The clinical expert committee has requested data on the effect for the subgroups MF and SS patients.

The available data for the MF and SS patients have been included in the reported results of each outcome in section 6.1.2. The differentiation between advanced MF with blood involvement and SS is not clear cut based on KOL opinion[24,25].

7.2 Treatment duration

The clinical expert committee has requested data on the treatment duration of mogamulizumab and the relevant comparators.

The results from the time on treatment (ToT) analysis showed a 2,6-month advantage with mogamulizumab (HR 0,57); median ToT was significantly longer for mogamulizumab (5,53 months) than for vorinostat (2,87 months) (p<0,0001).

7.3 Subsequent treatment

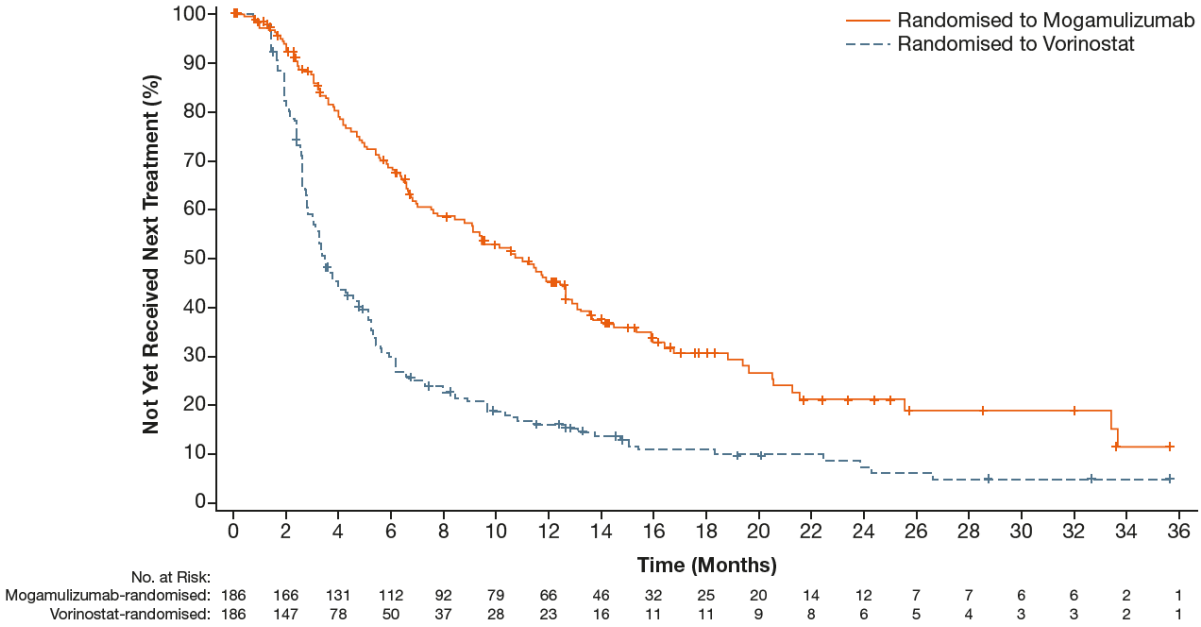
The clinical expert committee has requested information regarding the consequences of implementing mogamulizumab in clinical practice on subsequent treatment lines in terms of type of treatment, duration and effect.

TTNT is an important measure for CTCL patients as, unlike TTF, it is more closely aligned with symptoms and disease control. For this analysis, the median follow-up time was defined as time from start date of randomised treatment to start date of next systemic treatment. All patients were followed to monitor survival and to document any new treatments every 3 months (+/- 14 days).[2,33]

In the ITT population, median TTNT was significantly longer for mogamulizumab treatment compared with vorinostat (11,0 months [95% CI: 8,8, 12,6] versus 3,2 months [95% CI: 3,1, 4,3]; p<0,0001). It should also be noted that the median TTNT for mogamulizumab is more than double that reported historically for systemic treatments (11,0 versus 5,4 months, respectively)[39,40].

Figure 17 presents a Kaplan–Meier curve of TTNT for the ITT population.

Figure 17: Kaplan–Meier plot of TTNT: ITT population



ITT, intention-to-treat; TTNT, time to next treatment.

It is not clear how the introduction of mogamulizumab will impact subsequent treatment lines, although feedback from Danish KOLs indicates that subsequent treatment to mogamulizumab treatment would be chemotherapy or depending on which treatment alternatives they have tried before mogamulizumab. If the patients fail mogamulizumab they will most likely also try alemtuzumab or pembrolizumab and also brentuximab vedotin (if not tried prior) before palliative care.

8 Conclusion

While patients in early stages of the disease have a median survival of 21,5 years (stage IB), the survival is dramatically reduced to under 5 years for patients with advanced disease (stage IIB onwards); for patients with stage IVB disease median survival is under 2 years[3]. Alongside the psychological distress of living with an incurable cancer, patients face a significant, disfiguring physical burden with the skin often oozing and infected; patients report discomfort, cracking and bleeding and skin 'like tin foil' [17]. Importantly, pruritus has a significant impact on QoL with one patient quoted as saying 'you want to scratch yourself to pieces. You'd like to just rip your skin off'.

The disease also has a serious impact on patient's family life, can cause patients to miss work and due to its physical manifestation has a significant impact on social interactions such as participation in sports or hobbies[17,18]. Caregivers face a substantial burden with psychologically and emotionally demanding responsibilities. In particular, the physical burden of practical care, such as regular changing of dressings is often time consuming and overwhelming[19], resulting in a more intensive caregiver burden compared with other cancer indications.

As a result of the few effective available treatment options, patients can cycle through multiple treatments that have either previously failed, or are off label, imposing a substantial burden on individuals and health care systems[1].

There is a clear unmet need for new treatment options for MF and SS patients who require a systemic therapy that can target all disease compartments (skin, blood, lymph nodes and viscera) and provide a

durable response in order to extend patients' disease-free interval and, subsequently, time to receiving next therapy, as well as a meaningful survival benefit.

The efficacy of mogamulizumab in patients with MF or SS who have previously received at least one prior therapy has been demonstrated in the pivotal phase III randomised controlled trial (RCT), MAVORIC, the largest RCT in MF patients and for the first time included SS patients and a high proportion of MF patients with advanced disease and heavily pre-treated patients.

The clinical question specified in the Danish Medicines Council (DMC) protocol states that the value of mogamulizumab should be investigated in patients who have received at least two prior systemic treatments contrary to the European Medicines Agency (EMA) approved indication of one prior systemic treatment.

The protocol requests a comparison with at least one of the comparators within the two comparator groups: targeted therapies (brentuximab vedotin, alemtuzumab (off-label), pembrolizumab (off-label) or romidepsin) and chemotherapy (high dose methotrexate, doxorubicin or gemcitabine). Hence, according to the DMC the standard of care, for patients that have received at least two prior systemic treatments, is one of the treatments listed above, depending on the individual assessment of the patient.

The clinical expert committee states that the choice of therapy will depend on the individual patient characteristics, and consequently, selecting one specific comparator is not clinically meaningful. This is further substantiated by key opinion leader (KOL) input from two clinicians, a dermatologist and an oncologist[24,25]. Both clinicians stated that the choice of treatment would be based on the assessment of each individual patient, and no specific treatment could therefore be considered standard treatment.

As MF and SS are orphan disease populations, very limited data exist for the treatment of MF and SS patients with the regimens listed in the DMC protocol. As no efficacy data is available to differentiate the treatments from each other the DMC protocol groups the comparators in baskets as the clinical expert committee has not found it possible to make a prioritized treatment choice with the existing evidence base. No studies for the stated comparators which allowed for direct or indirect statistical comparison were identified.

The MAVORIC trial provides comparative data for MF and SS patients with at least one prior systemic treatment irrespective of CD30 status, whereas the treatments defined in the protocol lack comparative data for the specific protocol populations of MF and SS, although they are used in clinical practice. The ALCANZA study reports data for CD30+ positive CTCL patients (MF and primary cutaneous anaplastic large cell lymphoma (pcALCL)), but due to significant differences in baseline characteristics and inclusion criteria, it is not possible to compare ALCANZA with MAVORIC.

Vorinostat is assumed to be an appropriate proxy for the effectiveness of chemotherapy, as PFS outcomes with vorinostat were similar to progression-free survival (PFS) outcomes observed in the physician's choice arm (i.e. bexarotene and methotrexate) in the ALCANZA trial, the pivotal trial for brentuximab vedotin for the treatment of CTCL. The PFS curves from the intention-to-treat (ITT) population of these studies overlap, as illustrated in Figure 16. It should be noted that the differences between the studies i.e. disease severity of included patients and proportion of SS patients makes it impossible to conduct a statistical comparison in the population eligible for mogamulizumab, but the naïve comparison of the PFS curves indicates no statistical difference between the efficacy of vorinostat and bexarotene/methotrexate for PFS. As patients in MAVORIC were in more severe disease states, the efficacy of vorinostat may be underestimated in the naïve comparison.

Due to the high effectiveness, safety, and ease of use, bexarotene is preferred to chemotherapies in Denmark and is therefore used as first-line systemic treatment for MF and SS. Therefore, the use of vorinostat as a proxy for chemotherapy might overestimate the efficacy of chemotherapy especially given the differences in disease severity between the trials as explained above. Consequently, the observed efficacy

difference between mogamulizumab and chemotherapy might be underestimated by this approach. Therefore, this approach is considered conservative.

Historically, studies have used a skin only response assessment unlike the global composite multi compartment endpoint used in the MAVORIC study meaning historical comparisons are challenging as endpoints are not comparable. As such, a key strength for mogamulizumab in the population defined by the DMC protocol is its evidence base. The MAVORIC study was the largest comparative randomised controlled trial in MF and SS patients and the most robust study resulting in the least uncertainty, which provides the best evidence on the clinical benefits of mogamulizumab compared to Danish comparators.

OVERALL SURVIVAL

MF and SS are orphan diseases and therefore, it is not possible to statistically power studies in these indications to detect differences in OS. The treatment goal in MF and SS patients is to prevent disease progression and symptom relief, since the available treatments, excluding allogeneic stem cell transplantation, are not curative.

In the MAVORIC trial, OS was not pre-specified as a primary objective and thus the study was not powered to detect differences in OS. This is due to several factors confounding the assessment of OS, notably the one-way crossover, and the relatively long overall life span of the patient population, during which many events unrelated to disease can occur. As such, OS was pre-specified as an exploratory endpoint only. Nevertheless, due to the highly positive results seen for PFS, a survival benefit seen after cross-over adjustment with mogamulizumab is logical. Even though MAVORIC was not powered to detect differences in OS the results shows a trend of an OS improvement in the ITT and crossover adjusted analyses, which is remarkable within the limited study time frame and in an orphan disease.
In the MAVORIC trial, the median OS in the crossover adjusted analysis (IPCW) excluding patients receiving aSCT, was 51,7 months (95% CI: 40,07 - NE) with mogamulizumab and was 27,07 months (95% CI: 7,43 - NE) with vorinostat resulting in a HR of 0,57 (95% CI: 0,26, 1,25; p-value: 0,16). In the ITT population the median OS was not reached with mogamulizumab and was 43.9 months with vorinostat resulting in a hazard ratio (HR) of 0,93 (95% CI: 0,6-1,4; p-value: 0,94) in the ITT analysis.

The differences in trial designs, populations and limited data reported by the included studies makes it impossible to apply a statistical comparison of the interventions, but the available estimates indicates a trend of an overall survival benefit with mogamulizumab compared to chemotherapy.

PROGRESSION-FREE SURVIVAL

The primary efficacy endpoint in the MAVORIC trial was progression-free survival (PFS) based on investigator assessment using a global composite response criteria that took into account all potentially affected disease compartments (skin, blood, lymph nodes and viscera). PFS is considered an acceptable primary endpoint in particular, as MF and SS are characterized by frequent recurrences and an indolent course in early stages reflected by the relatively long OS.

The PFS estimates for mogamulizumab treatment versus chemotherapy, based on vorinostat as a proxy for the chemotherapy basket, showed statistically significant improvements in the ITT population, SS patients and MF patients with advanced disease (≥IIB).

Mogamulizumab treatment resulted in a statistically significant improvement in investigator-based PFS in the ITT analysis, with a median improvement of 4,6 months with mogamulizumab compared to vorinostat (7,7 vs. 3,1 months, respectively) with resulting in a HR of 0,53 (95% CI: 0,41-0,69), p<0,0001[2,33]. The median improvement of 4,6 months meets the minimally clinical important difference (MCID) of 4 months defined in the DMC protocol. According to the DMC methods guideline, the confidence interval of the ITT analysis indicates a large added value for PFS.

SKINDEX-29

The Skindex-29 is used to measure the effect of skin disease on HRQL; it consists of 29 items assessing three domains: emotions, symptoms, and functioning. Higher scores indicate a higher impact of skin disease.

Mogamulizumab demonstrated a clinically significant difference in Skindex-29 total score when assuming that vorinostat is a reasonable proxy for Danish clinical practice.

The Skindex-29 results from MAVORIC indicated significant HRQoL improvements following treatment with mogamulizumab compared with vorinostat. The least-square mean change from baseline (CFB) to cycle 11 of -15,7 (95% CI: -20,96 - -10,67) for treatment with mogamulizumab and -3,6 (95%: -9,93-2,7) for treatment with vorinostat on Skindex-29 total score resulted in LS mean CFB difference between mogamulizumab and vorinostat of -12,1 (95%: -19,47 - -4,69) p=0,0014.[35] The change from baseline exceeds the minimal clinical important difference (MCID) of 10 points as defined in DMC protocol[20].

ADVERSE EVENTS

Mogamulizumab demonstrated a tolerable and manageable safety profile in patients with MF and SS, and despite the duration of mogamulizumab therapy being double that of vorinostat, mogamulizumab demonstrated a comparable safety profile.

The incidence of Grade 3-4 adverse events (AEs) and serious adverse events (SAEs) in the control arms in the MAVORIC and ALCANZA are similar, although the patients included in MAVORIC were in more advanced disease states compared to patients in ALCANZA.

The estimates for mogamulizumab treatment versus chemotherapy, based on vorinostat as a proxy for the chemotherapy basket, indicates no difference in the incidence of Grade 3-5 AEs and significant improvements in the incidence of drug-related Grade 3-5 treatment-emergent adverse events (TEAEs). The drug-related TEAEs show that mogamulizumab is associated with fewer events compared to vorinostat.

UNMET NEED

The efficacy of mogamulizumab has been investigated in the, to-date, largest study within MF and SS and provides the greatest evidence base with least uncertainty for the comparison against chemotherapy in a disease area that is characterized by limited treatment options and off label use in patients severely affected by MF and SS. There is a clear unmet need for more treatment options within MF and SS.

Mogamulizumab addresses this unmet need by providing a novel immune-oncology agent which has provided improved efficacy and HRQoL compared to an active comparator in both advanced MF and SS patients.

Mogamulizumab is the only treatment available which specifically targets the malignant T cells in all four disease compartments; in particular the blood compartment, thus offering the potential for significant improvements in life expectancy for these patients.

9 References

1. Tsang Y, Gu T, Sharma G, Raspa S, Drake B, Tan H. Healthcare resource utilization, costs of care, and treatment of mycosis fungoides cutaneous T-cell lymphoma patterns in a large managed care population: a retrospective US claims-based analysis. J Dermatolog Treat [Internet]. 2018 Nov 17 [cited 2020 Sep 7];29(8):747–53. Available from: https://pubmed.ncbi.nlm.nih.gov/29733229/

2. Kim YH, Bagot M, Pinter-Brown L, Rook AH, Porcu P, Horwitz SM, et al. Mogamulizumab versus vorinostat in previously treated cutaneous T-cell lymphoma (MAVORIC): an international, open-label, randomised, controlled phase 3 trial. Lancet Oncol. 2018;19(9):1192–204.

3. Agar NS, Wedgeworth E, Crichton S, Mitchell TJ, Cox M, Ferreira S, et al. Survival Outcomes and Prognostic Factors in Mycosis Fungoides/Sézary Syndrome: Validation of the Revised International Society for Cutaneous Lymphomas/European Organisation for Research and Treatment of Cancer Staging Proposal. J Clin Oncol [Internet]. 2010 Nov 1;28(31):4730–9. Available from: http://ascopubs.org/doi/10.1200/JCO.2009.27.7665

4. Mayo Clinic. Cutaneous T-cell lymphoma - Symptoms and causes.

5. The Leukemia & Lymphoma Society (LLS). Cutaneous T-Cell Lymphoma Facts [Internet]. 2014 [cited 2020 Sep 6]. Available from: https://www.lls.org/sites/default/files/file_assets/cutaneoustcelllymphoma.pdf

6. Trautinger F, Eder J, Assaf C, Bagot M, Cozzio A, Dummer R, et al. European Organisation for Research and Treatment of Cancer consensus recommendations for the treatment of mycosis fungoides/Sézary syndrome – Update 2017. Vol. 77, European Journal of Cancer. Elsevier Ltd; 2017. p. 57–74.

7. J Scarisbrick J, L Haun P. Fast Facts Fast Facts : Diagnosing Cutaneous T-Cell Lymphoma | Semantic Scholar.

8. Wilcox RA. Cutaneous T-cell lymphoma: 2017 update on diagnosis, risk-stratification, and management. Am J Hematol. 2017 Oct;92(10):1085–102.

9. Bagherani N, Smoller BR. An overview of cutaneous T cell lymphomas [version 1; referees: 2 approved]. Vol. 5, F1000Research. Faculty of 1000 Ltd; 2016. p. 1882.

10. PDQ Adult Treatment Editorial Board. Mycosis Fungoides (Including Sézary Syndrome) Treatment (PDQ®): Health Professional Version. PDQ Cancer Information Summaries. National Cancer Institute (US); 2002.

11. Fujii K. New therapies and immunological findings in cutaneous T-cell lymphoma [Internet]. Vol. 8, Frontiers in Oncology. Frontiers Media S.A.; 2018 [cited 2020 Sep 7]. p. 1. Available from: www.frontiersin.org

12. Miles Prince H, Whittaker S, Hoppe RT. How I treat mycosis fungoides and Sézary syndrome How I treat How I treat mycosis fungoides and Sézary syndrome. 2011;

13. Damasco FM, Geskin L, Akilov OE. Onychodystrophy in Sézary syndrome. 2018 [cited 2020 Sep 7]; Available from: https://doi.org/10.1016/j.jaad.2018.06.023

14. Olsen EA, Whittaker S, Kim YH, Duvic M, Prince HM, Lessin SR, et al. Clinical end points and response criteria in mycosis fungoides and Sézary syndrome: A consensus statement of the International Society for Cutaneous Lymphomas, the United States Cutaneous Lymphoma Consortium, and the Cutaneous Lymphoma Task Force of the European Organisation for Research and Treatment of Cancer [Internet]. Vol. 29, Journal of Clinical Oncology. American Society of Clinical Oncology; 2011 [cited 2020 Aug 25]. p. 2598–607. Available from: /pmc/articles/PMC3422534/?report=abstract

15. Olsen E, Vonderheid E, Pimpinelli N, Willemze R, Kim Y, Knobler R, et al. Revisions to the staging and classification of mycosis fungoides and Sézary syndrome: A proposal of the International Society

for Cutaneous Lymphomas (ISCL) and the cutaneous lymphoma task force of the European Organization of Research and Treatment of Cancer (EORTC) [Internet]. Vol. 110, Blood. American Society of Hematology; 2007 [cited 2020 Sep 7]. p. 1713–22. Available from: https://ashpublications.org/blood/article-pdf/110/6/1713/1479709/zh801807001713.pdf

16. Scarisbrick JJ, Whittaker S, Evans A V., Fraser-Andrews EA, Child FJ, Dean A, et al. Prognostic significance of tumor burden in the blood of patients with erythrodermic primary cutaneous T-cell lymphoma. Blood [Internet]. 2001 Feb 1 [cited 2020 Sep 9];97(3):624–30. Available from: https://ashpublications.org/blood/article-pdf/97/3/624/1671034/624.pdf

17. Beynon T, Selman L, Radcliffe E, Whittaker S, Child F, Orlowska D, et al. We had to change to single beds because i itch in the night: A qualitative study of the experiences, attitudes and approaches to coping of patients with cutaneous T-cell lymphoma. Br J Dermatol [Internet]. 2015 Jul 1 [cited 2020 Sep 7];173(1):83–92. Available from: https://pubmed.ncbi.nlm.nih.gov/25688924/

18. Demierre MF, Gan S, Jones J, Miller DR. Significant impact of cutaneous T-cell lymphoma on patients' quality of life: Results of a 2005 National Cutaneous Lymphoma Foundation Survey. Cancer [Internet]. 2006 Nov 15 [cited 2020 Sep 7];107(10):2504–11. Available from: https://pubmed.ncbi.nlm.nih.gov/17048251/

19. Orlowska D, Selman LE, Beynon T, Radcliffe E, Whittaker S, Child F, et al. 'It's a traumatic illness, traumatic to witness': a qualitative study of the experiences of bereaved family caregivers of patients with cutaneous T-cell lymphoma. Br J Dermatol [Internet]. 2018 Oct 1 [cited 2020 Sep 7];179(4):882–8. Available from: https://pubmed.ncbi.nlm.nih.gov/29451670/

20. Medicinrådet. Medicinrådets protokol for vurdering af mogamulizumab til behandling af voksne med mycosis fungoides eller Sézarys syndrom , der har fået mindst to tidligere systemiske behandlinger. 2020;0–17.

21. Kempf W, Pfaltz K, Vermeer MH, Cozzio A, Ortiz-Romero PL, Bagot M, et al. EORTC, ISCL, and USCLC consensus recommendations for the treatment of primary cutaneous CD30-positive lymphoproliferative disorders: Lymphomatoid papulosis and primary cutaneous anaplastic large-cell lymphoma. In: Blood. Blood; 2011. p. 4024–35.

22. Willemze R, Hodak E, Zinzani PL, Specht L, Ladetto M. Primary cutaneous lymphomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol [Internet]. 2018;29(June):iv30–40. Available from: https://doi.org/10.1093/annonc/mdy133

23. Prince HM, Querfeld C. Integrating novel systemic therapies for the treatment of mycosis fungoides and Sézary syndrome. Vol. 31, Best Practice and Research: Clinical Haematology. Bailliere Tindall Ltd; 2018. p. 322–35.

24. Kyowa Kirin. KOL interview - Lena Specht. 2020.

25. Kyowa Kirin. KOL interview - Lars Iversen. 2020.

26. Prince HM, Kim YH, Horwitz S, Dummer R, Scarisbrick J, Quaglino P, et al. Brentuximab vedotin or physician's choice in CD30-positive cutaneous T-cell lymphoma (ALCANZA): an international, open-label, randomised, phase 3, multicentre trial. Lancet. 2017;390(10094):555–66.

27. Agency EM. Istodax (romidepsin) [Internet]. [cited 2020 Sep 7]. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/istodax

28. EMA. Measures to minimise risk of serious side effects of multiple sclerosis medicine Lemtrada [Internet]. EMA. 2019 [cited 2020 Sep 7]. Available from: https://www.ema.europa.eu/en/medicines/human/referrals/lemtrada

29. Kyowa Kirin. Summary of Product Characteristics. Poteligeo® (Mogamulizumab). 2019.

30. Dummer R, Prince HM, Whittaker S, Horwitz SM, Kim YH, Scarisbrick J, et al. Patient-reported quality of life in patients with relapsed/refractory cutaneous T-cell lymphoma: Results from the randomised phase III ALCANZA study. Eur J Cancer [Internet]. 2020;133:120–30. Available from:

https://doi.org/10.1016/j.ejca.2020.04.010

31. Dummer R, Quaglino P, Becker JC, Hasan B, Karrasch M, Whittaker S, et al. Prospective International Multicenter Phase II Trial of Intravenous Pegylated Liposomal Doxorubicin Monochemotherapy in Patients With Stage IIB, IVA, or IVB Advanced Mycosis Fungoides: Final Results From EORTC 21012. J Clin Oncol [Internet]. 2012 Nov 20 [cited 2020 Aug 26];30(33):4091–7. Available from: www.jco.org

32. Duvic M, Talpur R, Wen S, Kurzrock R, David CL, Apisarnthanarax N. Phase II evaluation of gemcitabine monotherapy for cutaneous T-cell lymphoma. Clin Lymphoma Myeloma [Internet]. 2006 Jul;7(1):51–8. Available from: http://dx.doi.org/10.3816/CLM.2006.n.039

33. European Medical Agency (EMA). Assessment Report - Poteligeo. 2018;44(September 2018).

34. Latimer NR, Abrams KR. NICE DSU Technical Support Document 16: Adjusting Survival Time Estimates in the Presence of Treatment Switching. NICE DSU Technical Support Document 16: Adjusting Survival Time Estimates in the Presence of Treatment Switching. National Institute for Health and Care Excellence (NICE); 2014.

35. Porcu P, Hudgens S, Quaglino P, Cowan R, Floden L, Leoni M, et al. Quality of life in cutaneous T-cell lymphoma subjects treated with anti-CCR4 monoclonal antibody mogamulizumab versus vorinostat: Results from the phase 3 MAVORIC trial. J Clin Oncol [Internet]. 2018 May 20 [cited 2020 Aug 31];36(15_suppl):7577–7577. Available from: http://ascopubs.org/doi/10.1200/JCO.2018.36.15_suppl.7577

36. Quaglino P. QUALITY OF LIFE IN CUTANEOUS T-CELL LYMPHOMA SUBJECTS TREATED WITH THE ANTI-CCR4 MONOCLONAL ANTIBODY MOGAMULIZUMAB VERSUS VORINOSTAT: RESULTS FROM THE PHASE 3 MAVORIC TRIAL [Internet]. EHA Library. 2018 [cited 2020 Sep 7]. Available from: https://library.ehaweb.org/eha/2018/stockholm/214748/pietro.quaglino.quality.of.life.in.cutaneous.t-cell.lymphoma.subjects.treated.html

37. Duvic M, Hymes K, Heald P, Breneman D, Martin AG, Myskowski P, et al. Bexarotene is effective and safe for treatment of refractory advanced-stage cutaneous t-cell lymphoma: Multinational phase II-III trial results. J Clin Oncol [Internet]. 2001 May 1 [cited 2020 Sep 9];19(9):2456–71. Available from: http://ascopubs.org/doi/10.1200/JCO.2001.19.9.2456

38. European Medicines Agency CHMP. Summary of Product Characteristics Adcetris.

39. Kim YH, Ortiz-Romero PL, Pro B, Sokol L, Scarisbrick J, Musiek A, et al. TIME TO NEXT TREATMENT IN PATIENTS WITH PREVIOUSLY TREATED CUTANEOUS T-CELL LYMPHOMA (CTCL) RECEIVING MOGAMULIZUMAB OR VORINOSTAT: A POST-HOC ANALYSIS OF THE MAVORIC STUDY. Hematol Oncol [Internet]. 2019 Jun [cited 2020 Aug 31];37:285–6. Available from: http://doi.wiley.com/10.1002/hon.95_2630

40. Hughes CFM, Khot A, McCormack C, Lade S, Westerman DA, Twigger R, et al. Lack of durable disease control with chemotherapy for mycosis fungoides and Sézary syndrome: A comparative study of systemic therapy. Blood [Internet]. 2015 Jan 1 [cited 2020 Sep 9];125(1):71–81. Available from: https://ashpublications.org/blood/article-pdf/125/1/71/1383658/71.pdf

41. Duvic M, Pinter-Brown LC, Foss FM, Sokol L, Jorgensen JL, Challagundla P, et al. Phase 1/2 study of mogamulizumab, a defucosylated anti-CCR4 antibody, in previously treated patients with cutaneous T-cell lymphoma. Blood [Internet]. 2015 Mar 19 [cited 2020 Sep 8];125(12):1883–9. Available from: https://ashpublications.org/blood/article-pdf/125/12/1883/1382918/1883.pdf

42. Bates SE, Eisch R, Ling A, Rosing D, Turner M, Pittaluga S, et al. Romidepsin in peripheral and cutaneous T-cell lymphoma: mechanistic implications from clinical and correlative data. Br J Haematol [Internet]. 2015 Jul 1 [cited 2020 Sep 8];170(1):96–109. Available from: http://doi.wiley.com/10.1111/bjh.13400

43. Belada D. Brentuximab vedotin in the treatment of relapsed CD30 positive cutaneous lymphoma - results of an international, open label, randomised, phase 3, multicentre trial - ALCANZA. Onkologie

[Internet]. 2018 Jun 1 [cited 2020 Sep 8];12(3):123–7. Available from: http://www.onkologiecs.cz/doi/10.36290/xon.2018.024.html

44. Piekarz RL, Frye R, Prince HM, Kirschbaum MH, Zain J, Allen SL, et al. Phase 2 trial of romidepsin in patients with peripheral T-cell lymphoma. Blood [Internet]. 2011 Jun 2 [cited 2020 Sep 8];117(22):5827–34. Available from: https://ashpublications.org/blood/article-pdf/117/22/5827/1337811/zh802211005827.pdf

45. Coiffier B, Pro B, Prince HM, Foss F, Sokol L, Greenwood M, et al. Romidepsin for the treatment of relapsed/refractory peripheral T-cell lymphoma: Pivotal study update demonstrates durable responses. J Hematol Oncol [Internet]. 2014 Jan 23 [cited 2020 Sep 8];7(1):1–9. Available from: https://link.springer.com/articles/10.1186/1756-8722-7-11

46. Illidge T, Chan C, Counsell N, Morris S, Scarisbrick J, Gilson D, et al. Phase II study of gemcitabine and bexarotene (GEMBEX) in the treatment of cutaneous T-cell lymphoma. Br J Cancer [Internet]. 2013 Nov 12 [cited 2020 Sep 8];109(10):2566–73. Available from: www.bjcancer.com

47. de Masson A, Guitera P, Brice P, Moulonguet I, Mouly F, Bouaziz J-D, et al. Long-term efficacy and safety of alemtuzumab in advanced primary cutaneous T-cell lymphomas. Br J Dermatol [Internet]. 2014 Mar 1 [cited 2020 Sep 8];170(3):720–4. Available from: http://doi.wiley.com/10.1111/bjd.12690

48. Khodadoust MS, Rook AH, Porcu P, Foss F, Moskowitz AJ, Shustov A, et al. Pembrolizumab in relapsed and refractory mycosis fungoides and Sézary syndrome: A multicenter phase II study. In: Journal of Clinical Oncology [Internet]. American Society of Clinical Oncology; 2020 [cited 2020 Sep 8]. p. 20–8. Available from: http://ascopubs.org/doi/10.1200/JCO.19.01056

49. Pellegrini C, Stefoni V, Casadei B, Maglie R, Argnani L, Zinzani PL. Long-term outcome of patients with advanced-stage cutaneous T cell lymphoma treated with gemcitabine. Ann Hematol [Internet]. 2014 Jun 8 [cited 2020 Sep 8];93(11):1853–7. Available from: https://link.springer.com/article/10.1007/s00277-014-2121-1

50. Duvic M, Tetzlaff MT, Gangar P, Clos AL, Sui D, Talpur R. Results of a phase II trial of brentuximab vedotin for CD30+ cutaneous T-cell lymphoma and lymphomatoid papulosis. J Clin Oncol [Internet]. 2015 Nov 10 [cited 2020 Sep 8];33(32):3759–65. Available from: /pmc/articles/PMC4737859/?report=abstract

51. Duvic M, Bates SE, Piekarz R, Eisch R, Kim YH, Lerner A, et al. Responses to romidepsin in patients with cutaneous T-cell lymphoma and prior treatment with systemic chemotherapy. Leuk Lymphoma [Internet]. 2018 Aug 31 [cited 2020 Sep 8];59(4):880–7. Available from: https://www.tandfonline.com/doi/full/10.1080/10428194.2017.1361022

52. Hui D, Lam W, Toze C, Delorme M, Noble M, Klimo P, et al. Alemtuzumab in clinical practice: A British Columbia experience. Leuk Lymphoma [Internet]. 2008 Feb [cited 2020 Sep 8];49(2):218–26. Available from: https://www.tandfonline.com/doi/abs/10.1080/10428190701760029

53. Skamene T, Crump M, Savage KJ, Reiman T, Kuruvilla J, Good D, et al. Salvage chemotherapy and autologous stem cell transplantation for peripheral T-cell lymphoma: a subset analysis of the Canadian Cancer Trials Group LY.12 randomized phase 3 study *. Leuk Lymphoma [Internet]. 2017 Oct 3 [cited 2020 Sep 8];58(10):2319–27. Available from: https://www.tandfonline.com/doi/abs/10.1080/10428194.2017.1312379

54. Shimony S, Horowitz N, Ribakovsky E, Rozovski U, Avigdor A, Zloto K, et al. Romidepsin treatment for relapsed or refractory peripheral and cutaneous T-cell lymphoma: Real-life data from a national multicenter observational study. Hematol Oncol [Internet]. 2019 Dec 25 [cited 2020 Sep 8];37(5):569–77. Available from: https://onlinelibrary.wiley.com/doi/abs/10.1002/hon.2691

55. Suri A, Mould DR, Liu Y, Jang G, Venkatakrishnan K. Population PK and Exposure–Response Relationships for the Antibody–Drug Conjugate Brentuximab Vedotin in CTCL Patients in the Phase III ALCANZA Study. Clin Pharmacol Ther [Internet]. 2018 Nov 1 [cited 2020 Sep 8];104(5):989–99. Available from: https://ascpt.onlinelibrary.wiley.com/doi/full/10.1002/cpt.1037%4010.1002/%28ISSN%291532-6535.immunotherapy

56. Straus DJ, Duvic M, Horwitz SM, Hymes K, Goy A, Hernandez-Ilizaliturri FJ, et al. Final results of phase II trial of doxorubicin HCL liposome injection followed by bexarotene in advanced cutaneous T-cell lymphoma. Ann Oncol. 2014 Jan 1;25(1):206–10.

57. Saulite I, Guenova E, Hoetzenecker W. Adverse Reactions of Antibody-Therapy for Primary Cutaneous Lymphomas: Rituximab, Brentuximab Vedotin, Alemtuzumab, and Mogamulizumab. In: Current Problems in Dermatology (Switzerland) [Internet]. S. Karger AG; 2018 [cited 2020 Sep 8]. p. 70–81. Available from: https://www.karger.com/Article/FullText/478079

58. Sarris AH, Phan A, Duvic M, Romaguera J, McLaughlin P, Mesina O, et al. Trimetrexate in relapsed T-cell lymphoma with skin involvement. J Clin Oncol [Internet]. 2002 Jun 15 [cited 2020 Sep 8];20(12):2876–80. Available from: https://pubmed.ncbi.nlm.nih.gov/12065565/

59. Prochazka V, Faber E, Raida L, Papajik T, Vondrakova J, Rusinakova Z, et al. Long-term outcome of patients with peripheral t-cell lymphoma treated with first-line intensive chemotherapy followed by autologous stem cell transplantation. Biomed Pap [Internet]. 2011 [cited 2020 Sep 8];155(1):63–70. Available from: https://pubmed.ncbi.nlm.nih.gov/21475380/

60. Pulini S, Rupoli S, Goteri G, Pimpinelli N, Alterini R, Tassetti A, et al. Pegylated liposomal doxorubicin in the treatment of primary cutaneous T-cell lymphomas. Haematologica [Internet]. 2007 May 1 [cited 2020 Sep 8];92(5):686–9. Available from: https://haematologica.org/article/view/4443

61. Quereux G, Marques S, Nguyen JM, Bedane C, D'incan M, Dereure O, et al. Prospective multicenter study of pegylated liposomal doxorubicin treatment in patients with advanced or refractory mycosis fungoides or sézary syndrome. Arch Dermatol [Internet]. 2008 Jun 1 [cited 2020 Sep 8];144(6):727–33. Available from: www.archdermatol.com

62. Atilla E, Atilla PA, Bozdag SC, Yuksel MK, Toprak SK, Topcuoglu P, et al. Extracorporeal photochemotherapy in mycosis fungoides. Transfus Clin Biol [Internet]. 2017 Nov 1 [cited 2020 Sep 8];24(4):454–7. Available from: https://pubmed.ncbi.nlm.nih.gov/28578935/

63. Bagot M, Hasan B, Whittaker S, Beylot-Barry M, Knobler R, Shah E, et al. A phase III study of lenalidomide maintenance after debulking therapy in patients with advanced cutaneous T-cell lymphoma - EORTC 21081 (NCT01098656): Results and lessons learned for future trial designs. Eur J Dermatology [Internet]. 2017 May 1 [cited 2020 Sep 8];27(3):286–94. Available from: https://link.springer.com/article/10.1684/ejd.2017.3008

64. Lewis DJ, Rook AH. Mogamulizumab in the treatment of advanced mycosis fungoides and Sézary syndrome: safety and efficacy. Expert Rev Anticancer Ther [Internet]. 2020 Jun 2 [cited 2020 Sep 8];20(6):447–52. Available from: https://www.tandfonline.com/doi/abs/10.1080/14737140.2020.1760096

65. Martinez-Escala ME, Kuzel TM, Kaplan JB, Petrich A, Nardone B, Rosen ST, et al. Durable responses with maintenance dose-sparing regimens of romidepsin in cutaneous t-cell lymphoma. JAMA Oncol [Internet]. 2016 Jun 1 [cited 2020 Sep 8];2(6):790–3. Available from: https://jamanetwork.com/

66. Maruyama D, Tobinai K, Ogura M, Uchida T, Hatake K, Taniwaki M, et al. Romidepsin in Japanese patients with relapsed or refractory peripheral T-cell lymphoma: a phase I/II and pharmacokinetics study. Int J Hematol [Internet]. 2017 Nov 1 [cited 2020 Sep 8];106(5):655–65. Available from: https://link.springer.com/article/10.1007/s12185-017-2286-1

67. Avilés A, Nambo MJ, Neri N, Castañeda C, Cleto S, Gonzalez M, et al. Interferon and Low Dose Methotrexate Improve Outcome in Refractory Mycosis Fungoides/Sézary Syndrome. Cancer Biother Radiopharm [Internet]. 2007 Dec 1 [cited 2020 Sep 8];22(6):836–40. Available from: http://www.liebertpub.com/doi/10.1089/cbr.2007.0402

68. Wollina U, Dummer R, Brockmeyer NH, Konrad H, Busch JO, Kaatz M, et al. Multicenter study of pegylated liposomal doxorubicin in patients with cutaneous T-cell lymphoma. Cancer [Internet]. 2003 Sep 1 [cited 2020 Sep 8];98(5):993–1001. Available from: https://acsjournals.onlinelibrary.wiley.com/doi/full/10.1002/cncr.11593

69. Sj W. Final Results from a Multicenter, International, Pivotal Study of Romidepsin in Refractory Cutaneous T-Cell Lymphoma. Vol. 28, J Clin Oncol. 2010.

70. Morgado-Carrasco D, Combalia A, Estrach Panella T. RF - Brentuximab as Treatment for CD30+ Primary Cutaneous Lymphoma. Actas Dermosifiliogr [Internet]. 2019 Nov 1 [cited 2020 Sep 8];110(9):769–70. Available from: https://pubmed.ncbi.nlm.nih.gov/31151669/

71. Novelli S, García-Muret P, Sierra J, Briones J. Alemtuzumab treatment for Sézary syndrome: A single-center experience. J Dermatolog Treat [Internet]. 2016 Mar 3 [cited 2020 Sep 8];27(2):179–81. Available from: https://www.tandfonline.com/doi/abs/10.3109/09546634.2015.1086479

72. Akpek G, Koh HK, Bogen S, O'Hara C, Foss FM. Chemotherapy with etoposide, vincristine, doxorubicin, bolus cyclophosphamide, and oral prednisone in patients with refractory cutaneous T-cell lymphoma. Cancer [Internet]. 1999 Oct 1 [cited 2020 Sep 8];86(7):1368–76. Available from: https://acsjournals.onlinelibrary.wiley.com/doi/full/10.1002/%28SICI%291097-0142%2819991001%2986%3A7%3C1368%3A%3AAID-CNCR37%3E3.0.CO%3B2-8

73. Mukai M, Mould D, Maeda H, Narushima K, Greene D. Exposure-Response Analysis for Mogamulizumab in Adults With Cutaneous T-Cell Lymphoma. J Clin Pharmacol [Internet]. 2020 Jan 16 [cited 2020 Sep 8];60(1):50–7. Available from: https://onlinelibrary.wiley.com/doi/abs/10.1002/jcph.1548

74. Aviles A, Neri N, Fernandez-Diez J, Silva L, Nambo M-J. Interferon and low doses of methotrexate versus interferon and retinoids in the treatment of refractory/relapsed cutaneous T-cell lymphoma. Hematology [Internet]. 2015 Oct 16 [cited 2020 Sep 8];20(9):538–42. Available from: https://www.tandfonline.com/doi/full/10.1179/1607845415Y.0000000002

10 Appendices

10.1 Literature search

Table 18 Inclusion and exclusion criteria

Inclusion criteria	Population: As defined in the protocol (amended to include ≥prior treatments) Intervention(s): As defined in the protocol Comparator(s): As defined in the protocol Outcomes: As defined in the protocol Settings (if applicable): Study design: Randomized trials irrespective of blinding status; Systematic reviews and meta-analyses of RCTs/non-RCTs Language restrictions: Danish and English Other search limits or restrictions applied: NA
Exclusion criteria	Population: Population not included in the protocol Intervention(s): Interventions not included in the inclusion list Comparator(s): Comparators not included in the inclusion list Outcomes: Not reporting outcomes defined in the protocol Settings (if applicable): NA Study design: preclinical studies, comments, letters, editorials, case reports, case series and non-systematic reviews Language restrictions: Other languages than Danish and English Other search limits or restrictions applied: NA

Table 19 PubMed search strategy

Search number	Query	Results
15	#13 NOT #14	347
14	Case Reports[pt] OR Comment[pt] OR Editorial[pt] OR Letter[pt] OR Review[pt] OR Systematic Review[pt]	6.306.388
13	#3 AND (#4 OR #12)	979
12	#5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11	153.562
11	gemcitabine[nm] OR gemcitabin*[tiab] OR Gemzar*[tiab]	17.078
10	Doxorubicin[mh] OR doxorubicin*[tiab] OR DOX[tiab] OR Adriablastin*[tiab] OR Adriamycin*[tiab] OR Adriblastin*[tiab] OR DOXO-cell*[tiab] OR Myocet*[tiab] OR Rubex*[tiab]	79.819
9	Methotrexate[mh] OR methotrexate[tiab] OR amethopterin[tiab] OR MTX[tiab] OR Mexate*[tiab]	55.771
8	romidepsin[nm] OR romidepsin[tiab] OR Istodax*[tiab] OR FK228[tiab] OR FR-901228[tiab] OR FR901228[tiab]	859

7	Alemtuzumab[mh] OR alemtuzumab[tiab] OR Campath*[tiab] OR Lemtrada*[tiab]	3.455
6	pembrolizumab[nm] OR pembrolizumab[tiab] OR Keytruda*[tiab] OR MK-3475[tiab] OR SCH-900475[tiab] OR lambrolizumab[tiab]	4.078
5	Brentuximab Vedotin[mh] OR brentuximab[tiab] OR Adcetris*[tiab] OR SGN-35[tiab] OR cAC10-vcMMAE[tiab]	1.051
4	mogamulizumab[nm] OR mogamulizumab[tiab] OR Poteligeo*[tiab] OR AMG-761[tiab] OR AMG761[tiab] OR KM-8761[tiab] OR KM8761[tiab] OR KW-0761[tiab] OR KW0761[tiab]	249
3	#1 OR #2	13.661
2	(cutaneous[tiab] AND t-Cell[tiab] AND lymphom*[tiab]) OR (mycosis[tiab] AND fungoides[tiab]) OR (sezary[tiab] AND (syndrom*[tiab] OR erythroderm*[tiab] OR lymphom*[tiab]))	11.624
1	Lymphoma, T-Cell, Cutaneous[mh]	9.751

Table 20 Cochrane search strategy

ID	Search	Hits
#1	[mh "Lymphoma, T-Cell, Cutaneous"]	93
#2	((cutaneous AND t-Cell AND lymphom*) OR mycosis fungoides OR (sezary AND (syndrom* OR erythroderm* OR lymphom*))):ti,ab,kw	351
#3	#1 OR #2	352
#4	(mogamulizumab OR AMG-761 OR AMG761 OR KM-8,761 OR KM8,761 OR KW-0,761 OR KW0,761 OR Poteligeo*):ti,ab,kw	70
#5	[mh "Brentuximab Vedotin"]	9
#6	(brentuximab* OR Adcetris* OR SGN-35):ti,ab,kw	249
#7	(pembrolizumab OR Keytruda* OR MK-3,475 OR SCH-900,475 OR lambrolizumab):ti,ab,kw	1.399
#8	[mh "Alemtuzumab"]	147
#9	(alemtuzumab OR Campath* OR Lemtrada*):ti,ab,kw	655
#10	(romidepsin OR FK228 OR FR-901,228 OR FR901,228 OR Istodax*):ti,ab,kw	52
#11	[mh "Methotrexate"]	4.118
#12	(methotrexate OR amethopterin OR MTX OR Mexate*):ti,ab,kw	11.853
#13	[mh "Doxorubicin"]	4.754
#14	(doxorubicin* OR DOX OR Adriablastin* OR Adriamycin* OR Adriblastin* OR DOXO-cell* OR Myocet* OR Rubex*):ti,ab,kw	8.631
#15	(gemcitabine OR Gemzar*):ti,ab,kw	5.692
#16	#5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15	27.435
#17	#3 AND (#4 OR #16)	94
#18	(clinicaltrials.gov OR trialsearch):so	329.027
#19	conference abstract:pt	157.292
#20	#18 OR #19	486.319
#21	#17 NOT #20 in Trials	26

Table 21 Full text exclusion

Authors	Title	Published Year	Journal	Exclusion reason
Duvic, M.	Phase 1/2 study of mogamulizumab, a defucosylated anti-CCR4 antibody, in previously	2015	Blood	Study design and outcomes

	treated patients with cutaneous T-cell lymphoma[41]			
Bates, S. E.	Romidepsin in peripheral and cutaneous T-cell lymphoma: mechanistic implications from clinical and correlative data[42]	2015	Br J Haematol	Wrong patient population
David Belada	Brentuximab vedotin in the treatment of relapsed CD30 positive cutaneous lymphoma - results of an international, open label, randomised, phase 3, multicentre trial - ALCANZA[43]	2018	Onkologie	Wrong language (Hungarian)
Piekarz, R. L.	Phase 2 trial of romidepsin in patients with peripheral T-cell lymphoma[44]	2011	Blood	Wrong patient population
Coiffier, B.	Romidepsin for the treatment of relapsed/refractory peripheral T-cell lymphoma: pivotal study update demonstrates durable responses[45]	2014	J Hematol Oncol	Wrong patient population
Illidge, T.	Phase II study of gemcitabine and bexarotene (GEMBEX) in the treatment of cutaneous T-cell lymphoma[46]	2013	Br J Cancer	Wrong intervention
de Masson, A.	Long-term efficacy and safety of alemtuzumab in advanced primary cutaneous T-cell lymphomas[47]	2014	Br J Dermatol	Wrong patient population
Khodadoust, M. S.	Pembrolizumab in Relapsed and Refractory Mycosis Fungoides and Sezary Syndrome: A Multicenter Phase II Study[48]	2020	J Clin Oncol	Wrong outcomes
Pellegrini, C.	Long-term outcome of patients with advanced-stage cutaneous T cell lymphoma treated with gemcitabine[49]	2014	Ann Hematol	Wrong study design
Duvic, M.	Results of a Phase II Trial of Brentuximab Vedotin for CD30+ Cutaneous T-Cell Lymphoma and Lymphomatoid Papulosis[50]	2015	J Clin Oncol	Wrong patient population
Duvic, M.	Responses to romidepsin in patients with cutaneous T-cell lymphoma and prior treatment with systemic chemotherapy[51]	2018	Leuk Lymphoma	Wrong patient population
Hui, D.	Alemtuzumab in clinical practice: a British Columbia experience[52]	2008	Leuk Lymphoma	Wrong patient population
Skamene, T	Salvage chemotherapy and autologous stem cell transplantation for peripheral T-cell lymphoma: a subset analysis of the Canadian Cancer Trials Group LY.12 randomized phase 3 study*[53]	2017		Wrong intervention
Shimony, S.	Romidepsin treatment for relapsed or refractory peripheral and cutaneous T-cell lymphoma: Real-life data from a national multicenter observational study[54]	2019	Hematol Oncol	Wrong study design
Suri, A.	Population PK and Exposure-Response Relationships for the Antibody-Drug Conjugate Brentuximab Vedotin in CTCL Patients in the Phase III ALCANZA Study[55]	2018	Clin Pharmacol Ther	Wrong outcomes
Straus, D. J.	Final results of phase II trial of doxorubicin HCl liposome injection followed by bexarotene in advanced cutaneous T-cell lymphoma[56]	2014	Ann Oncol	Wrong intervention
Saulite, I.	Adverse Reactions of Antibody-Therapy for Primary Cutaneous Lymphomas: Rituximab, Brentuximab Vedotin, Alemtuzumab, and Mogamulizumab[57]	2018	Curr Probl Dermatol	Wrong study design
Sarris, A. H.	Trimetrexate in relapsed T-cell lymphoma with skin involvement[58]	2002	J Clin Oncol	Wrong intervention
Prochazka, V.	Long-term outcome of patients with peripheral T-cell lymphoma treated with first-line intensive chemotherapy followed by autologous stem cell transplantation[59]	2011	Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub	Wrong intervention
Pulini, S.	Pegylated liposomal doxorubicin in the treatment of primary cutaneous T-cell lymphomas[60]	2007	Haematologica	Wrong patient population
Quereux, G.	Prospective multicenter study of pegylated liposomal doxorubicin treatment in patients with advanced or refractory mycosis fungoides or Sezary syndrome[61]	2008	Arch Dermatol	Wrong comparator
Atilla, E.	Extracorporeal photochemotherapy in mycosis fungoides[62]	2017	Transfus Clin Biol	Wrong intervention
Bagot, M	A phase III study of lenalidomide maintenance after debulking therapy in patients with advanced cutaneous T-cell lymphoma - EORTC 21081 (NCT01098656): results and lessons learned for future trial designs[63]	2017		Wrong intervention

Lewis, D. J.	Mogamulizumab in the treatment of advanced mycosis fungoides and SÃ©zary syndrome: safety and efficacy[64]	2020	Expert Rev Anticancer Ther	Wrong study design
Martinez-Escala, M. E.	Durable Responses With Maintenance Dose-Sparing Regimens of Romidepsin in Cutaneous T-Cell Lymphoma[65]	2016	JAMA Oncol	Wrong outcomes
Maruyama, D.	Romidepsin in Japanese patients with relapsed or refractory peripheral T-cell lymphoma: a phase I/II and pharmacokinetics study[66]	2017	Int J Hematol	Wrong patient population
Avilés, A.	Interferon and low dose methotrexate improve outcome in refractory mycosis fungoides/Sezary syndrome[67]	2007	Cancer Biother Radiopharm	Wrong outcomes
Wollina, U.	Multicenter study of pegylated liposomal doxorubicin in patients with cutaneous T-cell lymphoma[68]	2003	Cancer	Wrong outcomes
Whittaker, S. J.	Final results from a multicenter, international, pivotal study of romidepsin in refractory cutaneous T-cell lymphoma[69]	2010	J Clin Oncol	Wrong outcomes
Morgado-Carrasco, D.	RF - Brentuximab as Treatment for CD30(+) Primary Cutaneous Lymphoma[70]	2019	Actas Dermosifiliogr	Wrong language
Novelli, S.	Alemtuzumab treatment for Sezary syndrome: A single-center experience[71]	2016	J Dermatolog Treat	Wrong study design
Akpek, G.	Chemotherapy with etoposide, vincristine, doxorubicin, bolus cyclophosphamide, and oral prednisone in patients with refractory cutaneous T-cell lymphoma[72]	1999	Cancer	Wrong study design
Mukai, M.	Exposure-Response Analysis for Mogamulizumab in Adults With Cutaneous T-Cell Lymphoma[73]	2020	J Clin Pharmacol	Wrong outcomes
Aviles, A.	Interferon and low doses of methotrexate versus interferon and retinoids in the treatment of refractory/relapsed cutaneous T-cell lymphoma[74]	2015	Hematology	Wrong outcomes

10.2 Main characteristics of included studies

10.2.1 Study characteristics

10.2.1.1 MAVORIC

Table 22 Study characteristics - MAVORIC

Trial name	**MAVORIC**
NCT number	NCT01728805
Objective	The purpose of this study is to compare the progression free survival of KW-0761 versus vorinostat for subjects with relapsed or refractory CTCL.
Publications – title, author, journal, year	Mogamulizumab versus vorinostat in previously treated cutaneous T-cell lymphoma (MAVORIC): an international, open-label, randomised, controlled phase 3 trial, Kim, Lancet Oncol, 2018
Study type and design	Open-label, multi-center, randomized phase 3 study. Enrolled patients were randomized 1:1 using an interactive voice web response system to receive mogamulizumab or vorinostat and stratified by cutaneous T-cell lymphoma subtype (mycosis fungoides vs Sézary syndrome) and disease stage (IB–II vs III–IV). This was an open-label study. Blinding of treatment groups was not considered appropriate due to different routes of administration (IV vs. oral) and different side effect profiles. Subjects randomized to vorinostat who progress or suffer intolerable toxicities could cross over to the mogamulizumab arm, given that they had 2 cycles of vorinostat treatment.
Follow-up time	The median duration of follow-up was 17.0 months (IQR 11.6–26.9) overall in the randomised part of the study.

Population (inclusion and exclusion criteria)	Inclusion Criteria: • Male and female subjects ≥ 18 years of age at the time of enrollment, except in Japan where subjects must be ≥ 20 years of age at the time of enrollment • Histologically confirmed diagnosis of mycosis fungoides (MF) or Sezary Syndrome (SS) • Stage IB, II-A, II-B, III and IV • Subjects who had failed at least one prior course of systemic therapy. Psoralen plus ultraviolet light therapy (PUVA) is not considered to be a systemic therapy • Eastern Cooperative Oncology Group (ECOG) performance status score of ≤ 1 at study entry • Resolution of all clinically significant toxic effects of prior cancer therapy to grade ≤1 by the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0 (NCI-CTCAE, v.4.0) • Adequate hematological, renal and hepatic function • Subjects previously treated with anti-CD4 antibody or alemtuzumab were eligible provided their CD4+ cell counts were ≥ 200/mm3 • Subjects with mycosis fungoides (MF) and a known history of non-complicated staphylococcus infection/colonization were eligible provided they continued to receive stable doses of prophylactic antibiotics • Women of childbearing potential (WOCBP) must have had a negative pregnancy test within 7 days of receiving study medication • WOCBP and male subjects as well as their female partners of childbearing potential must have agreed to use effective contraception throughout the study and for 3 months after the last dose of KW-0761 Exclusion Criteria: • Prior treatment with KW-0761 or vorinostat. • Large cell transformation. However, subjects with a history of LCT but without current aggressive disease and no current evidence of LCT on pathology in skin and lymph nodes would be eligible. • Diagnosed with a malignancy in the past two years. However, subjects with non-melanoma skin cancers, melanoma in situ, localized cancer of the prostate with current PSA of <0.1 ng/mL, treated thyroid cancer or cervical carcinoma in situ or ductal/lobular carcinoma in situ of the breast within the past two years could enroll as long as there was no current evidence of disease. • Clinical evidence of central nervous system (CNS) metastasis. • Psychiatric illness, disability or social situation that would have compromised the subject's safety or ability to provide consent, or limited compliance with study requirements. • Significant uncontrolled intercurrent illness • Known or tested positive for human immunodeficiency virus (HIV), human T-cell leukemia virus (HTLV-1), hepatitis B or hepatitis C. • Active herpes simplex or herpes zoster. Subjects on prophylaxis for herpes who started taking medication at least 30 days prior to study entry, and had no active signs of active infection, and whose last active infection was more than 6 months ago, could enter the study, and should have continued to take the prescribed medication for the duration of the study. • Experienced allergic reactions to monoclonal antibodies or other therapeutic proteins. • Known active autoimmune disease were excluded. (For example, Grave's disease; systemic lupus erythematosus; rheumatoid arthritis; Crohn's disease; psoriasis). • Was pregnant (confirmed by beta human chorionic gonadotrophin [β-HCG]) or lactating. • History of allogeneic transplant.
Intervention	A total of 372 patients were randomized (n=186 mogamulizumab; n=186 vorinostat) and included in the ITT analysis set.

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Mogamulizumab 1.0 mg/kg as an IV infusion over at least 1 hour on days 1, 8, 15, and 22 of the first 28-day cycle and on days 1 and 15 of subsequent 28-day cycles.
Vorinostat (Zolinza) 400 mg orally once daily beginning on day 1 for 28-day cycles, administered on an outpatient basis.

For both study treatments, each treatment cycle was 28 days and treatment were to be continued until progressive disease, drug intolerance or unacceptable toxicity.
</td></tr>
<tr><td>Baseline characteristics</td><td>
In the ITT set, 54.8% of patients had MF, and 45.2% SS. Most patients had stage III or IV (62.4%), and the median time from initial diagnosis was 3.1 years. CCR4 expression was ≥ 10% in 75.3% of patients (and the analysis was missing in 22%).
Except for one patient, all randomized patients had received at least one prior systemic CTCL therapy. The vast majority (>80%) had received more than one prior systemic therapy. When specified by disease stage it is noted that stage IB/II subjects were the most heavily pretreated population enrolled in the study.
Use of premedications recommended prior to infusion of mogamulizumab (acetaminophen or paracetamol orally and diphenhydramine 50 mg iv or equivalent antihistamine) was more frequent in the mogamulizumab arm. Other medications used by a higher percentage of patients in the mogamulizumab arm were primarily anti-infective agents. A higher rate of anti-propulsive use was observed for patients receiving vorinostat (23.7%) compared to those receiving mogamulizumab (3.3%) during randomized treatment. The use of steroids was comparable between subjects randomized to mogamulizumab and those randomized to vorinostat, but higher in the stage III/IV subjects (48%) than in the stage IB/II subjects (19%). Among the Safety Analysis Set, pruritus medication use was similar for the two treatment groups: 136 (73.1%) patients in the vorinostat group and 140 (76.1%) patients in the mogamulizumab group.
<table>
<tr><th></th><th>Mogamulizumab (n=186)</th><th>Vorinostat (n=186)</th></tr>
<tr><td>Median age, years (range)</td><td>63.5 (25–101)</td><td>65.0 (25–89)</td></tr>
<tr><td><65 years, n (%)</td><td>99 (53.2)</td><td>89 (47.8)</td></tr>
<tr><td>Male, n (%)</td><td>109 (58.6)</td><td>107 (57.5)</td></tr>
<tr><td>Race, n (%)</td><td></td><td></td></tr>
<tr><td>White</td><td>125 (67.2)</td><td>135 (72.6)</td></tr>
<tr><td>Black or African American</td><td>24 (12.9)</td><td>13 (7.0)</td></tr>
<tr><td>Other</td><td>13 (7.0)</td><td>13 (7.0)</td></tr>
<tr><td>Not reported</td><td>24 (12.9)</td><td>25 (13.4)</td></tr>
<tr><td>ECOG performance status[a], n (%)</td><td></td><td></td></tr>
<tr><td>0</td><td>106 (57.0)</td><td>104 (55.9)</td></tr>
<tr><td>1</td><td>78 (41.9)</td><td>82 (44.1)</td></tr>
<tr><td>Time from initial diagnosis (months), median (IQR)</td><td>41.0 (17.4–78.8)</td><td>35.4 (16.2–68.2)</td></tr>
<tr><td>Current clinical stage, n (%)</td><td></td><td></td></tr>
<tr><td>IB–IIA</td><td>36 (19.4)</td><td>49 (26.3</td></tr>
<tr><td>IIB</td><td>32 (17.2)</td><td>23 (12.4)</td></tr>
<tr><td>IIIA-IIIB</td><td>22 (11.8)</td><td>16 (8.6)</td></tr>
<tr><td>IVA_1</td><td>73 (39.2)</td><td>82 (44.1)</td></tr>
<tr><td>IVA_2</td><td>19 (10.2)</td><td>12 (6.5)</td></tr>
<tr><td>IVB[b]</td><td>4 (2.2)</td><td>4 (2.2)</td></tr>
<tr><td>Current sites of disease, n (%)</td><td></td><td></td></tr>
<tr><td>Skin</td><td>186 (100.0)</td><td>186 (100.0)</td></tr>
<tr><td>Nodes</td><td>124 (66.7)</td><td>122 (65.6)</td></tr>
<tr><td>Viscera</td><td>3 (1.6)</td><td>3 (1.6)</td></tr>
<tr><td>Blood</td><td>122 (65.6)</td><td>122 (65.6)</td></tr>
<tr><td>Other (including bone marrow)</td><td>13 (7.0)</td><td>7 (3.8)</td></tr>
<tr><td>Blood involvement, n (%)</td><td></td><td></td></tr>
<tr><td>Yes</td><td>123 (66.1)</td><td>122 (65.6)</td></tr>
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	No	63 (33.9)	62 (33.3)
	Previous CTCL therapies[c], n (%)		
	Skin-directed therapies		
	PUVA	80 (43.0)	63 (33.9)
	Topical steroid	67 (36.0)	65 (34.9)
	Bexarotene-topical	11 (5.9)	6 (3.2)
	Systemic therapies		
	Bexarotene-oral	107 (57.5)	110 (59.1)
	Interferon-alpha	81 (43.5)	94 (50.5)
	Methotrexate	69 (37.1)	73 (39.2)
	ECP	71 (38.2)	65 (34.9)
	Romidepsin	45 (24.2)	32 (17.2)
	Nitrogen mustard	28 (15.1)	40 (21.5)
	Doxorubicin HCL liposome	23 (12.4)	19 (10.2)
	Pralatrexate	14 (7.5)	13 (7.0)
	Carmustine	13 (7.0)	13 (7.0)
	Brentuximab vedotin	16 (8.6)	4 (2.2)
	Denileukin diftitox	5 (2.7)	3 (1.6)
	Chlorambucil	3 (1.6)	4 (2.2)
	Etoposide	3 (1.6)	4 (2.2)
	IL-12	0 (0)	1 (0.5)
	Other (skin-directed and systemic)	131 (70.4)	121 (65.1)
	Median prior systemic therapies (IQR)	3.0 (2–5)	3.0 (2–5)
	CR or PR to last prior CTCL therapy	62 (33.3)	69 (37.1)
	CCR4, C-C chemokine receptor type 4; CR, complete response; CTCL, cutaneous T cell lymphoma; ECOG, Eastern Cooperative Oncology Group; ECP, extracorporeal photopheresis; HCL, hydrochloride; IQR, interquartile range; NR, not reported; PR, partial response; PUVA, psoralen plus ultraviolet light therapy [a], two patients had ECOG=1 at pre-treatment but ECOG=2 on Cycle 1, Day 1; [b], two patients (one in each treatment group) were noted to have stage IVB disease at baseline but did not have measurable visceral disease at baseline; [c], all patients in the ITT population had received at least one prior CTCL therapy.		
Primary and secondary endpoints	<u>Primary endpoint:</u> – Progression-free survival (PFS) as assessed by the Investigator based on the global composite response score, i.e. response in each compartment (skin, blood, lymph nodes and viscera). <u>Secondary endpoints:</u> – Overall response rate (ORR: CR or PR) as assessed by the Investigator. – Change in Skindex-29 score from baseline through the 6-month assessment – Change in FACT-G total score from baseline through the 6-month assessment – Change in EQ-5D-3L index score from baseline through the 6-month assessment – PFS as assessed by independent review (IR) – ORR by IR – Best overall response – Duration of response (DOR; INV and IR based) – Time to response (TTR) – ORR in the crossover portion of the trial – Changes from baseline in Skindex-29, FACT-G, and EQ-5D-3L at other time points – Changes from baseline in Pruritus Evaluation (Likert scale & Itchy QoL) <u>Exploratory efficacy endpoints</u> – Overall survival (OS) – Time to treatment failure (TTF)		

	Response in skin and blood was evaluated every 4 weeks. Response in lymph nodes and viscera was evaluated at 4 weeks, then every 8 weeks in the first year, and then every 16 weeks thereafter.
Method of analysis	Efficacy analysis sets Intent-to-treat (ITT): Includes all patients randomized to a therapy (mogamulizumab or vorinostat) and assigned a study number. Efficacy evaluable set: Includes all patients who received the first cycle of treatment (at least one dose) and who had a baseline tumour assessment and at least one post-baseline assessment for response. The ITT population included 372 patients: 186 in the mogamulizumab arm, and 186 in the vorinostat arm. The Efficacy Evaluable Set included 361 patients. Primary endpoint analysis The primary efficacy variable was PFS based upon the assessment by the Investigator, defined as the time from the day of randomization to a treatment arm until documented PD or death due to any cause. The primary comparison of PFS between mogamulizumab and vorinostat was performed on the ITT set based upon the results of the on-site investigator's assessment using a stratified Log-rank test at the one-sided 2.5% significance level. A Cox proportional hazard model with treatment, disease type, disease stage, and region (U.S., Japan, and Rest of World) as covariates was used to assess the magnitude of the treatment difference in PFS. The median PFS and the 2-sided 95% CI for each treatment was estimated using the Kaplan–Meier survival analysis methods
Subgroup analyses	Pre-planned subgroup analyses were performed within the following patient populations: – Disease type (MF, SS) – Disease stage (IB/II, III/ IV) – Blood involvement (yes, no) – Region (US, Japan, Rest of World) – Age group (<65 years, ≥65 years) – Gender (male, female) – Race category (Black or African American, White, Other) – Lactate dehydrogenase (LDH) (normal, elevated) Of which the most relevant for this submission are the analyses of PFS, ORR and TTNT in patients with advanced disease (≥Stage IIB MF and all SS patients)

10.2.1.2 ALCANZA

Table 23 Study characteristics - ALCANZA

Trial name	ALCANZA
NCT number	NCT01578499
Objective	The purpose of this study is to determine objective response rate (ORR), lasting at least 4 months (ORR4), with brentuximab vedotin in participants with cluster of differentiation antigen 30 positive (CD30+) cutaneous T-cell lymphoma [mycosis fungoides (MF) and primary cutaneous anaplastic large cell lymphoma (pcALCL)]compared to that achieved with therapy in the control arm.
Publications – title, author, journal, year	Brentuximab vedotin or physician's choice in CD30-positive cutaneous T-cell lymphoma (ALCANZA): an international, open-label, randomised, phase 3, multicentre trial, Prince, Lancet, 2017 Patient-reported quality of life in patients with relapsed/refractory cutaneous T-cell lymphoma: Results from the randomised phase III ALCANZA study, Dummer, Eur J Cancer, 2020
Study type and design	Open-label, randomised, phase 3, multicentre trial,

	Patients were randomised 1:1 to either receive brentuximab vedotin, or to receive the physician's choice of either bexarotene or methotrexate using an interactive voice response system, stratified by baseline disease diagnosis (MF or pcALCL).
Follow-up time	Median follow-up of 22·9 months (95% CI 18·4–26·1).
Population (inclusion and exclusion criteria)	Inclusion Criteria: - Male or female participants 18 years or older with diagnosis of mycosis fungoides (MF) or primary cutaneous anaplastic large cell lymphoma (pcALCL) - Participants with pcALCL who have received prior radiation therapy or at least 1 prior systemic therapy; participants with MF who have received at least 1 prior systemic therapy - Histologically confirmed CD30+ disease by central laboratory assessment and pathology review - Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2 - Female participants who are post menopausal, surgically sterile, or agree to practice 2 effective methods of contraception or agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the participant - Male participants who agree to practice effective barrier contraception or agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the participant - Clinical laboratory values as specified in protocol - A 3-week washout period is required from previous treatments (with the exception of a 12-week washout for antibody-directed or immunoglobulin-based immune therapy, or other monoclonal antibody therapies), unless it is not in the best interest of the patient in the opinion of the investigator. Individual cases should be discussed with the project clinician before enrollment. Exclusion Criteria: - A concurrent diagnosis of systemic ALCL, or other non Hodgkin lymphoma (excluding LyP) or Sezary syndrome or B2 disease - Participants with cardiovascular conditions specified in protocols - Participants with history of another primary malignancy not in remission for at least 3 years - Known active cerebral/meningeal disease, including signs or symptoms of progressive multifocal leukoencephalopathy (PML); - Known human immunodeficiency virus (HIV) infection, hepatitis B or Hepatitis C infection - Oral retinoid therapy for any indication within 3 weeks of study entry - Corticosteroid therapy within 3 weeks or immunosuppressive chemotherapy or any antibody-directed or immunoglobulin-based immune therapy (e.g., immunoglobulin replacement, other monoclonal antibody therapies) within 12 weeks of first dose of study drug - Female participants who are lactating and breastfeeding or have a positive serum pregnancy test during the screening period or a positive urine pregnancy test on Day 1 of any cycle - Previous receipt of brentuximab vedotin Please note that there are additional inclusion and exclusion criteria. The study center will determine if you meet all of the criteria.
Intervention	Brentuximab vedotin (n=64) 1.8 mg/kg by IV infusion (outpatient) over approximately 30 minutes on Day 1 of each 21-day cycle. In patients above 100 kg the dose was based on 100 kg. Patients could receive a maximum of 16 cycles (approximately 48 weeks) of brentuximab vedotin. Physicians choice (n=64): - Methotrexate once weekly as a single dose of 5 to 50 mg orally. Dosages adjustments (to max.50mg /week) to achieve optimal clinical response/lowest effective dose were allowed according to protocol. Patients could receive methotrexate for a maximum of 48 weeks.

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Bexarotene once daily 300 mg/m^2 orally, dose reduction was allowed to 200 mg/m^2/day or 100 mg/m^2/day. Bexarotene could be temporarily suspended for toxicity. Pre-treatment with fenofibrate 145 to 200 mg for 7 days (or reduced dose in case of creatinine≥1.5 mg/dL or nephrotic syndrome) was required. Concurrently a low dose of synthetic thyroxine (T4) was to be taken (adjusted along with dose of bexarotene). Continual monitoring of lipid and T4 concentrations was required during bexarotene treatment. Patients could receive bexarotene for a maximum of 48 weeks.

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<tr><td>Baseline characteristics</td><td>
The majority of patients with pcALCL had skin only lesions with 9 (56%) patients treated with brentuximab vedotin and 11 (73%) with physician's choice of therapy, while 7 (44%) and 4 patients (27%) had extracutaneous disease, respectively.

In MF patients a median of 2 prior systemic therapies was observed in both arms and in pcALCL subjects a median of 1 in the brentuximab vedotin and 2 in the control arm were observed. All but 1 pcALCL patient (see above) received prior systemic therapy in this study. The median time since progression from last line of prior therapy (radiotherapy excluded) was 2.4 months (range 0-112) in the brentuximab vedotin arm and 1.4 months (range 0-55) in the control arm.
In the physician's choice arm, 3 patients (8%) had previously received bexarotene for their CTCL and were assigned by their physician to bexarotene in this study. Similarly, 2 patients (8%) in the physician's choice arm had previously received methotrexate and received methotrexate as study drug. The listing of individual patient data indicate that for the 2 methotrexate retreated patients the best response on previous methotrexate was SD and PR. Both patients had also previously received bexarotene. For the bexarotene retreated patients the previous responses to bexarotene were documented as unknown. Only one of the bexarotene retreated patients was previously treated with methotrexate. Four patients (3 (5%) in the brentuximab vedotin arm and 1 (2%) in the physician's choice arm) had prior bone marrow or stem cell transplant.
The most common prior skin directed therapies in the ITT population were radiotherapy (64%), phototherapy (48%) and topical steroids (17%). The most common prior systemic therapies in the ITT population were chemotherapy (71%), immunotherapy (43%) and bexarotene (38%).

<table>
<tr><th></th><th>Brentuximab (n=64)</th><th>Methotrexate or Bexarotene (n=64)</th></tr>
<tr><td>Median age, years (range)</td><td>62.0 (22-83</td><td>58.5 (22-83)</td></tr>
<tr><td>Male, n (%)</td><td>33 (52)</td><td>37 (58)</td></tr>
<tr><td>Race, n (%)</td><td></td><td></td></tr>
<tr><td>White</td><td>56 (88)</td><td>53 (83)</td></tr>
<tr><td>Black or African American</td><td>3 (5)</td><td>3 (5)</td></tr>
<tr><td>Other</td><td>1 (2)</td><td>2 (3)</td></tr>
<tr><td>Not reported</td><td>3 (5)</td><td>1 (2)</td></tr>
<tr><td>ECOG performance status[a], n (%)</td><td></td><td></td></tr>
<tr><td>0</td><td>43 (67)</td><td>46 (72)</td></tr>
<tr><td>1</td><td>18 (28)</td><td>16 (25)</td></tr>
<tr><td>2</td><td>3 (5)</td><td>2 (3)</td></tr>
<tr><td>Mean (std dev)</td><td>75.2 (118.7)</td><td>62.23 (65.08)</td></tr>
<tr><td>Median</td><td>42.17</td><td>36.99</td></tr>
<tr><td>Current clinical stage, n (%)</td><td></td><td></td></tr>
<tr><td>IA</td><td>4 (8)</td><td>1 (2)</td></tr>
<tr><td>IB</td><td>6 (13)</td><td>12 (24)</td></tr>
<tr><td>IIA</td><td>5 (10)</td><td>5 (10)</td></tr>
<tr><td>IIB</td><td>19 (4)</td><td>19 (39)</td></tr>
<tr><td>IIA</td><td>4 (8)</td><td>2 (4)</td></tr>
<tr><td>IIIB</td><td>0 (0)</td><td>0 (0)</td></tr>
<tr><td>IVA_1</td><td>0 (0)</td><td>1 (2)</td></tr>
<tr><td>IVA_2</td><td>2 (4)</td><td>8 (16)</td></tr>
<tr><td>IVB</td><td>7 (15)</td><td>0(0)</td></tr>
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	Unknown	1 (2)	1 (2)
	Bone marrow involvement, n (%)		
	Yes	2 (3)	2 (3)
	No	62 (97)	62 (97)
	Previous CTCL therapies, n (%)		
	Skin-directed therapies	**52 (83)**	**51 (80)**
	Topical steroid	7 (11))	14 (22)
	Topical retinoids	1 (2)	0
	Topical chemotherapy	3 (5)	2 (3)
	Radiotherapy	40 (63)	41 (64)
	Phototherapy	32 (51)	29 (45)
	Other	2 (3)	0
	Systemic therapies	63 (100)	64 (100)
	Bexarotene	26 (41)	22 (34)
	Methotrexate	26 (41)	25 (39)
	Other chemotherapy	30 (41)	32 (50)
	Nontopical retinoids	5 (8)	4 (6)
	Photopheresis	3 (5)	4 (6)
	Denileukin diftitox	0	1 (2)
	Immunotherapy	26 (41)	29 (45)
	Median prior systemic therapies	4.0	3.5
Primary and secondary endpoints	Primary endpoint: ORR4 is the proportion of patients who achieved an objective response (CR or PR) that lasted at least 4 months, as determined by an independent review facility (IRF). Objective responses will be based on a Global Response Score (GRS), which consists of skin evaluation (mSWAT assessment) by investigator, nodal and visceral radiographic assessment by IRF, and detection of circulating Sézary cells (MF only) by IRF. – Skin evaluation (mSWAT) performed at screening, before dosing on Day 1 of Cycles 1, -3 and at the end of every cycle beginning at Cycle 3, EOT, and at post treatment follow-up visits – CT scans for patients without nodal or visceral involvement were performed at screening and during the cycle following the first skin response and 6 cycles (or ≥ 4 months) after that or in case of suspected new/progressive disease in the LN/viscera – CT scans for patients with baseline nodal/visceral disease, were performed at screening and at the end of Cycles 3, 6, 9, 12, and 15, and per the follow-up schedule until PD or suspected new/progressive disease in the LN/viscera and at EOT – Blood sample for Sézary cell enumeration in patients with MF performed at screening; at the end of Cycles 3, 6, 9, 12, and 15, at EOT, and per the follow-up schedule until PD or study closure Secondary endpoints: – CR - proportion of patients who achieved a CR as their best response on study as determined by an IRF by GRS criteria – PFS- time from randomisation until PD per IRF or death due to any cause, whichever occurs first – Changes in symptom domain (7 items) according to Skindex-29 questionnaire (administered on Day 1 of Cycles 1 and subsequent even number cycles) – Other secondary endpoints: – DOR- analysed for patients in the ITT population with a confirmed response per IRF – DOR in skin- analysed for patients in the ITT population with skin response (CR or PR in skin) per investigator		

	– EFS- time from randomisation until any cause of treatment failure per IRF: PD, discontinuation of treatment for any reason, or death due to any cause, whichever occurs first. – Concentrations of brentuximab vedotin (serum) and MMAE (plasma) – Immunogenicity assessment – QOL assessments according to Skindex-29 and FACT-G questionnaires – AEs and SAEs, according to NCI CTCAE version 4.03 and assessments of clinical laboratory values <u>Exploratory endpoints:</u> – Qualitative and quantitative measures of CD30 expression in biopsied tumour assessed before and after brentuximab vedotin treatment. The Quest clinical trial assay was initially used for screening to determine CD30 expression in tissue samples from skin biopsies. This assay was later replaced by the Ventana anti-CD30 (Ber-H2) assay (Amendment 3). – Serum concentration of PD markers such as sCD30 – Presence or absence of gene or protein variation associated with CTCL or brentuximab vedotin mechanism of action – Utilisation of health resources
Method of analysis	The ITT population included all patients who were identified as CD30+ by the Ventana anti- CD30 (Ber-H2) assay and were randomised to treatment; analysed according to randomisation treatment. The ITT population was used for the primary efficacy analysis and for all other efficacy analyses unless specified otherwise. The Per-Protocol (PP) population included a subset of ITT patients who received study drug and did not have major protocol violations as determined by the project clinician; analysed according to received treatment. The PP population was used for supplemental analysis of the primary endpoint ORR4 The Safety population included patients who received at least 1 dose of study drug. All patients were analysed according to the actual treatment received. Stratified log-rank test statistics will be used to compare PFS between the 2 treatment arms. The HRs and 95% CIs will be estimated using a stratified Cox regression model. The Kaplan-Meier method will be used to estimate the distribution of the time-to event endpoints for each treatment. An alpha level of 0.01 (2-sided) was specified per the weighted Holm procedure.
Subgroup analyses	Pre-specified subgroups analyses were performed for the following subgroups: baseline disease diagnosis, ECOG PS, sex, age (<65, ≥65), region, race and physician's choice. Baseline disease involvement and baseline skin tumour involvement were not pre-specified.

10.2.1.3 EORTC 21012

Table 24 Study characteristics - EORTC 21012

Trial name	EORTC 21012
NCT number	NCT00074087
Objective	To evaluate the effectiveness of liposomal doxorubicin in treating patients who have stage IIB, stage IVA, or stage IVB recurrent or refractory mycosis fungoides.
Publications – title, author, journal, year	Prospective international multicenter phase II trial of intravenous pegylated liposomal doxorubicin monochemotherapy in patients with stage IIB, IVA, or IVB advanced mycosis fungoides: final results from EORTC 21012, Dummer, J Clin Oncol, 2012
Study type and design	Single-arm open label phase II study.
Follow-up time	Median follow-up of 10.6 months (range not reported).

<table>
<tr><td>Population (inclusion and exclusion criteria)</td><td>Inclusion criteria:
– Histologically confirmed mycosis fungoides
o Stage IIB, IVA, or IVB
– Refractory or recurrent disease after at least 2 of the following prior therapies:
o Local and/or systemic steroids
o Retinoids
o Interferon alfa
o Local carmustine
o Systemic chemotherapy
o Psoralen and ultraviolet A (PUVA) light therapy
– Karnofsky Performance status 60-100%
– Prior systemic chemotherapy allowed provided all of the following conditions are met:
o Cumulative anthracycline dose is less than 200 mg/m^2
o No allergy to anthracyclines
o Prior methotrexate is low dose (i.e., weekly dose less than 30 mg)
Exclusion criteria:
– No CNS involvement
– No erythroderma (T4)</td></tr>
<tr><td>Intervention</td><td>49 patients received 20 mg/m^2 pegylated liposomal doxorubicin hydrochloride IV over 1 hour on days 1 and 15. Treatment repeats every 28 days for up to 6 courses.</td></tr>
<tr><td>Baseline characteristics</td><td>Most patients had a PS of 0 or 1 (96%), had refractory disease (71%), were men (67%), and were between the ages of 56 and 75 years (63%). Prior therapies included combination therapy with or without chemotherapy (22% and 41%, respectively), chemotherapy alone, and topical treatment with or without chemotherapy (14% and 12%, respectively).

<table>
<tr><th></th><th>Doxorubicin (n=49)</th></tr>
<tr><td>Age category, years</td><td>59 (27-84)</td></tr>
<tr><td>26-35</td><td>2 (4.1)</td></tr>
<tr><td>36-45</td><td>1 (2.0)</td></tr>
<tr><td>46-55</td><td>7 (14.3)</td></tr>
<tr><td>56-65</td><td>16 (32.7)</td></tr>
<tr><td>66-75</td><td>15 (30.6)</td></tr>
<tr><td>>75</td><td>8 (16.3)</td></tr>
<tr><td>Male, n (%)</td><td>33 (67.3)</td></tr>
<tr><td>ECOG performance status[a], n (%)</td><td></td></tr>
<tr><td>0</td><td>21 (42.9)</td></tr>
<tr><td>1</td><td>26 (53.1)</td></tr>
<tr><td>2</td><td>2 (4.1)</td></tr>
<tr><td>Skin patches/plaques</td><td></td></tr>
<tr><td>No</td><td>1 (2.0)</td></tr>
<tr><td>Yes, % BSA</td><td></td></tr>
<tr><td><10</td><td>8 (16.3)</td></tr>
<tr><td>≥10</td><td>40 (81.6)</td></tr>
<tr><td>Skin tumors</td><td></td></tr>
<tr><td>Yes</td><td>10 (20.4)</td></tr>
<tr><td>No</td><td>39 (79.6)</td></tr>
<tr><td>Clinical lymph node</td><td></td></tr>
<tr><td>Yes</td><td>24 (49.0)</td></tr>
<tr><td>No</td><td>25 (51.0)</td></tr>
<tr><td>Histologic lymph node</td><td></td></tr>
<tr><td>Yes</td><td>34 (69.4)</td></tr>
<tr><td>No</td><td>15 (30.6)</td></tr>
</table>
</td></tr>
</table>

	Visceral disease	
	Yes	44 (89.8)
	No	5 (10.2)
	Refractory/recurrent disease	
	Refractory	35 (71.4)
	Recurrent	14 (28.6)
	Prior therapy, no of pts (%)	
	Immunotherapy	3 (6.1)
	Radiotherapy	2 (4.1)
	Chemotherapy	7 (14.3)
	Topical treatment	6 (12.2)
	Combination treatment	
	With chemotherapy	11 (22.4)
	Without chemotherapy	20 (40.8)
	Duration from last treatment to trial entry/registration, days	
	Median	44.0
Primary and secondary endpoints	Primary endpoints: – Response (complete clinical [CCR] and partial resp. [PR]) rate by Tumor Burden Index for cutaneous disease and appearance or disappearance of lesions for noncutaneous disease every 8 wks during treatment and then every 12 wks until progression Secondary endpoints: – Time to progression measured by Tumor Burden Index for cutaneous disease and appearance or disappearance of lesions for noncutaneous disease every 8 weeks during treatment – Duration of response measured by Tumor Burden Index for cutaneous disease and appearance or disappearance of lesions for noncutaneous disease every 8 weeks during treatment and then every 12 weeks until progression – Toxicity assessed by CTC v.2.0 at the end of each course	
Method of analysis	All analyses were carried according to per-protocol population, eligible patients who started treatment. Statistical methods are not reported in the publication or on clinicaltrials.gov	
Subgroup analyses	Subgroup analyses not reported in the publication	

10.2.1.4 Duvic et al. 2006

Trial name	**Duvic et al. 2006**
NCT number	Not reported in the published article or identified through online search.
Objective	The purpose of this study was to investigate safety and efficacy of gemcitabine monotherapy for cutaneous T-cell lymphoma (CTCL).
Publications – title, author, journal, year	Phase II evaluation of gemcitabine monotherapy for cutaneous T-cell lymphoma, Duvic, Clin Lymphoma Myeloma, 2006
Study type and design	Single-arm, prospective, single-center, phase II, open-label.
Follow-up time	Median follow-up of 38,5 months.
Population (inclusion and exclusion criteria)	The study is not registered at www.clinicaltrials.gov. As an alternative the eligibility criteria reported in the publication is provided:

<table>
<tr><td></td><td>Patients were aged > 16 years with biopsy-proven CTCL. No exposure to fludarabine was allowed within 6 months. Life expectancy was > 12 weeks, and patients with active infections, cancer, or central nervous system disease were excluded. Mycosis fungoides was staged by the TNM system.22 Patients with stage IB or IIA disease at baseline must have experienced treatment failure with another systemic therapy, whereas those with tumors (T3), erythroderma (T4), or nodal disease were eligible for treatment.</td></tr>
<tr><td>Intervention</td><td>Gemcitabine was infused at 1000 mg/m^2 and dissolved in 250 mL saline over 30-60 minutes on days 1, 8, and 15 each month for 6 months. Patients received acetaminophen and ondansetron before infusions.</td></tr>
<tr><td>Baseline characteristics</td><td>Two patients were classified as primary cutaneous CD30+ anaplastic large T-cell lymphoma and 31 were classified as MF, including 11 with SS. Three patients were MF stage IA-IIA and 28 patients were MF stage IIB-IVB. 11 patients were SS. Thirteen patients with cutaneous tumors had large-cell transformation, and 6 patients also had nodal involvement. All had been previously heavily treated with a median of 5 previous therapies (range, 2-13 therapies)

<table>
<tr><th></th><th>Gemcitabine (n=33)</th></tr>
<tr><td>Median age, years (range)</td><td>62.0 (22-83</td></tr>
<tr><td>Male, n (%)</td><td>33 (52)</td></tr>
<tr><td>Current clinical stage, n</td><td></td></tr>
<tr><td>IB-IIA</td><td>3</td></tr>
<tr><td>IIB</td><td>13</td></tr>
<tr><td>IVA</td><td>7</td></tr>
<tr><td>IVB</td><td>8</td></tr>
<tr><td>Previous therapies, n</td><td></td></tr>
<tr><td>Skin-directed therapies</td><td>61</td></tr>
<tr><td>Topical steroid</td><td>9</td></tr>
<tr><td>Topical retinoids</td><td>5</td></tr>
<tr><td>Nitrogen mustard</td><td>17</td></tr>
<tr><td>Phototherapy</td><td>13</td></tr>
<tr><td>Local radiation therapy</td><td>6</td></tr>
<tr><td>TBSEB</td><td>11</td></tr>
<tr><td>Biologic Response Modifiers</td><td>76</td></tr>
<tr><td>Steroids</td><td>4</td></tr>
<tr><td>Retinoids</td><td>35</td></tr>
<tr><td>Isotretinoin</td><td>9</td></tr>
<tr><td>L-Atra</td><td>4</td></tr>
<tr><td>Bexarotene</td><td>22</td></tr>
<tr><td>Interferon</td><td>12</td></tr>
<tr><td>Etanercept</td><td>2</td></tr>
<tr><td>Phototherapies</td><td>9</td></tr>
<tr><td>Targeted therapies</td><td>16</td></tr>
<tr><td>Denileukin Diftilox</td><td>14</td></tr>
<tr><td>Alemtuzumab</td><td>2</td></tr>
<tr><td>Chemotherapy (single-agent)</td><td>13</td></tr>
<tr><td>Methotrexate</td><td>5</td></tr>
<tr><td>Liposomal Doxorubicin</td><td>1</td></tr>
<tr><td>Pentostatin</td><td>7</td></tr>
<tr><td>Median prior systemic therapies, range</td><td>5.0 (2-13)</td></tr>
</table>
</td></tr>
<tr><td>Primary and secondary endpoints</td><td>The publication does not report primary and secondary endpoints.
The study includes assessment of complete and partial responses, safety and overall survival.</td></tr>
</table>

Method of analysis	The publication only provides very limited information on the methods of analysis. Overall survival in patients with CTCL treated with gemcitabine was plotted using the Kaplan-Meier product-limit method. Associations between markers (LDH, sIL-2R, absolute CD4, absolute CD8, and the ratio of absolute CD4 and CD8) and response were evaluated by Wilcoxon rank sum test.
Subgroup analyses	NA

10.3 Results per study

10.3.1.1 MAVORIC

Table 25 Results of MAVORIC

Trial name:	**MAVORIC**										
NCT number:	NCT01728805										
				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 (OS)	Mogamulizumab	186	Not reached	NE			HR: 0,93	(0,61-1,43)	0,9439	Exploratory endpoint. Time from the date of randomization until the date of death due to any cause.	[2,33]
	Vorinostat	186	43,93 (43,57- NR)								
Median overall survival (OS) crossover adjusted IPCW	Mogamulizumab	173	51,7 (40,7-NE)	24,63			HR: 0,57	(0,26-1,25)	0,16	Exploratory endpoint. Time from the date of randomization until the date of death due to any cause. Crossover adjusted via IPCW method models	Data on file
	Vorinostat	177	27,07 (28,37-NE)								
Median progression-free survival (PFS)	Mogamulizumab	186	7,7 (5,67– 10,33) months	4,6			HR: 0,53	(0,41-0,69)	<0,0001	Investigator based on the ITT set, with a stratified log rank test at the one-sided 2,5% significance level, adjusted for stratification factors disease type (MF or SS,	[2,33]
	Vorinostat	186	3,1 (2,87– 4.07) months								

										disease stage (IB/II or III/IV) and region (U.S., Japan, and rest of the world). The median PFS and the 2-sided 95% CI for each treatment was estimated using the Kaplan–Meier survival analysis methods	
Skindex-29 total score	Mogamulizumab	155	LS Mean: -15,7 (-20,96, -10,67)	-12,1	-19,47--4,69)	0,0014				HRQoL: Changes from baseline in Skindex-29 total score Changes from baseline	Data on file (Extended CSR)
	Vorinostat	164	LS Mean: -3,6 (-9,93, 2,7)								
Proportion of patients with adverse events grade 3-4	Mogamulizumab	184	45,7%	-0,5	-10,74-9,57	0,9102	RR: 0,98	(0,79-1,23)	0,91	According to NCI/CTCAE. Risk ratio calculated based on Mantel-Haenszel method	Data on file (CSR)
	Vorinostat	186	46,2%								
Proportion of patients with serious adverse events (SAEs)	Mogamulizumab	184	39,7%	14,94	0,55-24,35	0,0018	RR: 1.60	(1,18-2,18)	0.0026	According to NCI/CTCAE. Risk ratio calculated based on Mantel-Haenszel method	[2,33]
	Vorinostat	186	24,7%								

10.3.1.2 ALCANZA

Table 26 Results of ALCANZA

Trial name:	**ALCANZA**										
NCT number:	NCT01578499										
				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 (OS)	Brentuximab vedotin	64	NE (30,4-NE)	NE			HR: 0,89	(0,43-1,84)	0,74	Stratified log-rank test statistics was used to compare between the 2 treatment arms. The HRs and 95% CIs was estimated using a stratified Cox regression model. The Kaplan-Meier method was used to estimate the distribution of the time-to event endpoints for each treatment	[26]
	MTX or Bexarotene	64	NE (NE-NE)								
Median progression-free survival (PFS)	Brentuximab vedotin	64	16,7 (14,9-22,8)	13,2			HR: 0,27	(0,17-0,43)	<0,01	Stratified log-rank test statistics was used to compare between the 2 treatment arms. The HRs and 95% CIs was estimated using	[26]
	MTX or Bexarotene	64	3,5 (2,4-4,6)								

										a stratified Cox regression model. The Kaplan-Meier method was used to estimate the distribution of the time-to event endpoints for each treatment	
Skindex-29 total score	Brentuximab vedotin	64	-14,84 (SD: 22,68)	13,88						Changes from baseline in Skindex-29 total score	[26]
	MTX or Bexarotene	64	-0,96 (SD: 18,97)								
Proportion of patients with adverse events grade 3-4	Brentuximab vedotin	66	27 (41%)	-5,87	-23,04-11,31	0,5033	RR: 0,87	0,59-1,29	0,5042	According to NCI/CTCAE. Risk ratio calculated based on Mantel-Haenszel method	[26]
	MTX or Bexarotene	62	29 (47%)								
Proportion of patients with serious adverse events (SAEs)	Brentuximab vedotin	66	19 (29%)	-0,24	-15,96-15,47	0,9757	RR: 0,99	0,58-1,71	0,9757	According to NCI/CTCAE. Risk ratio calculated based on Mantel-Haenszel method	[26]
	MTX or Bexarotene	62	18 (29%)								

10.3.1.3 EORTC 21012

Trial name:	**EORTC 21012**										
NCT number:	NCT00074087										
				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 time to progression (TTP)	Doxorubicin	49	7,4 (4,5-8,6)	NA			NA			NR	[31]
Proportion of patients with adverse events grade 3-4	Doxorubicin	49	20 (41%)	NA			NA			NR	[31]

10.3.1.4 Duvic et al 2006

Trial name:	**Duvic et al 2006**										
NCT number:	Not reported										
				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 (OS)	Gemcitabine	25	20,4 (NR-NR)	NA			NA			Patients treated with gemcitabine was plotted using the Kaplan-Meier product-limit method	[32]

Proportion of patients with adverse events grade 3-4	Gemcitabine	33	22 (41%)	NA			NA			NR	[32]
Proportion of patients with serious adverse events (SAEs)	Gemcitabine	33	12 (36.3%)	NA			NA			NR	[32]

10.4 Results per PICO (clinical question)

Table 27 Results referring to clinical question 1 (chemotherapy)

Results per outcome		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 (OS)	1	NE	NE	NE	HR: 0,93	0,61-1,43	0,9439	Only one study included hence no method quantitative analysis
Median overall survival (OS) crossover adjusted IPCW	1	24,63	NA	NA	HR: 0,57	0,26-1,25	0,16	Only one study included hence no method quantitative analysis.
Median progression-free survival (PFS)	1	4,6	NA	NA	HR: 0,53	0,41-0,69	<0,0001	Only one study included hence no method quantitative analysis.
Skindex-29 total score	1	-12,1	-19,47 - 4,69	0,0014	NA	NA	NA	Only one study included hence no method quantitative analysis.
Proportion of patients with adverse events grade 3-4	1	-0,5	-10,74- 9,57	0,9102	RR: 0,98	0,79-1,23	0,91	Only one study included hence no method quantitative analysis.
Proportion of patients with serious adverse events (SAEs)	1	14,94	0.55-24.35	0.0018	RR: 1,60	1,18-2,18	0,0026	Only one study included hence no method quantitative analysis.

10.5 ITT population vs. at least 2 prior systemic treatments

ITT population vs. at least 2 prior systemic treatments

Figure 18. KM plot of ITT population vs. at least 2 prior systemic treatments, PFS, MAVORIC trial

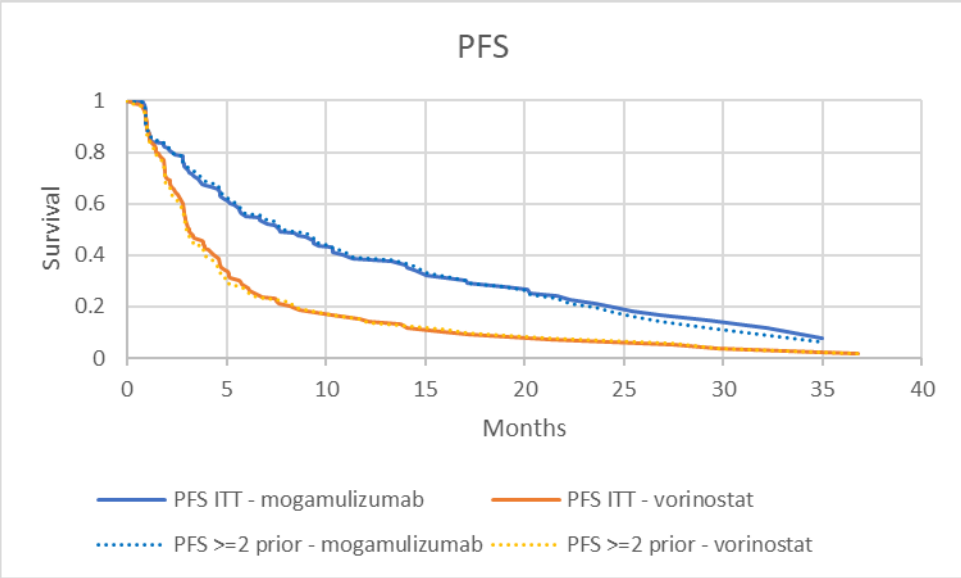
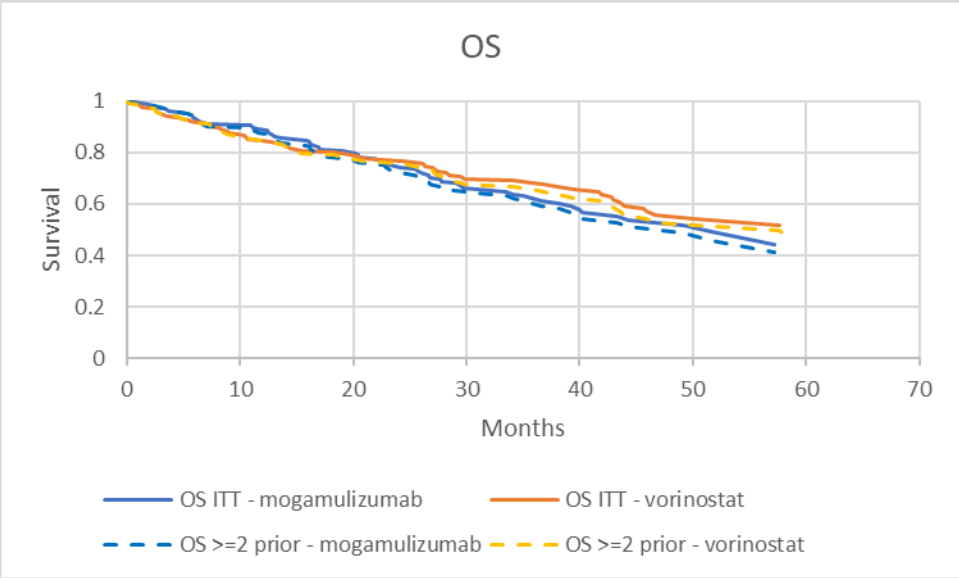


Figure 19. KM plot of ITT population vs. at least 2 prior systemic treatments, OS, MAVORIC trial



Cost-per-patient and budget impact analysis of Poteligeo® (mogamulizumab) for treatment of patients with mycosis fungoides and Sézary syndrome, who have received at least two prior systemic treatments

Technical document – application for the Danish Medicine Council

Contact person: Linda McNamara
Position: Market Access Director – Northern Cluster (UK, Ireland, Nordics, Baltics)
✉: Linda.McNamara@kyowakirin.com

EXECUTIVE SUMMARY

Baggrund

Den 15. juni 2020 offentliggjordes Medicinrådets protokol for vurdering af mogamulizumab til behandling af voksne med mycosis fungoides (MF) eller Sézarys syndrom (SS), der har fået mindst to tidligere systemiske behandlinger. Protokollen omfattede følgende kliniske spørgsmål:

1. Hvilken værdi har mogamulizumab sammenlignet med nuværende behandling for patienter med mycosis fungoides eller Sézarys syndrom, der har fået mindst to tidligere systemiske behandlinger?

Både kemoterapi og targeteret behandling anses for at være relevante komparatorer for mogamulizumab af fagudvalget i Medicinrådets protokol, og er derfor inkluderet som komparatorer i denne analyse.

Dette tekniske dokument beskriver de økonomiske analyser, hhv. omkostningsanalyser og budgetkonsekvensanalyser, som er udarbejdet som en del af ansøgningen til Medicinrådet for ovenstående kliniske spørgsmål. Formålet med dette dokument er at beskrive de økonomiske modeller, deres funktioner, datagrundlaget, antagelserne, samt de overordnede resultater.

Metode

En partitioned survival model med tre stadier (progressionsfri sygdom [PFS], progredieret sygdom [PPS], og død) blev udviklet for at estimere de inkrementelle omkostninger per patient for mogamulizumab, sammenlignet henholdsvis med kemoterapi og targeteret behandling. Omkostningsanalysen er delvist indlejret i budgetkonsekvensmodellen, og resultaterne fra omkostningsanalysen er således anvendt som direkte input til budgetkonsekvensmodellen.

Modellen er baseret på resultaterne MAVORIC studiet, et fase 3 studie, der sammenlignede mogamulizumab og vorinostat. MAVORIC inkluderede MF og SS patienter i forsøgspopulation, og data fra disse patienter er inkluderet i modellen. Patientdata er anvendt som input til den økonomiske model.

I sammenligningen med kemoterapi er der ikke blevet identificeret KM data på PFS og OS, som kunne tillade for ekstrapolering af disse til modellen. I stedet er en behandlingslængde på 20 uger med doxorubicin rapporteret i EORTC 21012 studiet blevet anvendt til estimering af omkostninger af behandling. Ved denne tilgang sammenlignes kun behandlingsomkostninger af mogamulizumab og kemoterapi.

Eftersom valg af behandling er baseret på en individuel vurdering, er det ikke klinisk meningsfuldt af udvælge én specifik komparator. Derfor blev de relevante targeteret behandlinger inkluderet som en kurv, og omkostningerne af targeteret behandlinger blev estimeret ved en vægtning af omkostningerne af de inkluderede targeteret behandlingsregimer. For kemoterapi, er omkostninger for doxorubicin anvendt til at estimere omkostningerne ved en kemoterapi kurv. Dette kunne dog lede til en overestimering af de inkrementelle omkostninger for mogamulizumab sammenlignet med kemoterapi, da både methotrexat og gemcitabin regimet administreres mere frekvent end doxorubicin regimet og derfor vil være associeret med meromkostninger for administration af disse. Tilgangen anses af denne grund at være konservativ ift. estimering af omkostningerne for kemoterapi.

Modellen anvender en livstidshorisont (30 år). Omkostninger diskonteres med 4% per år i overensstemmelse med Medicinrådets metodevejledning. Modellen har et begrænset samfundsperspektiv, og inkluderer lægemiddelomkostninger, administrationsomkostninger, monitoreringsomkostninger, omkostninger til uønskede hændelser, patientomkostninger, og transportomkostninger.

Resultater

Base casen viser en inkrementel diskonteret meromkostning på [redacted] DKK for mogamulizumab sammenlignet med kemoterapi og inkrementel diskonteret meromkostning på [redacted] DKK for mogamulizumab sammenlignet med den targeteret behandling.

Budgetkonsekvenserne estimeres i år 5 (steady state) til at være [redacted] DKK ved anbefaling af mogamulizumab som standard behandling.

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Abbreviations

AE	Adverse event
AIC	Akaike Information Criterion
aSCT	Autologous stem cell transplant
BIC	Bayesian Information Criterion
BIM	Budget Impact Model
CFB	Change From Baseline
CI	Confidence interval
CTCL	Cutaneous T-cell lymphomas
DMC	Danish Medicines Council
DRG	Diagnosis Related Group
ECOG	Eastern Cooperative Oncology Group
ECP	Extracorporeal photopheresis
EMA	European Medicines Agency
EORTC	European Organisation for Research and Treatment of Cancer
ESMO	European Society for Medical Oncology
HR	Hazard ratio
IPCW	Inverse probability of censoring weights
IPD	Individual patient data
ITT	Intention-to-treat population
IV	Intravenous
KM	Kaplan-Meier
KOL	Key opinion leader
LDH	Lactate dehydrogenase
MF	Mycosis fungoides
N/A	Not applicable
NR	Not reported
OS	Overall survival
PartSA	Partition survival analysis
PFS	Progression-free survival
PS	Performance status
PUVA	Narrow spectrum UVB or 8-Methoxypsoralen + UV-A
RCT	Randomized controlled trial
SS	Sézary syndrome
TOT	Time on treatment

TSE	Two-stage estimation
TTNT	Time to next treatment
TSEBT	Total skin electron beam therapy

1 Introduction

1.1 Background

Cutaneous t-cell lymphomas (CTCL) are a very small subset of non-Hodgkin's lymphoma that manifests in the skin, leading to rash-like skin redness, slightly raised or scaly patches on the skin and skin tumours[1]. Mycosis fungoides (MF) accounts for 55% of all CTCLs and is characterized by patches and plaques in the early stages[2]. Around 30% of patients develop advanced disease, characterised by tumours, ulceration, systemic/blood involvement with lymph node or visceral spread, and is therefore, linked with significant morbidity and mortality[3]. Sézary syndrome (SS) accounts for 2.5% of all CTCLs and is a more aggressive, leukemic form of CTCL characterised by the presence of malignant lymphocytes called 'Sézary cells' in the peripheral blood[3,4]. SS patients also suffer from erythroderma, lymphadenopathy and have thickened, scaly and fissured skin all over their body leading to opportunistic infections, sepsis and death[5,6].

In Denmark, approximately 400-500 patients live with treatment intensive CTCL (local as well as systemic treatment), approximately 55% of the CTCL patients are MF patients, 200-250 patients and 2.5% of the CTCL patients are SS patients, 10-13 patients. The Danish Medicine Council (DMC) estimates that there are approximately 15 patients who are candidates for mogamulizumab (prevalence) and that there will be an incidence of approximately 5 new patients per year[7]. While patients in early stages of the disease have a median survival of 21.5 years (stage IB) from the time of diagnosis, this dramatically reduces to under 5 years for patients with advanced disease from the time of diagnosis (stage IIB onwards); for patients with stage IVB disease, median survival is under 2 years from the time of diagnosis[8].

Alongside the psychological distress of living with incurable cancer, patients face a significant, disfiguring physical burden with the skin often oozing and becoming infected; patients report discomfort, cracking and bleeding and skin 'like tin foil'[9]. Importantly, the skin manifestations of CTCL have a significant impact on the quality of life (QoL). The poor condition and continuous itching of the skin affects both the patient's sleep and daily activity, due to affection of the skin on their hands and feet. The disease has a serious impact on patient's family life, as there is a substantial burden of caring for the individuals caring for the patient[10]. CTCL can cause patients to miss work and due to its physical manifestation has a significant impact on social interactions such as participation in sports or hobbies[9,11].

1.2 Standard treatment

The treatment of cutaneous T-cell lymphoma in Denmark is carried out by the dermatological departments in the initial stages, while the treatment of advanced patients are carried out by oncology departments in cooperation with the dermatology and haematology and/or oncology departments[12]. The treatment follows international guidelines from European Society for Medical Oncology (ESMO) and European Organisation for Research and Treatment of Cancer (EORTC)[13,14]. There is no defined standard treatment as treatment is individualised based on the characteristics of the cutaneous lymphoma, the severity of the disease, the patient's performance status, comorbidities, previous treatments, patient preferences, etc.[12,15].

The aim of the treatment for most patients is good disease control by receiving a highly tolerable treatment which addresses the cancer by providing symptom relief and is demonstrated in improving a patient's quality of life. For CTCL most treatments except allogeneic stem cell transplantation are not curative. The aim is to reduce tumour burden followed by disease control. The disease management strategy is therefore, to relieve symptoms, improve quality of life, induce remissions, delay progression, and avoid significant treatment-related toxicity.

In early stages of MF (stage IA-IIA), topical therapy is used in the form of e.g. corticosteroids in combination with ultraviolet phototherapy (narrow spectrum UVB or 8-Methoxypsoralen + UV-A) (PUVA) or chlormethine (nitrogen-mustard)[7].

In later, more advanced stages (stage IIB-IV) of MF, low-dose total skin electron beam therapy (TSEBT), local radiotherapy are used against the tumour or first-line systemic medical treatment in the form of interferon-α, retinoids (e.g. acitretin and bexarotene) or low-dose methotrexate.

The treatment following the first line of systemic treatments is planned at the multidisciplinary conference with the haematology department and targeted treatments, pathway inhibitors or chemotherapy (e.g. high-dose methotrexate, gemcitabine, or doxorubicin) are used[7].

The targeted treatments include brentuximab vedotin (anti CD30), alemtuzumab (anti CD52), and pembrolizumab (PD-1 inhibitor). The pathway inhibitor includes histone deacetylase (HDAC) inhibitor romidepsin. These treatment regimens are considered equal treatment alternatives by the clinical expert committee. The choice of treatment is individualised and is guided by the patient's biomarker expression. None of the targeted treatments/pathway inhibitors can be considered standard treatments in Denmark, and only brentuximab vedotin is indicated for the treatment of CD30 positive CTCL. The pivotal trial for brentuximab vedotin, ALCANZA, included MF patients but the effect on Spatients was not investigated[16]. Treatment with these alternatives is therefore, dependent on individual applications to the pharmaceutical committees. The EMA has previously rejected marketing authorisation for romidepsin for this indication. Treatment with pembrolizumab, alemtuzumab and romidepsin is therefore used outside the approved indication (off-label).

SS is characterized by malignant lymphocytes in the peripheral blood and therefore, requires systemic treatment. Extracorporeal photopheresis (ECP), either alone or in combination with e.g. interferon-α and/or retinoids, TSEBT and PUVA have been proposed as initial treatment options for SS[7]. Targeted treatments/pathway inhibitors are used as second-line treatment as described above.

1.3 Intervention treatment

Mogamulizumab (Poteligeo®) is a humanised IgG1 kappa immunoglobulin that selectively binds to CCR4, a G-protein-coupled-receptor involved in trafficking of lymphocytes to various organs including the skin[17]. CCR4 is expressed in high concentrations on the surface of some cancer cells including T cell malignancies, such as MF and SS in which CCR4 expression is inherent.

Mogamulizumab is indicated for adult patients with MF or SS who have received at least one prior systemic treatment. Mogamulizumab was designated an orphan drug in 2016 for the following condition: Treatment of cutaneous T-cell lymphoma.

The DMC considers that mogamulizumab will be a relevant treatment alternative for patients with advanced disease (MF, stage II-IV and SS) who have been treated in Danish clinical practice with at least two systemic treatments (e.g. extracorporeal photochemotherapy, methotrexate, retinoids and interferon-α) or have a contraindication for one or more of these systemic treatments. Mogamulizumab should therefore be used in line with the targeted treatments and pathway inhibitors described in section 1.2.

2 Purpose

The economic model was developed to estimate the incremental costs per patient as well as the budget impact of mogamulizumab for treating patients with mycosis fungoides or Sézary syndrome, who have received at least two prior systemic treatments compared to the standard treatment. The model will utilise a restricted societal perspective.

3 Clinical evidence

3.1 Clinical data on mogamulizumab

The efficacy and safety of mogamulizumab were assessed in the MAVORIC pivotal phase 3 trial, where it was compared to vorinostat in patients with stage IB to IVB MF or SS who have failed at least one prior therapy[18]. Patients were aged at least 18 years (in Japan, ≥20 years), and had an ECOG performance score of 1 or less and adequate haematological, hepatic, and renal function. For the MAVORIC trial, vorinostat was chosen as the comparator, as an alternative to other current standard of care that patients were already refractory to, and was required to enable high recruitment of patients where re-challenge would have been inappropriate in a clinical trial setting and to ensure robust sample size for the MAVORIC study.

MAVORIC is the largest randomized Phase III study conducted in any CTCL subgroup to date, with 372 patients enrolled[18]. Approximately 80% of patients had advanced disease (i.e. stage ≥IIB MF and all SS patients) and 45% of all patients recruited had SS; this is the largest number of SS patients to ever be recruited to a randomized trial. Patients were also heavily pre-treated with a median of 3 previous systemic treatments received including 58% of patients previously treated with bexarotene, 47% with interferon-alpha and 66% with chemotherapy; 5% of patients previously received brentuximab vedotin.

Table 1. Baseline demographic and disease characteristics of patients in the MAVORIC trial[18,19].

	MAVORIC	
	Mogamulizumab (n=186)	**Vorinostat (n=186)**
Age, median years (range)	63 (25-101)	65 (56-72)
Male, n (%)	109 (59)	107 (58)
Race, n (%)		
White	125 (67,2)	135 (73)
Other	37 (19,9)	26 (14)
ECOG PS, n (%)		
0	106 (57,0)	104 (56)
1	78 (41,9)	82 (44)
2	2 (1,1)	0
Time from initial diagnosis, median months (range)	41,0 (17,4-78,8)	35,4 (16,2-68,2)
Disease type, n (%)		
MF	105 (56,5)	99 (53)
SS	81 (43,5)	87 (47)
Disease stage, n (%)		
IB-IIA	36 (19,4)	49 (26)
IIB	32 (17,2)	23 (12)
IIIA-IIIB	22 (11,8)	16 (9)
IVA_1	73 (39,2)	82 (44)
IVA_2	19 (10,2)	12 (6)
IVB	4 (2,2)	4 (2)
Lines of prior systemic therapy, median (IQR)	3 (2-5)	3 (2-5)

Key: ECOG, Eastern Cooperative Oncology Group; IQR, Interquartile range MF, mycosis fungoides; PS, performance status; SS, Sezary syndrome

In the ITT population mogamulizumab resulted in:

- Significantly better progression-free survival (PFS) with a HR of 0,53 (95% CI 0,41-0,69) (median 7,7 vs. 3,1 months for mogamulizumab vs. vorinostat respectively)
- Significantly higher overall response by Global Composite Response: 28% vs. 5% for mogamulizumab vs. vorinostat respectively with p-value <0,0001
- Significantly better quality of life at the 6-month assessment using Skindex-29, FACT-G, EQ-5D, and ItchyQol

- In post-hoc analyses significantly longer time to next treatment (TTNT): with a HR of 0,36 (95% CI 0,27-0,48) (median of 11 months vs. 3,5 months for mogamulizumab vs. vorinostat respectively with p value <0,0001)

A systematic literature review was conducted for the targeted comparators included in the protocol. No studies that reported relevant data (OS and PFS KM-curves) for a partition survival model were identified to inform the clinical question. As mentioned in the protocol, most of the relevant comparator treatments are used off-label, and therefore there is a lack of available evidence for the efficacy of the treatments for this population. Consequently, since there is no available evidence available for any of the comparators to inform the clinical question, the MAVORIC trial was used to inform the efficacy of all included comparators in the model.

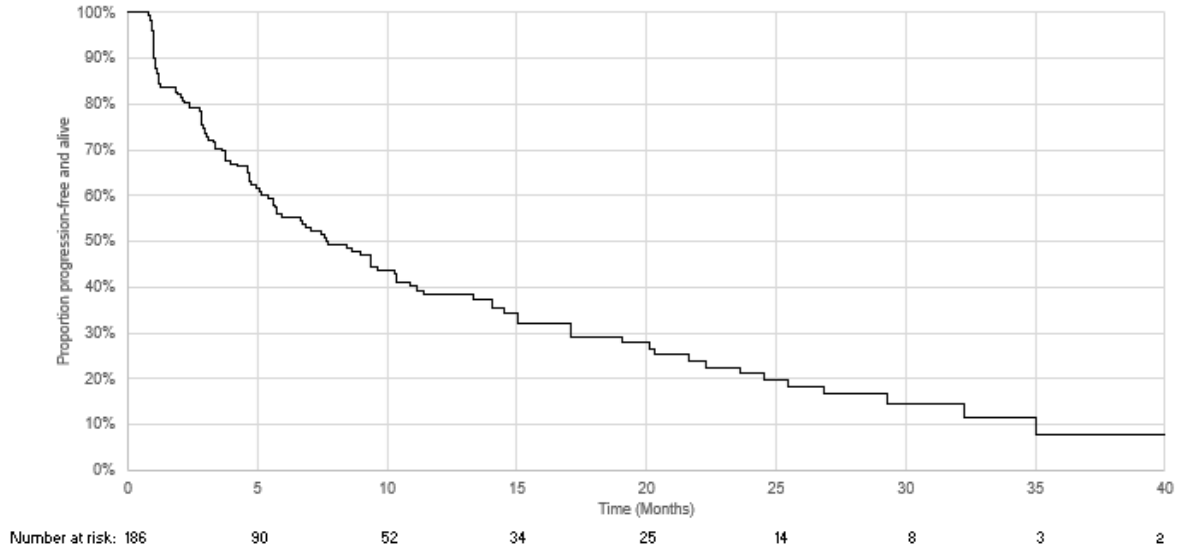
The intention-to-treatment (ITT) population of the MAVORIC trial was used to inform the model, as the population who have received at least two prior systemic treatments is included within the ITT population. The ITT population also includes patients who had only received one prior systemic treatment, however, this only constitutes 18,3% of the ITT population[19].

To investigate whether using the ITT population would be appropriate to answer the clinical question, a subgroup analysis was conducted comparing the ITT population with the subgroup of patients from the MAVORIC trial, who had received at least two prior systemic treatments. No significant difference in OS, PFS and overall response rate (ORR) was observed between the ITT population and the subgroup, who had received at least two prior systemic treatments. It was therefore concluded that it was appropriate to use the ITT population as the data analysis set. The median number of prior systemic treatment in the MAVORIC trial was 3, which supports the findings of the subgroup analysis. By using the ITT population, we avoid breaking the randomization and reducing the sample size. This approach was also approach considered appropriate by the DMC secretariat in dialogue leading up to the submission.

3.2 Progression-free survival

The PFS of the ITT population from the MAVORIC trial is presented in Figure 1. The PFS data was used to inform the PFS in the model.

Figure 1. MAVORIC PFS KM data, ITT population.

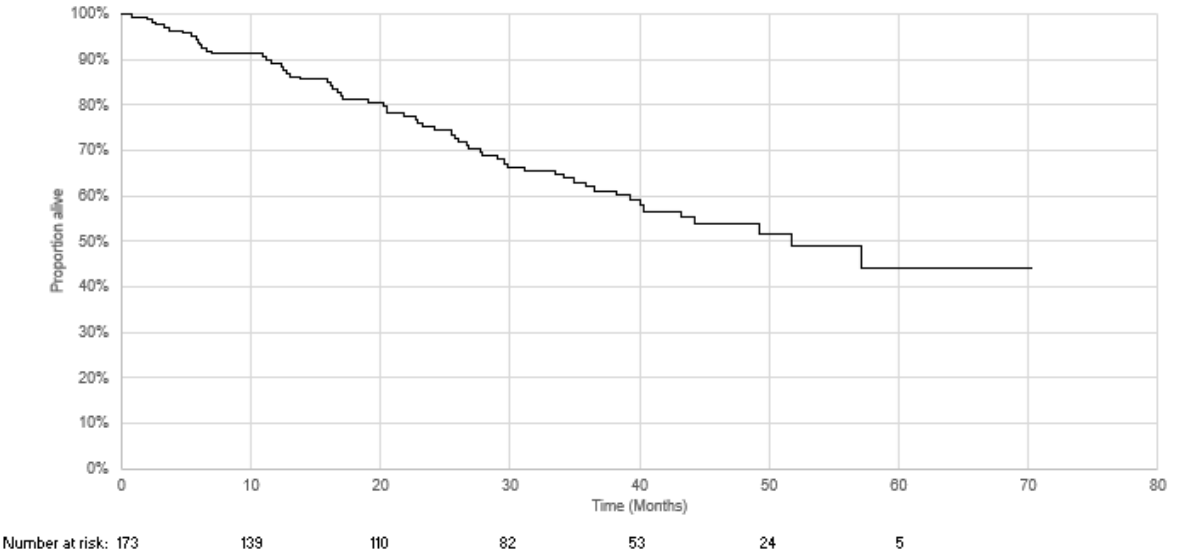


3.3 Overall survival

For overall survival (OS), all analyses below have excluded patients receiving allogeneic stem cell transplant (aSCT) to reflect the effect of mogamulizumab without the use of aSCT.

The observed OS from the MAVORIC trial in the ITT population is presented in Figure 2.

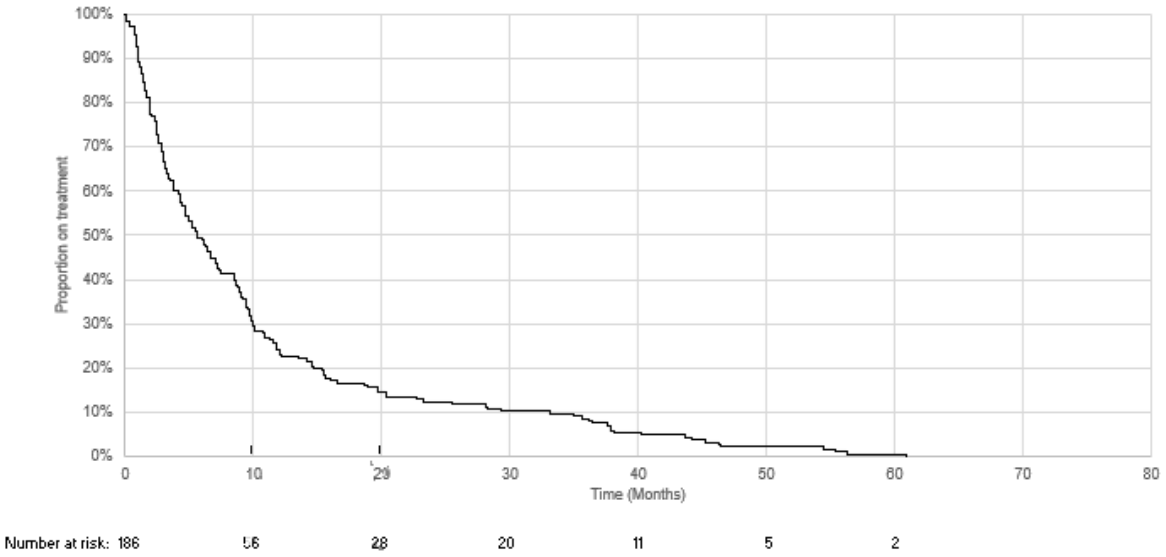
Figure 2. MAVORIC OS KM data, ITT population.



3.4 Time on treatment

To accurately capture treatment costs, MAVORIC time on treatment (TOT) KM data were used. Figure 3 presents the MAVORIC KM data for the mogamulizumab arm for the TOT data. The data is complete for the TOT endpoint.

Figure 3. MAVORIC time on treatment KM data, ITT population.



3.5 Time to next treatment

Time to next treatment (TTNT) is defined as the time from randomisation to the start of the next treatment. The TTNT is included to inform the model of the initiation of subsequent treatments.

[redacted]

[redacted]

[redacted]

3.6 Clinical data on chemotherapy

For the clinical application, a literature search was conducted for comparative studies with chemotherapy on MF and SS patients. One publication, EORTC 21012 [20], was identified as relevant for implementation in the health economic model. This was a single-arm phase II study of intravenous pegylated liposomal doxorubicin in patients with stage IIA, IVA, or IVB advanced MF. The main baseline characteristics of EORTC 21012 are reported in Table 2, for comparison, baseline characteristics of MAVORIC can be found in Table 1. Eligible patients were registered to receive PLD

as monotherapy at a dose of 20 mg/m^2 on days 1 and 15, every 28 days (28-day cycle). Although, EORTC 21012 did not report PFS or OS, it did report time-to-progression [20]. The time-to-progression data was not deemed appropriate for a comparison with the PFS in the MAVORIC trial, and the KM-data were not sufficient to generate a valid pseudo KM data set, due to the small number of patients and events. However, the publication did report a median TOT of 20 weeks (range: 4-20 weeks).

Table 2. Main study baseline characteristics of EORTC 21012

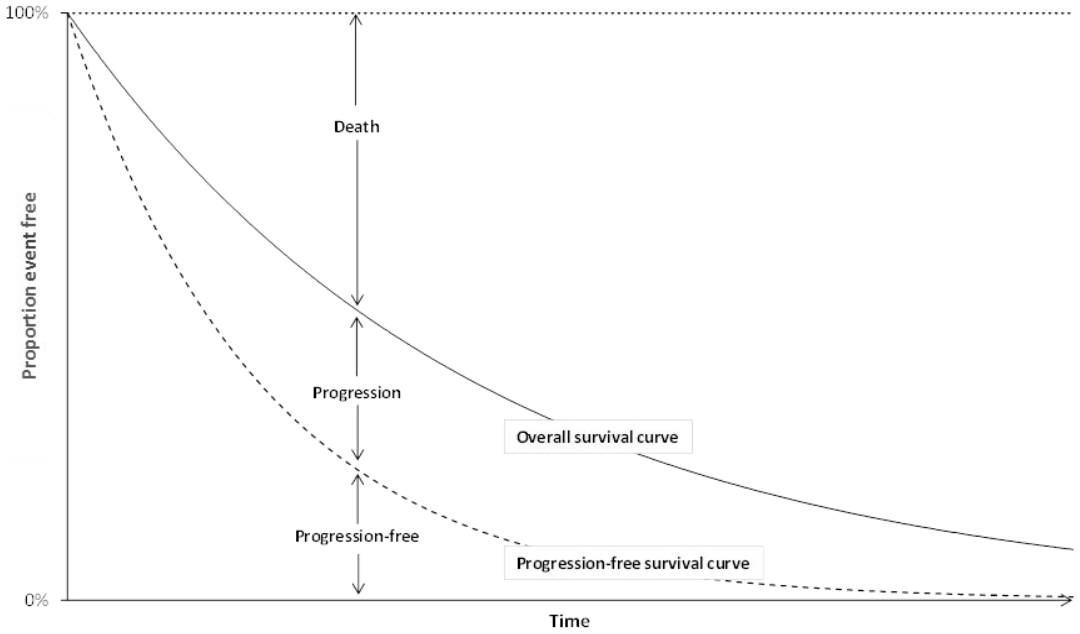
	EORTC 21012 (n=49)
Median age, years (range)	59 (27-84)
Male, n (%)	33 (67,3)
ECOG performance status, n (%)	
0	21 (42,9)
1	26 (53,1)
2	2 (4,1)
Time from initial diagnosis in months, median (range)	NR
MF	49 (100)
SS	0 (0)

4 Health economic model structure

4.1 Model description

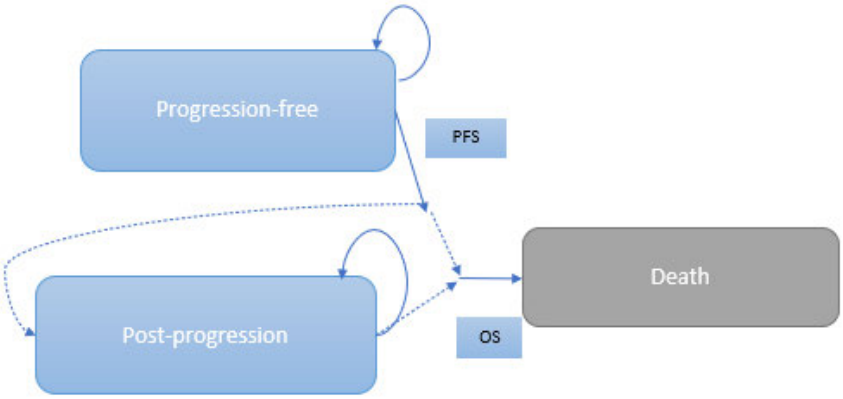
The health economic model used in the analysis is a 3-health state partitioned survival model with health states consisting of progression-free, post-progression, and death. Within a partitioned survival model, health states are based on the partitioning of the patients alive into a surviving without progression health state (PFS) and surviving post-progression health state (PPS) at discrete time points. The proportion of patients in the PPS health state at a given point in time is calculated as the difference in the proportion of patients who are alive and the proportions of progression-free patients. This type of model allows for usage of the available clinical study data whilst also relying on the most used health stages in previous oncology models, i.e. the mutually exclusive healing states of progression-free, post-progression, and death.

Figure 5. Example of a partitioned survival model



Patients enter the model in the progression-free state. In each cycle, patients can either remain in the progression-free health state or transition to the post-progression or death health state (Figure 5). Patients who have progressed can remain in the post-progression state or transition to the death state but never go back to the progression-free state. All patients eventually enter the death state.

Figure 6. Diagram of the model for a partitioned survival model



4.2 The rationale for model structure

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

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

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

4.3 Model cycle duration

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

5 Model input

5.1 Intervention and comparators

Based on the DMC protocol, the intervention and the comparators in the model are:

- Intervention: Mogamulizumab
- Comparator: Chemotherapy basket
  - Methotrexate
  - Doxorubicin
  - Gemcitabine
- Comparator: Targeted/Pathway inhibitor basket
  - Brentuximab vedotin
  - Alemtuzumab
  - Pembrolizumab
  - Romidepsin

The dosing regimens for the intervention and comparators are based on the regimens provided in the DMC protocol. A dermatologist and an oncologist were consulted for validation of the preferences in the clinical practice in both the chemotherapy basket and the targeted therapy basket[12,15].

For the chemotherapy regimens, the oncologist preferred the use of gemcitabine, while the dermatologist mentioned the use of methotrexate and doxorubicin in their practice[12,15]. However, as the EORTC 21012 publication reported on doxorubicin, the drug cost was calculated with the doxorubicin regimen. As both the methotrexate-regimen and the gemcitabine-regimen is more costly and requires more frequent administrations, in turn accruing more cost for the chemotherapy arm. The use of only doxorubicin could potentially lead to an underestimation of the drug cost for the chemotherapy comparison. The outcome of this model is incremental cost, and therefore lower calculated cost for the chemotherapy arm and would result in a higher incremental cost for the comparison of mogamulizumab vs. chemotherapy, which is not beneficial for the mogamulizumab arm. We therefore considered this approach conservative for estimation of the drug cost for the chemotherapy basket.
For the targeted therapy regimens, the dermatologist primarily uses brentuximab vedotin for CD30+ patients and alemtuzumab for CD52+ patients[15]. The oncologist primarily uses brentuximab vedotin for CD30+ patients, and noted that pembrolizumab might be used for some patients, however, she had the most experience with brentuximab[12]. As no single comparator was considered clinically meaningful by any of the clinicians, brentuximab vedotin, alemtuzumab and pembrolizumab are assumed to have an equal share in the targeted therapy basket, 1/3, as reported in Table 3. Romidepsin has not been included in the basket due to lack of available price data on medicinpriser.dk, due to the lack of marketing authorisation at the European Medicines Agency.

Table 3. Composition of targeted therapy basket in the model

Treatment	Share
Brentuximab vedotin	33,3%
Alemtuzumab	33,3%
Pembrolizumab	33,3%
Romidepsin	0,0%

5.2 Clinical inputs

5.2.1 Efficacy assumptions

5.2.1.1 Targeted therapy

The mogamulizumab data from the MAVORIC trial is used to model the mogamulizumab arm in the model. The DMC committee considers all treatments in the targeted therapy basket as equal treatment options for the patient population. Due to the lack of data for the other targeted therapies to model efficacy, the mogamulizumab data from the MAVORIC trial is assumed to be a proxy for the efficacy of the targeted therapies, as mogamulizumab is a targeted therapy. Therefore, the parametric fits for the targeted therapy basket will be based on the same data used for the mogamulizumab arm. The targeted therapy basket will thereby have the same duration of TOT, TTNT, PFS and OS as the mogamulizumab arm. To allow for flexibility, it is possible to vary the effect ratio for TOT, TTNT, PFS and OS for the targeted therapy arm.

5.2.1.2 Chemotherapy

Partitioned survival models (which are a type of "area under the curve" [AUC] models) are used to estimate mean outcomes and costs of treatments. IPD or pseudo IPD (generated from digitizing published KM-curves[21]) are necessary to generate the parametric curves used to generate mean values in the models. The EORTC publication only provided KM-data for time-to-progression (assumed as a proxy for PFS in the clinical application), however, not for OS and TOT[20]:

1. The model requires estimation of TOT in order to calculate drug costs. KMs of the TOT were not provided in the EORTC data. Additionally, it is not possible to use PFS as a surrogate for TOT, as doxorubicin (treatment within the comparator arm) has a fixed cycle length, with a maximum treatment duration of 6 cycles (5,54 months)[20]. Therefore, using the PFS as a surrogate in this case, would overestimate the costs of chemotherapy, as the median time-to-progression reported in the EORTC is 7,4 months, thereby underestimating the incremental cost of the use of mogamulizumab.
2. Modelling OS requires the use of external data sources as the EORTC publication does not report this data. The use of external data sources introduces uncertainty in terms of heterogeneity (as the EORTC trial is different to that of the MAVORIC), for instance in terms of baseline characteristics. This in turn decreases the validity of the analysis, as undue uncertainty is added to the comparison.
3. The time a patient spends on treatment is not directly calculated based upon OS or PFS, but rather TOT. The only costs that are directly associated with OS and PFS are monitoring costs. As the majority of cost in each arm is associate to treatment acquisition and administration, the overall cost in each arm is not driven by OS and PFS

In an ideal world, one would have IPD or a KM curve to generate pseudo IPD, as this would allow the calculation of proportion of patients on treatment overtime. However, for the EORTC trial, only a median TOT was reported. The median TOT of doxorubicin in the EORTC trial was 20 (4-20) weeks [22]. Doxorubicin has a maximum treatment length of 24 weeks (6 cycles).

It important to use means rather than medians within the cost analysis as these reflect the overall aggregate average of the cohort, rather than just reflecting the middle point of the distribution. Means can be estimated from medians, where an exponential distribution is assumed (Equation 1).

Equation 1. Estimation of the mean value of an exponential distribution from a median value

$$Estimated\ mean = \frac{1}{-LN(0{,}5)/median\ TOT}$$

Using equation 1, the mean is estimated to be 28,5 weeks, which is more than the maximum treatment duration allowed (24 weeks). As the estimated mean is clinically implausible, the next best

option is to use the median (20 weeks). Additionally, it should be noted that as the range is from 4-20, it is very likely that the true mean is close to 20.

The estimated TOT (based on a median of 20 weeks) is then used to calculate the treatment cost of the chemotherapy arm.

To provide a non-biased comparison, no monitoring costs are included in the base case analysis, as no monitoring costs can be properly estimated for chemotherapy, due to the lack of both PFS and OS data. Inclusion of monitoring costs would result in biased results, overestimating the incremental costs for mogamulizumab, as monitoring cost cannot be estimated for both for OS and PFS for chemotherapy. A scenario was explored, where monitoring cost were included. In this scenario, the monitoring costs for mogamulizumab were based on PartSA, and the monitoring costs for chemotherapy were based on the time-to-progression data (7,4 months) presented in EORTC 21012 [22], as a proxy for PFS. The mean “PFS” was estimated from the median by assuming an exponential distribution, as described above, resulting in a mean “PFS of 10,7 months for chemotherapy. However, this scenario is also biased, as monitoring costs associated with PPS for chemotherapy are not included in this analysis, thereby overestimating the incremental costs for mogamulizumab. Consequently, we consider the base case to provide the most useful results for decision making.

5.3 Parametric Fit overview

Extrapolation beyond the MAVORIC trial was performed by fitting parametric distributions to the observed time to event data from MAVORIC trial.

5.3.1 Goodness of fit

Parametric distributions were assessed for their goodness of fit to the data using:

- Visual inspection of diagnostic plots, including log cumulative hazard plots, Schoenfeld residuals plot, piecewise hazard plot and quantile-quantile plots
- The Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC). Low values for BIC indicate a better statistical fit of the parametric function to the actual data.
- Visual assessment of each parametric function.

5.3.2 Progression-free survival

Test of proportional hazards (PH)

No test of PH is necessary, as only a single arm of the MAVORIC trial is extrapolated on.

Goodness of fit

Table 4 provides the AIC and BIC statistics for the fitted parametric functions used to model PFS in the model. The mogamulizumab data is used to model the PFS for mogamulizumab and the targeted therapy basket in the model. Based on the AIC and BIC statistics, the best fit overall would be obtained with a log-normal distribution for the mogamulizumab data. Upon visual inspection of the parametric extrapolations of the mogamulizumab data, [redacted], the log-normal function appears to fit the KM data well and provide a conservative projection for the tail. The log-normal distribution appears to provide a slightly more conservative long-term project of the PFS compared to the generalized gamma distribution. A figure illustrating the long-term extrapolation of PFS has been included in the appendix, Figure 10.

Based on the overall assessment of the parametric curves, a log-normal distribution is therefore used in the base case for extrapolating the PFS in the model. The choice of parametric distribution for PFS will be analysed in a scenario analysis.

[redacted]

[redacted]

[redacted]

[redacted]

5.3.3 Overall survival

Test of proportional hazards (PH)

No test of PH is necessary, as only a single arm of the MAVORIC trial is extrapolated on.

Goodness of fit

[redacted] provides the AIC and BIC fit statistics for the parametric curves fitted to OS. For the mogamulizumab data, the AIC statistics indicate that the log-logistic distribution to be the best statistical fit, with the exponential distribution as the second-best fit. For BIC, the exponential distribution is the best statistical fit. Upon visual inspection, the exponential function fits the KM well for the mogamulizumab data, while providing a conservative tail. A figure illustrating the long-term extrapolation of the OS have been included in the Appendix A. Parametric fits, long-term extrapolations.

Based on the overall assessment of the parametric curves, the exponential distribution has been chosen for extrapolation of OS.

[redacted]

[redacted]

[redacted]

[redacted]

5.3.4 Time on treatment

Patients start on treatment from cycle 1. Given the complete nature of the data for this endpoint, the KM data was used directly to capture the TOT of the patients in the model. The use of KM data reflects the actual proportion of patients that receive treatment in each model cycle, as observed in the MAVORIC trial. Parametric distributions are available in the model for scenario analysis. A treatment cap of 12 weeks has been applied for the Alemtuzumab regimen, as per the DMC protocol[7]. No treatment cap has been applied for the remaining regimens included in the model, based on the KOL input from two clinicians[12,15].

5.3.5 Time to next treatment

TTNT is used to capture the time to the initiation of the subsequent treatment in the model. [redacted] reports the AIC and BIC statistics for the fitted function used to model TTNT in the model based on data from the MAVORIC trial. Based on the AIC and BIC statistics, the best fit appears to be the log-normal distribution for the mogamulizumab data set, with the log-logistic as the second-best fit based

on BIC statistics. On visual inspection of the parametric functions, the log-normal and log-logistic distributions fit well to the mogamulizumab arm KM data and projects similar long-term tails.

Based on the overall assessment of both data set, a log-logistic distribution has been chosen for the mogamulizumab data set. The choice of parametric distribution will be analysed in a scenario analysis.

[redacted]

[redacted]

[redacted]

[redacted]

5.4 Time horizon

It is recommended that the selected time horizon should be long enough to reflect all the important differences in costs between the technologies being compared[23].

For the base-case analysis, a time horizon of 30 years has been selected. At 30 years more than 99% of the cohort have stopped treatment and approximately 99% of the cohort is dead, as predicted by the model using the TOT and OS parametric distributions.

5.5 Perspective

The perspective of the economic model is a restricted societal perspective, which includes cost related to drug acquisition, drug administration, monitoring, adverse events, patient time, and transportation. Indirect costs are not included following the DMC's guidelines[23].

5.6 Discounting rate

In the base case, the annual discount rate for future costs were 4% in alignment with DMC's guidelines, where the use of the Danish Ministry of Finance's discount rate is recommended[24].

5.7 Adverse events

In the model, all grade 3+ adverse events (AE) in the MAVORIC trial have been included. The number of occurrences and the number of patients has been included in the sheet "Adverse event". A cycle probability of each AE has been estimated based on the number of occurrences and the total patient months at risk. This cycle probability is used to estimate an average cycle cost of AE during the time-on-treatment of each arm.

The MAVORIC trial reported on the AEs of mogamulizumab and vorinostat. The AE rates for the targeted therapy arm was assumed to be equal to the AE rates of the mogamulizumab arm of the MAVORIC trial. Therefore, the AEs frequencies of mogamulizumab were used as a proxy for the AEs of the targeted therapies and the pathway inhibitor included in the model. Due to the lack of AE data for the chemotherapies, an assumption of equal AE rates between vorinostat and chemotherapy was made. Exposure-adjusted AE rates, based on the MAVORIC trial, were used for mogamulizumab. Including AE rates from EORTC 21012 directly would result in biased results, since the data available do not allow for exposure adjustment per type of AE[22]. Therefore, the AE rates for the chemotherapy arm were assumed to be equal to the AE rates of the vorinostat arm in the MAVORIC trial and have been applied accordingly in the model. To assess the impact of this assumption, a scenario analysis has been conducted, where the AEs cost were excluded in both arms. This scenario, however, is biased against mogamulizumab, as chemotherapy is often avoided due to side effects observed in patients and is therefore expected to have higher AE costs compared to mogamulizumab. This was validated by KOL testimony.[12,15].

5.8 Cost inputs

5.8.1 Drug dosing and acquisition costs

The baseline characteristics for the European patients included in MAVORIC are illustrated in Table 7.

Table 7. Baseline patient characteristics from the MAVORIC trial

Input	
Average age	63 years
Average body weight	76,77 kg
Average body surface area	1,91 m2
Proportion of men	41,9 %

The dosing of mogamulizumab and the comparators are listed in Table 8. The patients are assumed to be treated until treatment discontinuation, following the TOT curve from the MAVORIC trial. Due to lack of data for the comparators, the following assumptions were made: Treatment with chemotherapies (doxorubicin) follows the TOT of the EORTC 21012 publication[20]. Treatment with targeted therapies (mogamulizumab, brentuximab vedotin, alemtuzumab, pembrolizumab and romidepsin) is assumed to follow the TOT curve of the mogamulizumab arm of the MAVORIC trial. A

maximum of 12 weeks of treatment with alemtuzumab is applied in the model in line with the DMC protocol.

The dose per administration was based on average dose intensity as recorded in the MAVORIC trial. [redacted] is observed in the MAVORIC trial. Due to the absence of data for the comparators in the protocol, the dose intensity of all comparators was assumed to be equal to the intensity applied to mogamulizumab, [redacted].

In the model, the dosing of mogamulizumab is based on the actual dose observed in the MAVORIC trial. Dose banding with 10% discrepancy was used, based on the patient characteristics data from the MAVORIC trial, to estimate the dosing for mogamulizumab in the model. Wastage is assumed for all comparators in the base case, where the remainder of an opened vial is assumed to be wasted.

Table 8. Drug cost and dosing used in the model. Dosing regimen sourced from the DMC protocol.

Treatment	Package size	Composition	Cost per pack (DKK)	Dosing Regimen
Mogamulizumab	1 vial	20 mg	11.734,00[1]	1 mg/kg IV Day 1, 8, 15 and 22 of the first 28-day cycle. Then Day 1 and 15 of each subsequent 28-day cycle
Methotrexate	1 vial	500 mg	80,00[2]	240 mg/m2 IV 1-2 day per week
Doxorubicin	1 vial	50 mg	120,00[2]	20 mg/m2 IV Day 1 of 21-day cycle
Gemcitabine	1 vial	2000 mg	385,00[2]	1.000 mg/m2 IV Day 1 and 8 of 21-day cycle
Brentuximab vedotin	1 vial	50 mg	21.629,38[2]	1,8 mg/kg IV, every 3rd week
Alemtuzumab	1 vial	12 mg	46.871,09[2]	10 mg IV 3 times weekly for 12 weeks
Pembrolizumab	1 vial	100 mg	24.409,84[2]	200 mv IV, every 3rd week
Romidepsin	N/A	N/A	N/A	14 mg/m2 IV on dag 1, 8 and 15 every 28 day cycle (until progression)

1. Source: Kyowa Kirin internal price
2. Source: Medicinpriser.dk – accessed 06-08-2020
N/A: Pricing was not available for Romidepsin on Medicnpriser.dk

5.8.2 Drug administration costs

In addition to the drug acquisition costs, the cost of administration was also considered within the model.

The unit cost of administration was estimated using Interactive DRG 2020, with the diagnosis code DC840: "Mycosis fungoides" and the procedure code BWHA62: "Medicingivning ved intravenøs infusion". Interactive DRG 2020 identified 17MA98: "MDC17 1-dagsgruppe, pat. mindst 7 år". The DRG tariff was applied to all comparators at each administration, according to the dosing table provided in the DMC protocol. The unit costs of administration are presented in Table 9.

Table 9. Drug administration cost of Mogamulizumab and comparators

Treatment	Unit cost per administration (DKK)	DRG code	Source
Mogamulizumab	3.235	17MA98	Interactive DRG 2020
Methotrexat	3.235	17MA98	Interactive DRG 2020
Doxorubicin	3.235	17MA98	Interactive DRG 2020
Gemcitabin	3.235	17MA98	Interactive DRG 2020
Brentuximab vedotin	3.235	17MA98	Interactive DRG 2020
Alemtuzumab	3.235	17MA98	Interactive DRG 2020
Pembrolizumab	3.235	17MA98	Interactive DRG 2020
Romidepsin	3.235	17MA98	Interactive DRG 2020

5.8.3 Monitoring costs

The details of the health state costs are described in table 9-11. The resource use associated with monitoring has been based on KOL interview with two Danish clinicians, a dermatologist and an oncologist[12,15]. Both clinicians agreed that the resource use would be similar between the different therapies, and rather be based on the progress of the disease[12,15]. Based on this, the monitoring cost is assumed to be the same for all treatments. Both clinicians stated a PET/CT scan was conducted before the first consultation and the continuous monitoring of the patient would consist of an oncologist consultation with a duration of 20 min. along with a blood count and a paraclinical test pack. Frequencies were assumed based on the KOL input by two clinicians[12,15]. For the costing of oncologist time, the DMC's "Estimating unit costs" has been used[25]. The cost of the blood count and the paraclinical test was sourced from "Rigshospitalets Labportal".

The cycle costs of monitoring have been estimated for the state, pre-progression and post-progression, and are reported in Table 12.

Table 10. Unit cost for the paraclinical test

Resource	Unit cost (DKK)	Notes
Liver function test	144	"Rigshospitalets Labportal"
Urea and electrolytes test	26	"Rigshospitalets Labportal"
LDH (lactate dehydrogenase)	23	"Rigshospitalets Labportal"
Total	**193**	

Table 11. Unit cost of disease monitoring

Resource	Unit cost (DKK)	Notes	Source
Oncologist consultation	439	At every monitoring, assumption of consultation to be 20 mins long	Danish Medicine Council's "Estimating unit costs", Oncologist wage
Blood count	30	At every monitoring	"Rigshospitalets Labportal"
Paraclinical test	193	At every monitoring, Liver function, urea and electrolytes and LHD test	"Rigshospitalets Labportal"
PET/CT-scan	2.470	Once at the start of treatment	DRG 2020, 36PR07: Klinisk fysiologi/nuklearmedicin grp. G, Diagnosis: DC848: Kutant T-celle lymfom UNS Procedure: WMACPXYXX CT WB på PET/CT

Table 12. Monitoring cost per cycle stratified in health state included in the model

Health state	Cost per cycle (DKK)	Notes
Pre-progression	76	Every other month, an oncologist consultation, a blood count and paraclinical test based on two KOLs
Post-progression	153	Once monthly, an oncologist consultation, a blood count and paraclinical test based on two KOLs

5.8.4 Adverse event costs

For the analysis, only grade 3-4 AEs were considered. The costs of AEs during the TOT were calculated separately for all treatment arms based on the number of treatment-related adverse events in the MAVORIC trial and DRG tariff of each specific AE. The DRG tariffs were estimated using Interactive DRG 2020. A cost of an AE per administration cycle has been estimated and applied at each administration for all comparators in the model. Due to the lack of complete data for the chemotherapy comparators and the targeted therapies and pathway inhibitors, the AE profile of the vorinostat arm in the MAVORIC trial has been used as a proxy for the chemotherapy and the AE profile of mogamulizumab have been used for the targeted therapies and pathway inhibitors.

The cycle probabilities of the AEs included in the model are reported in Table 13, the estimated cost per AE are reported in Table 14, and the estimated cost per administration for AE are illustrated in Table 15.

Table 13. Cycle probabilities of AEs

Adverse event	Mogamulizumab and targeted therapies	Chemotherapy
Aspartate aminotransferase increased	0,0003	0,0002
Asthenia	0,0000	0,0009
Cellulitis	0,0005	0,0009
Constipation	0,0001	0,0005
Decreased appetite	0,0003	0,0005
Diarrhoea	0,0001	0,0021
Drug eruption	0,0011	0,0000
Dysgeusia	0,0000	0,0002
Fatigue	0,0004	0,0025
Headache	0,0000	0,0002
Hypertension	0,0011	0,0027
Infusion-related reaction	0,0004	0,0000
Muscle spasms	0,0000	0,0005
Nausea	0,0001	0,0007
Peripheral oedema	0,0000	0,0002
Pneumonia	0,0010	0,0002
Pulmonary embolism	0,0000	0,0011
Pyrexia	0,0001	0,0000
Sepsis	0,0003	0,0009
Thrombocytopenia	0,0000	0,0030
Upper respiratory tract infection	0,0000	0,0005
Vomiting	0,0000	0,0002
Weight decreased	0,0001	0,0005

Table 14. Unit cost related to AE management

Adverse event	Unit cost (DKK)	Notes
Aspartate aminotransferase increased	1.748	DRG 2020, 23MA98: MDC23 1-dagsgruppe, pat. mindst 7 Year, Diagnosis: DR740: Transaminase- og laktatdehydrogenaseforhøjelse
Asthenia	4.082	DRG 2020, 23MA03: Symptomer og fund, u. kompl. bidiag., Diagnosis: DR539A: Udmattelse
Cellulitis	1.800	DRG 2020, 09MA98: MDC09 1-dagsgruppe, pat. mindst 7 Year, Diagnosis: DL039: Flegmone UNS
Constipation	5.297	DRG 2020, 06MA11: Malabsorption og betændelse i spiserør, mave og tarm, pat. mindst 18 Year, u. kompl. bidiag., Diagnosis: DK590: Forstoppelse
Decreased appetite	1.540	DRG 2020, 10MA98: MDC10 1-dagsgruppe, pat. mindst 7 Year, Diagnosis: DR630: Appetitløshed
Diarrhoea	5.297	DRG 2020, 06MA11: Malabsorption og betændelse i spiserør, mave og tarm, pat. mindst 18 Year, u. kompl. bidiag., Diagnosis: DK529B: Ikke-infektiøs diaré UNS
Drug eruption	1.800	DRG 2020, 09MA98: MDC09 1-dagsgruppe, pat. mindst 7 Year, Diagnosis: DL270: Generaliseret dermatitis forYearsaget af indtaget lægemiddel
Dysgeusia	3.375	DRG 2020, 01MA98: MDC01 1-dagsgruppe, pat. mindst 7 Year, Diagnosis: DR432: Forandret smagsoplevelse
Fatigue	4.082	DRG 2020, 23MA03: Symptomer og fund, u. kompl. bidiag., Diagnosis: DR539A: Udmattelse
Headache	4.082	DRG 2020, 23MA03: Symptomer og fund, u. kompl. bidiag., Diagnosis: DR519: Hovedpine UNS
Hypertension	1.847	DRG 2020, 05MA08: Andre hjertesygdomme, Diagnosis: DI952: Hypotension forYearsaget af lægemiddel
Infusion-related reaction	1.704	DRG 2020, 21MA98: MDC21 1-dagsgruppe, pat. mindst 7 Year, Diagnosis: DT809: Kompl kation efter infusion, transfusion eller injektion UNS
Muscle spasms	1.676	DRG 2020, 08MA15: Reumatologiske sygdomme i bløddele, Diagnosis: DM626: Muskelspændinger
Nausea	5.297	DRG 2020, 06MA11: Malabsorption og betændelse i spiserør, mave og tarm, pat. mindst 18 Year, u. kompl. bidiag., Diagnosis: DR119C: Opkastning
Peripheral oedema	4.082	DRG 2020, 23MA03: Symptomer og fund, u. kompl. bidiag., Diagnosis: DR609: Ødem UNS
Pneumonia	37.050	DRG 2020, 04MA13: Lungebetændelse og pleurit, pat. mindst 60 Year, Diagnosis: DJ189: Pneumoni UNS
Pulmonary embolism	31.882	DRG 2020, 04MA04: Lungeemboli, Diagnosis: DI269A: Lungeemboli UNS
Pyrexia	10.990	DRG 2020, 18MA98: MDC18 1-dagsgruppe, pat. Mindst 7 Year. & 18MA04: Feber af ukendt Yearsag, pat. mindst 18 Year, uden biopsi og/eller scopi, Diagnosis: DR509: Feber UNS
Sepsis	43.180	DRG 2020, 18MA01: Sepsis, Diagnosis: DA419: Sepsis UNS
Thrombocytopenia	20.376	DRG 2020, 16MA98: MDC16 1-dagsgruppe, pat. Mindst 7 Year. & 16MA03: Granulo- og trombocytopeni, Diagnosis: DD696: Trombocytopeni UNS
Upper respiratory tract infection	15.484	DRG 2020, 03MA05: Mellemørebetændelse og øvre luftvejsinfektion, pat. mindst 18 Year, u. kompl. bidiag., Diagnosis: DJ069: Akut øvre luftsvejsinfektion UNS
Vomiting	5.297	DRG 2020, 06MA11: Malabsorption og betændelse i spiserør, mave og tarm, pat. mindst 18 Year, u. kompl. bidiag., Diagnosis: DR119C: Opkastning
Weight decreased	1.540	DRG 2020, 10MA98: MDC10 1-dagsgruppe, pat. mindst 7 Year, Diagnosis: DR634: Abnormt vægttab

Table 15. Cost related to AE management per cycle on treatment

Treatment	Cost per therapy cycle (DKK)
Mogamulizumab	59
Methotrexate	196
Doxorubicin	196
Gemcitabine	196
Brentuximab vedotin	59
Alemtuzumab	59
Pembrolizumab	59
Romidepsin	59

5.8.5 Patient and transportation cost

Patient costs are included in the model in line as per the DMC's method guidelines. The unit cost per hour is assumed to be DKK 179,00 in line with the DMC guidelines[25]. Due to lack of direct data, time usage for the administration has been based on Amgros' "Udvidet sammenligningsgrundlag - Adjuverende behandling af modermærkekræft", where Pembrolizumab treatment was included every 3rd week[26]. The time usage has been assumed for all IV drug administrations. Time usage for disease monitoring has been assumed based on the resource use of disease monitoring.

Table 16. Patient cost per drug administration

Resource	Time usage	Reference
IV administration	120 min	Amgros' "Udvidet sammenligningsgrundlag - Adjuverende behandling af modermærkekræft", Pembrolizumab every 3rd week, time usage associated with administration
Time usage per administration	**2 hour(s)**	
Patient cost per administration	**DKK 358**	

Table 17. Monthly patient cost associated with monitoring

Resource	Proportion of patients	Monthly frequency	Time usage	Reference
Oncologist	100%	1 x	20 min	Assumed to be 20 mins long
Blood count	100%	1 x	20 min	Assumed to be 20 mins including waiting time
Paraclinical test	100%	1 x	20 min	Assumed to be 20 mins including waiting time
Monthly time usage			**1 hour(s)**	
Monthly patient cost of monitoring			**DKK 179**	

Transportation costs are included in the model. An average rate of DKK 3,52 per km is assumed with an average distance of 28 km per hospital visit in line with DMC's methods guidelines[25]. In the model, the transportation cost is applied at each occurrence of an activity, drug administration or disease monitoring. Transportation costs for drug administration and disease monitoring are reported in Table 18.

Table 18 Transportation costs per health state

Activity	Cost per activity (DKK)
Drug administration	98,56
Disease monitoring	98,56

5.8.6 Subsequent treatment costs

Due to the nature of MF and SS, patients are continuously treated to reduce the skin symptoms until they die. Two KOLs (a dermatologist and an oncologist, both experts within CTCL[12,15]) were consulted, and both confirmed that the treatment of MF and SS patients will be continued until the patients die to reduce the burden of the symptoms as much as possible[12,15].

It is essential to capture current Danish clinical practice, and also ensure that the cost reflects the efficacy estimated within the model. As such when modelling both the chemotherapy and targeted treatment arms, the subsequent treatments applied must match those expected in clinical practice, this will not only ensure that the correct treatments (and therefore cost) are applied, but also that this equates to the efficacy applied.

Clinical practice for these patients is known for the first two lines in Denmark[7]. However, the treatment lines following chemotherapy and targeted treatment have not been documented and therefore we have consulted two KOLs, who are specialists in CTCL[12,15].

The two KOLs, stated that chemotherapy would be succeeded by a targeted treatment if it has not been used previously. Therefore to capture Danish clinical practice, all patients are assumed to receive a targeted treatment as the subsequent treatment following chemotherapy (Table 19).

For the targeted treatment arms, e.g. mogamulizumab or the targeted treatment basket arm, the KOLs suggested a proportion of patients may be eligible for a subsequent targeted therapy, depending on their prior treatment and the results of a flow cytometry following the initial targeted therapy. The oncologist stated that approx. 1/3 would be eligible for targeted therapy, while the remaining patients would be treated with alternative treatments (e.g. chemotherapy). The dermatologist mentioned chemotherapy would be used following the targeted options. A total allocation of patients to chemotherapy in the following line could potentially underestimate the cost of the subsequent treatments for the targeted treatment arm. Therefore to be conservative, we assume 1/3 of the cohort will receive a targeted therapy as the subsequent treatment, as this was the upper-bound of the two KOL statements (Table 19). Therefore, this assumes the remaining 2/3 of the cohort receive chemotherapy as the subsequent treatment following targeted therapy.

Table 19. Distribution of patient on subsequent treatment regimens stratified on the model arms

Subsequent treatment regimen	Share of patients receiving subsequent treatment		
	Mogamulizumab	Targeted basket	Chemotherapy basket
Methotrexat	22,2%	22,2%	0,0%
Doxorubicin	22,2%	22,2%	0,0%
Gemcitabin	22,2%	22,2%	0,0%
Brentuximab vedotin	11,1%	11,1%	33,3%
Alemtuzumab	11,1%	11,1%	33,3%
Pembrolizumab	11,1%	11,1%	33,3%
Romidepsin	0,0%	0,0%	0,0%

Subsequent treatment costs have been included in the model as a one-off cost given the PartSA only allows simple estimation of subsequent health states (PartSAs do not allow calculations of transitions of subsequent treatment health states as in a Markov model). Subsequent costs include: drug acquisition cost, administration cost, patient cost, and transportation cost.

The subsequent treatment regimens applied align with those outlined in the DMC protocol (Table 19), as this reflects Danish clinical practice. In an ideal world, the TOT for each of the subsequent treatments would be modelled directly from TOT KM data for each subsequent treatment. However, no TOT data are available for each subsequent treatment and therefore an alternative approach has been taken.

To enable calculation of the subsequent chemotherapy cost, the TOT for the chemotherapies have been based on the median TTNT of the vorinostat arm in the MAVORIC trial, i.e. 118,9 days[19].We assume TTNT to be a proxy for TOT for chemotherapy, given that the TTNT endpoint reflects the time to initiation of the subsequent treatment. We acknowledge that the TTNT could potentially include a small treatment gap. However, the median TTNT of the vorinostat arm is shorter than the median TOT of doxorubicin in the EORTC 21012 trial, 20 weeks (140 days)[22], and it is reasonable to assume that the TOT would be shorter with chemotherapy compared to vorinostat. Additionally, as a longer TOT would result in higher cost for the subsequent treatment with chemotherapy, this is a conservative assumption.

In the MAVORIC trial, the majority of patients crossed over to receive mogamulizumab (72,6%), and as such the TTNT of these patients is assumed to be a proxy of the TOT of those that receive subsequent targeted therapy (TTNT, following vorinostat in the MAVORIC trial was 195,6 days [19]). For alemtuzumab regimen, a TOT of 12 weeks was applied as stated in the DMC protocol.

The drug acquisition cost, administration cost and patient and transportation cost are estimated using the same methods as described in section 5.8.1, 5.8.2, and 5.8.5. The estimated total drug acquisition cost, administration cost and patient and transportation cost of the subsequent treatments are based on the distributions reported in Table 19 and are reported in Table 20.

Table 20. Stratified cost of subsequent treatment

Resource	Mogamulizumab (DKK)	Targeted basket (DKK)	Chemotherapy basket (DKK)
Drug acquisition cost	[redacted]	[redacted]	[redacted]
Administration cost	[redacted]	[redacted]	[redacted]
Patient and transportation cost	[redacted]	[redacted]	[redacted]

5.9 Sensitivity and scenario analyses

5.9.1 Scenario analysis

Scenario analyses were undertaken to assess the impact of varying structural and methodological assumptions implemented in the model. Table 21 report the scenarios tested in the scenario analysis.

Table 21. Scenario assessed in the scenario analysis

Nummer	Scenarios	*Rationale*
1	Time Horizon - 10 years	*To test impact of shorter time horizon*
2	Time Horizon - 20 years	*To test impact of shorter time horizon*
3	Dosing calculation - cost per mg	*To test impact of cost per mg instead of dose banding*

Nummer	Scenarios	*Rationale*
4	[redacted]	*To test impact of different parametric distribution*
5	[redacted]	*To test impact of different parametric distribution*
6	[redacted]	*To test impact of different parametric distribution*
7	[redacted]	*To test impact of different parametric distribution*
8	[redacted]	*To test impact of different parametric distribution*
9	[redacted]	*To test impact of different parametric distribution*
10	[redacted]	*To test impact of different parametric distribution*
11	[redacted]	*To test impact of different parametric distribution*
12	[redacted]	*To test impact of different parametric distribution*
13	[redacted]	*To test impact of different parametric distribution*
14	[redacted]	*To test impact of different parametric distribution*
15	[redacted]	*To test impact of different parametric distribution*
16	[redacted]	*To test impact of different parametric distribution*
17	[redacted]	*To test impact of different parametric distribution*
18	[redacted]	*To test impact of different parametric distribution*
19	[redacted]	*To test impact of different parametric distribution*
20	[redacted]	*To test impact of different parametric distribution*
21	[redacted]	*To test impact of different parametric distribution*
22	[redacted]	*To test impact of different parametric distribution*
23	[redacted]	*To test impact of different parametric distribution*
24	[redacted]	*To test impact of different parametric distribution*
25	Time on treatment - Chemotherapy - 4 weeks treatment	*To test impact of lower end of the range for the TOT for chemotherapy*
26	Time on treatment - Chemotherapy - 40 weeks treatment	*To test impact of longer TOT for chemotherapy, despite it being longer than label*
27	Chemotherapy result - Inclusion of monitoring cost for Mogamulizumab	*To test the impact of including all monitoring cost for the mogamulizumab arm from PartSA model and estimating monitoring cost and associated patient cost and transportation cost during pre-progression for chemotherapy based on the time-to-progression data (7,4 months) presented in EORTC 21012* [22].
28	Chemotherapy - Exclusion of cost associated with adverse events	*To test the impact of excluding the cost associated with adverse events in the comparison between mogamulizumab and chemotherapy.*

5.10 Base case settings

Element	Base-case	*Rationale*
Population	ITT Population	*Consistent with population in DMC protocol* [7]
Perspective	Restricted societal perspective	As per DMC guidelines[23]
Discount rate (per annum)	4%	As per DMC guidelines[23]
Time horizon	30 years	Sufficiently long to capture all relevant cost and effects
Comparator(s)	Targeted therapy basket & Chemotherapy	*Consistent with population in DMC protocol* [7]
Wastage	Wastage assumed	*To reflect the clinical practice with IV treatments*
Dosing option for Mogamulizumab	Dose banding	*To reflect the dosing in the MAVORIC trial*
Progression-free survival (PFS)		
PFS Mogamulizumab & targeted therapy basket - option	[redacted]	[redacted]
Overall Survival (OS)		
OS Mogamulizumab & targeted therapy basket - option	[redacted]	[redacted]
Time on treatment (TOT)		
TOT Mogamulizumab & targeted therapy basket - option	[redacted]	[redacted]
Time to next treatment (TTNT)		
TTNT Mogamulizumab & targeted therapy basket - option	[redacted]	[redacted]

6 Results

6.1 Base case vs. targeted therapy

In the base-case, the cost per patient analysis results in a cost of [redacted] per patient for the mogamulizumab arm and [redacted] per patient for the targeted therapy basket.

6.2 Incremental cost per patient

The cost analysis results in an average incremental cost per patient of [redacted] for mogamulizumab compared to the targeted therapy basket arm. The pairwise comparison results between mogamulizumab and targeted therapy basket are presented in Table 22.

Table 22. Incremental cost per patient, pairwise comparison: Mogamulizumab vs. Targeted therapy basket

	Mogamulizumab (DKK)	Targeted therapy basket (DKK)	Incremental cost (DKK)
Drug cost	[redacted]	[redacted]	[redacted]
Administration cost	[redacted]	[redacted]	[redacted]
Monitoring cost	[redacted]	[redacted]	[redacted]
Subsequent treatment cost	[redacted]	[redacted]	[redacted]
Adverse event cost	[redacted]	[redacted]	[redacted]
Patient and transportation cost	[redacted]	[redacted]	[redacted]
Total cost	[redacted]	[redacted]	[redacted]

6.3 Base case vs. chemotherapy

In the base-case vs. chemotherapy, only drug cost was considered. This analysis results in a cost of [redacted] per patient for the mogamulizumab arm and [redacted] in the chemotherapy basket arm.

6.4 Incremental cost per patient

The cost analysis results in an average incremental cost per patient of [redacted] for mogamulizumab compared to the chemotherapy arm. The pairwise comparison results between mogamulizumab and chemotherapy basket are presented in Table 23.

Table 23. Incremental cost per patient, pairwise comparison: Mogamulizumab vs. Chemotherapy basket

	Mogamulizumab (DKK)	Chemotherapy basket (DKK)	Incremental cost (DKK)
Drug cost	[redacted]	[redacted]	[redacted]
Administration cost	[redacted]	[redacted]	[redacted]
Subsequent treatment cost	[redacted]	[redacted]	[redacted]
Adverse event cost	[redacted]	[redacted]	[redacted]
Patient and transportation cost	[redacted]	[redacted]	[redacted]
Total cost	[redacted]	[redacted]	[redacted]

6.5 Scenario analyses

The results of the scenario analyses are reported in Table 24. The analysis indicated log-logistic and log-normal as distributions for the TOT extrapolations would result in the highest incremental cost, both vs. the chemotherapy basket and the targeted therapy basket. This is likely due to the long tail of these distributions, thereby increasing the area under the curve. The lowest incremental cost vs. chemotherapy and vs. the targeted therapy basket was observed using the 'cost per mg'-dosing calculation. Changes in TOT for the chemotherapy arm, did not affect the incremental results of mogamulizumab vs. chemotherapy significantly.

Table 24. Results of the scenario analyses

Scenarios	Chemo basket Incremental cost (DKK)	Targeted basket Incremental cost (DKK)
Base-case	[redacted]	[redacted]
Time Horizon - 10 years	[redacted]	[redacted]
Time Horizon - 20 years	[redacted]	[redacted]
Dosing calculation - cost per mg	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Time on treatment - Chemotherapy - 4 weeks treatment	[redacted]	[redacted]

Scenarios	Chemo basket Incremental cost (DKK)	Targeted basket Incremental cost (DKK)
Time on treatment - Chemotherapy - 40 weeks treatment	[redacted]	[redacted]
Chemotherapy result - Inclusion of monitoring cost	[redacted]	[redacted]
Chemotherapy - Exclusion of cost associated with adverse events	[redacted]	[redacted]

7 Budget impact analysis

7.1 Methods

The budget impact model was developed to estimate the expected budget impact of recommending mogamulizumab as a possible standard treatment in Denmark over the chemotherapy basket and the targeted therapy basket. The budget impact was estimated per year for the first 5 years after the introduction of mogamulizumab in Denmark.

The cost per patient model was partially nested within the budget impact model, and therefore any changes in the settings of the cost per patient model would affect the results of the budget impact model. The budget impact result is representative of the population in the cost per patient models.

The analysis was developed by comparing the costs for the Danish regions per year over five years in the scenario where mogamulizumab is recommended as a possible standard treatment and the scenario where mogamulizumab is not recommended as possible standard treatment. The total budget impact per year is the difference between the two scenarios in the analysis.

7.1.1 Number of patients eligible for Mogamulizumab treatment

The Danish Medicine Council expert committee estimates a prevalence of 15 patients and a yearly incidence of approx. 5 new patients, who would be eligible for mogamulizumab treatment.

Table 25. Patient count over time

	Year 1	Year 2	Year 3	Year 4	Year 5
Patient count	15 pts	5 pts	5 pts	5 pts	5 pts

7.1.2 Market Share

This comparison without a recommendation of mogamulizumab, it is assumed the chemotherapy basket and the targeted therapy basket have 50% market share each. In the scenario, where mogamulizumab is recommended, a slow market uptake is assumed with mogamulizumab.

Table 26. Market share for budget impact model

	Without recommendation of Mogamulizumab					With recommendation of Mogamulizumab				
Treatment	Year 1	Year 2	Year 3	Year 4	Year 5	Year 1	Year 2	Year 3	Year 4	Year 5
Moga	0%	0%	0%	0%	0%	40%	55%	70%	85%	100%
Chemo	50%	50%	50%	50%	50%	30%	23%	15%	8%	0%
Targeted	50%	50%	50%	50%	50%	30%	23%	15%	8%	0%

7.1.3 Scenario analysis

An alternative scenario were tested to assess the result of a high market uptake. The market shares for this scenario are presented in Table 27.

Table 27. Market share for high uptake scenario

	Without recommendation of Mogamulizumab					With recommendation of Mogamulizumab				
Treatment	Year 1	Year 2	Year 3	Year 4	Year 5	Year 1	Year 2	Year 3	Year 4	Year 5
Moga	0%	0%	0%	0%	0%	100%	100%	100%	100%	100%
Chemo	50%	50%	50%	50%	50%	0%	0%	0%	0%	0%
Targeted	50%	50%	50%	50%	50%	0%	0%	0%	0%	0%

7.2 Results

The estimated budget impact for recommending mogamulizumab as standard treatment [redacted] in year 5. The negative budget impact in year 1 to 4 is observed primarily due to all the high drug costs of the Alemtuzumab regimen, where all administration occur within the first 12 weeks of treatment initiation, and therefore acrrue a high cost within the first year.

Table 28. Results: Estimated budget impact per year

	Year 1	Year 2	Year 3	Year 4	Year 5
Not recommendation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Recommended	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total budget impact	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

7.3 Scenario analysis

For the high uptake scenario, the budget impact of recommending mogamulizumab as standard treatment is [redacted] in year 5, as shown in Table 29.

Table 29. Results: Estimated budget impact per year, high uptake scenario

	Year 1	Year 2	Year 3	Year 4	Year 5
Not recommendation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Recommended	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total budget impact	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

8 Discussion

The analysis of the model estimated that treatment of MF and SS patient with mogamulizumab resulted in an incremental cost of [redacted] versus the targeted therapy basket and an incremental cost of [redacted] versus the chemotherapy. In the base case, the cost of mogamulizumab arm and the targeted therapy arm is primarily driven by the drug acquisition costs, due to the higher drug costs and the longer TOT.

For both the targeted treatment- and the chemotherapy arm conservative approaches were chosen. The approach is in line with the KOL expert testimonies and the impact around the different variables was assessed in the scenario analysis. Therefore, we consider this cost analysis is in line with the focus and population relevant for the clinical questions too.

The budget impact was low, which is a result of the very few patients and the limited incremental costs. Due to the limited data for the included comparators there is a high degree of uncertainty around the results.

The budget impact model is imbedded within the cost per patient models. In the chemotherapy arm, only drug costs have been included and therefore the budget impact of recommending mogamulizumab could be potentially overestimated. This is due to monitoring cost being included for the other arms, while no monitoring cost has been included for the chemotherapy arm in the budget impact, which results in a higher overall budget impact for the recommendation of mogamulizumab.

9 Reference list

1. Mayo Clinic. Cutaneous T-cell lymphoma - Symptoms and causes [Internet]. [cited 2020 Jul 13]. Available from: https://www.mayoclinic.org/diseases-conditions/cutaneous-t-cell-lymphoma/symptomscauses/%0Asyc-20351056

2. Trautinger F, Eder J, Assaf C, Bagot M, Cozzio A, Dummer R, et al. European Organisation for Research and Treatment of Cancer consensus recommendations for the treatment of mycosis fungoides/Sézary syndrome – Update 2017 [Internet]. Eur. J. Cancer. Elsevier Ltd; 2017 [cited 2020 Aug 4]. p. 57–74. Available from: http://creativecommons.org/licenses/by-nc-nd/4.0/

3. J Scarisbrick J, L Haun P. Fast Facts Fast Facts : Diagnosing Cutaneous T-Cell Lymphoma | Semantic Scholar [Internet]. [cited 2020 Aug 13]. Available from: https://www.semanticscholar.org/paper/Fast-Facts-Fast-Facts-%3A-Diagnosing-Cutaneous-T-Cell-Haun-Scarisbrick/dae6d3bdbbca783cd2236b93006588e5636ea976

4. Wilcox RA. Cutaneous T-cell lymphoma: 2017 update on diagnosis, risk-stratification, and management. Am J Hematol. Wiley-Liss Inc.; 2017;92:1085–102.

5. Bagherani N, Smoller BR. An overview of cutaneous T cell lymphomas [version 1; referees: 2 approved] [Internet]. F1000Research. Faculty of 1000 Ltd; 2016 [cited 2020 Aug 13]. p. 1882. Available from: https://doi.org/10.12688/f1000research.8829.1

6. PDQ Adult Treatment Editorial Board. Mycosis Fungoides (Including Sézary Syndrome) Treatment (PDQ®): Health Professional Version [Internet]. PDQ Cancer Inf. Summ. National Cancer Institute (US); 2002 [cited 2020 Aug 13]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26389288

7. Medicinrådet. Medicinrådets protokol for vurdering af mogamulizumab til behandling af voksne med mycosis fungoides eller Sézarys syndrom , der har fået mindst to tidligere systemiske behandlinger. 2020;0–17.

8. Agar NS, Wedgeworth E, Crichton S, Mitchell TJ, Cox M, Ferreira S, et al. Survival outcomes and prognostic factors in mycosis fungoides/Sézary syndrome: Validation of the revised International Society for Cutaneous Lymphomas/European Organisation for Research and Treatment of Cancer staging proposal. J Clin Oncol [Internet]. J Clin Oncol; 2010 [cited 2020 Aug 13];28:4730–9. Available from: https://pubmed.ncbi.nlm.nih.gov/20855822/

9. Beynon T, Selman L, Radcliffe E, Whittaker S, Child F, Orlowska D, et al. 'We had to change to single beds because I itch in the night': a qualitative study of the experiences, attitudes and approaches to coping of patients with cutaneous T-cell lymphoma. Br J Dermatol [Internet]. Blackwell Publishing Ltd; 2015 [cited 2020 Aug 13];173:83–92. Available from: http://doi.wiley.com/10.1111/bjd.13732

10. Williams K, Gibson A, McNamara L, Jones T, Lloyd AJ. Health state utilities associated with caring for an individual with cutaneous T-cell lymphoma (CTCL). J Med Econ [Internet]. Taylor and Francis Ltd; 2020 [cited 2020 Sep 3]; Available from: https://pubmed.ncbi.nlm.nih.gov/32644862/

11. Demierre MF, Gan S, Jones J, Miller DR. Significant impact of cutaneous T-cell lymphoma on patients' quality of life: Results of a 2005 National Cutaneous Lymphoma Foundation Survey. Cancer [Internet]. John Wiley & Sons, Ltd; 2006 [cited 2020 Aug 13];107:2504–11. Available from: https://acsjournals.onlinelibrary.wiley.com/doi/full/10.1002/cncr.22252

12. Kyowa Kirin. KOL interview - Lena Specht. 2020.

13. Kempf W, Pfaltz K, Vermeer MH, Cozzio A, Ortiz-Romero PL, Bagot M, et al. EORTC, ISCL, and USCLC consensus recommendations for the treatment of primary cutaneous CD30-positive lymphoproliferative disorders: Lymphomatoid papulosis and primary cutaneous anaplastic large-cell lymphoma. Blood [Internet]. Blood; 2011 [cited 2020 Aug 4]. p. 4024–35. Available from: https://pubmed.ncbi.nlm.nih.gov/21841159/

14. Willemze R, Hodak E, Zinzani PL, Specht L, Ladetto M. Primary cutaneous lymphomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol [Internet]. Elsevier Masson SAS; 2018;29:iv30–40. Available from: https://doi.org/10.1093/annonc/mdy133

15. Kyowa Kirin. KOL interview - Lars Iversen. 2020.

16. Prince HM, Kim YH, Horwitz SM, Dummer R, Scarisbrick J, Quaglino P, et al. Brentuximab vedotin or physician's choice in CD30-positive cutaneous T-cell lymphoma (ALCANZA): an international, open-label, randomised, phase 3, multicentre trial. Lancet [Internet]. 2017;390:555–66. Available from: NS -

17. Kyowa Kirin. Summary of Product Characteristics. Poteligeo® (Mogamulizumab). 2019.

18. Kim YH, Bagot M, Pinter-Brown L, Rook AH, Porcu P, Horwitz SM, et al. Mogamulizumab versus vorinostat in previously treated cutaneous T-cell lymphoma (MAVORIC): an international, open-label, randomised, controlled phase 3 trial. Lancet Oncol [Internet]. 2018;19:1192–204. Available from: NS -

19. Kyowa Kirin. MAVORIC CSR [Data on file]. 2017.

20. Dummer R, Quaglino P, Becker JC, Hasan B, Karrasch M, Whittaker S, et al. Prospective international multicenter phase II trial of intravenous pegylated liposomal doxorubicin monochemotherapy in patients with stage IIB, IVA, or IVB advanced mycosis fungoides: final results from EORTC 21012. J Clin Oncol [Internet]. 2012;30:4091–7. Available from: NS -

21. Guyot P, Ades AE, Ouwens MJNM, Welton NJ. Enhanced secondary analysis of survival data: Reconstructing the data from published Kaplan-Meier survival curves. BMC Med Res Methodol [Internet]. BioMed Central Ltd.; 2012 [cited 2020 Oct 15];12:9. Available from: https://bmcmedresmethodol.biomedcentral.com/articles/10.1186/1471-2288-12-9

22. Dummer R, Quaglino P, Becker JC, Hasan B, Karrasch M, Whittaker S, et al. Prospective international multicenter phase II trial of intravenous pegylated liposomal doxorubicin monochemotherapy in patients with stage IIB, IVA, or IVB advanced mycosis fungoides: final results from EORTC 21012. J Clin Oncol [Internet]. 2012;30:4091–7. Available from: NS -

23. Medicinrådet. Metodevejledning for omkostningsanalyser af nye laegemidler og indikationer i hospitalssektoren.

24. Finansministeriet. Den samfundsøkonomiske diskonteringsrente. 2018.

25. Medicinrådet. Værdisætning af enhedsomkostninger. 2020;1–16. Available from: https://medicinraadet.dk/media/12930/vaerdisaetning-af-enhedsomkostninger-vers-13.pdf

26. Amgros. Udvidet sammenligningsgrundlag - Adjuverende behandling af modermærkekræft. 2020.

Appendix A. Parametric fits, long-term extrapolations

Figure 10. Long-term extrapolation of PFS

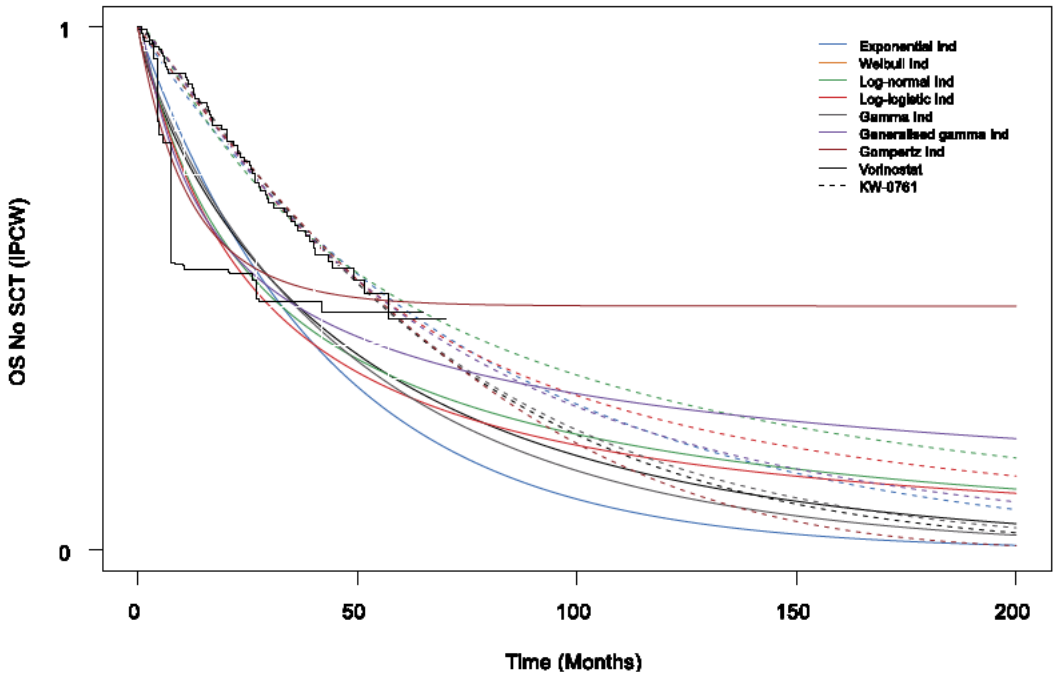


Figure 11. Long-term extrapolation of the OS

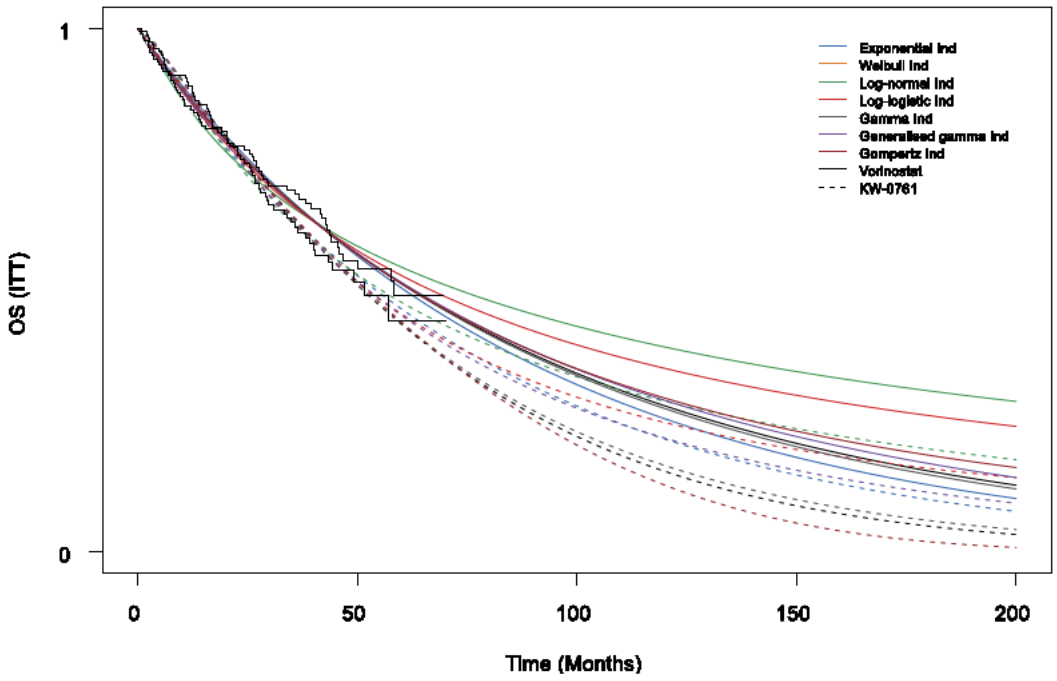
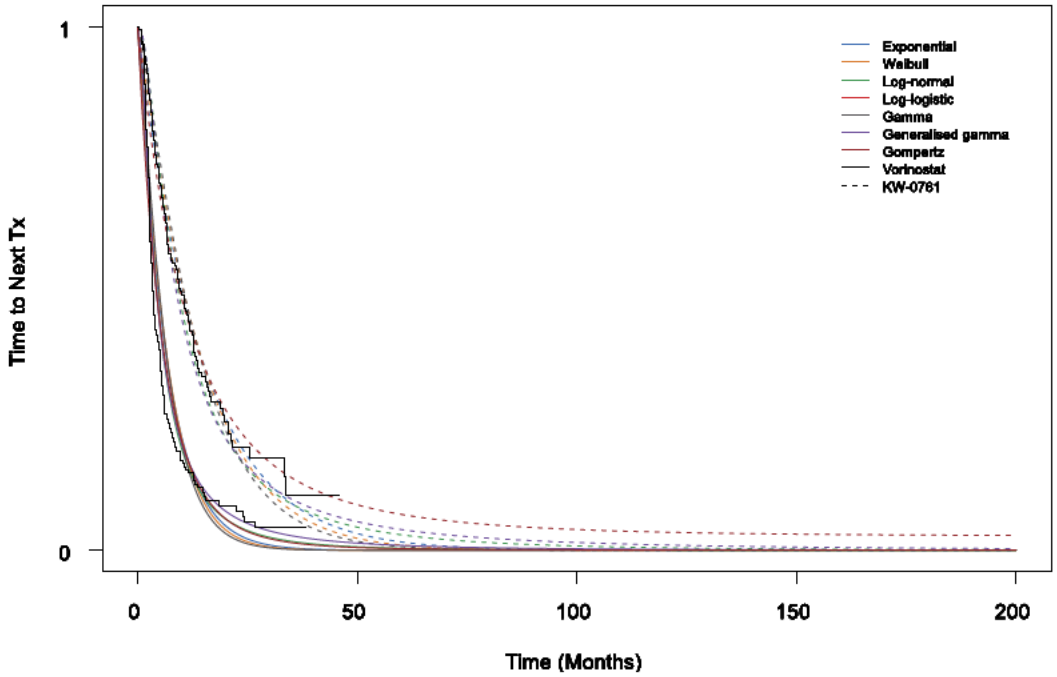


Figure 12. Long-term extrapolation of TTNT

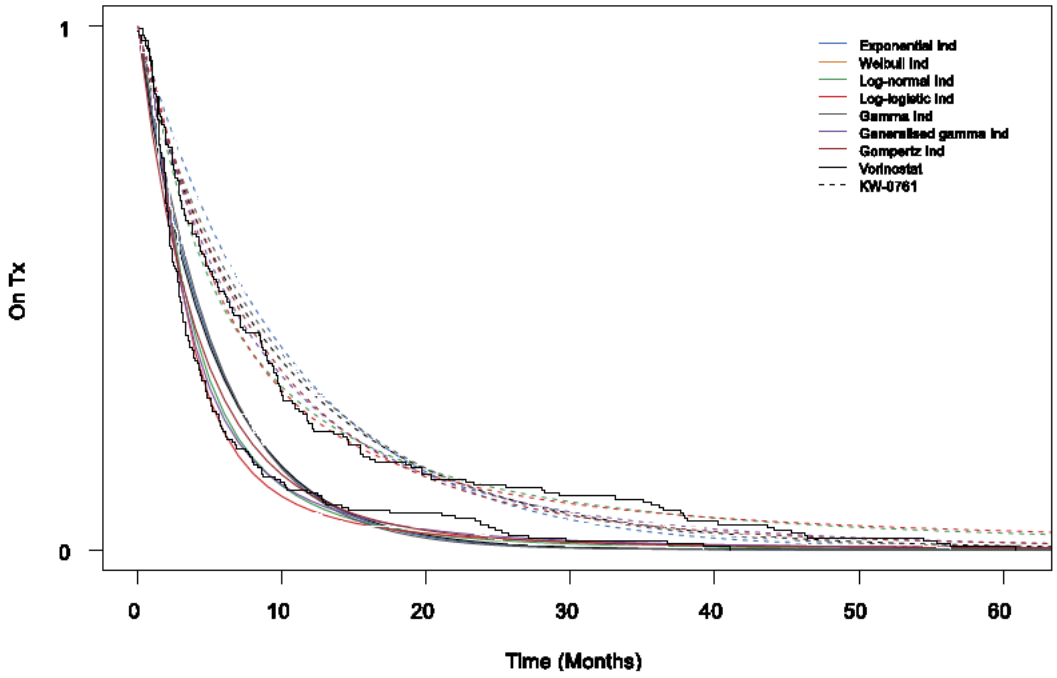


9.1 Time on treatment parametric curves

Table 30. AIC and BIC statistics for the fitted parametric on time on treatment for the mogamulizumab from the MAVORIC trial

	Mogamulizumab	
	AIC	BIC
Exponential	1248,1	1251,3
Generalised Gamma	**1239,5**	1249,2
Gompertz	1242,1	1248,5
Log-logistic	1243,3	1249,8
Log-normal	1248,5	1255,0
Weibull	1243,8	1250,3

Figure 13. Parametric curve extrapolation of TOT for the mogamulizumab and vorinoistat arm from the MAVORIC trial



Medicinrådet

Medicinrådets protokol for vurdering af mogamulizumab til behandling af voksne med mycosis fungoides eller Sézarys syndrom, der har fået mindst to tidligere systemiske behandlinger

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 den 15. juli 2020
Dokumentnummer 79528
Versionsnummer 1.0

Medicinrådet, Dampfærgevej 27-29, 3. th., 2100 København Ø
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1 Begreber og forkortelser

CCR4	C-C kemokinreceptor type 4
CI	Konfidensinterval
ECP	Ekstrakorporal fotoferese
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*)
HDAC	Histondeacetylase
HR	*Hazard ratio*
ITT	*Intention to treat*
KTCL	Kutant T-cellelymfom
MF	Mycosis fungoides
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
SMD	*Standardized Mean Difference*
SS	Sézarys syndrom

2 Introduktion

Protokollen er udarbejdet, fordi Medicinrådet har modtaget en foreløbig ansøgning fra Kyowa Kirin Holdings B.V., som ønsker, at Medicinrådet vurderer mogamulizumab til behandling af voksne patienter med mycosis fungoides (MF) eller Sézarys syndrom (SS), der har fået mindst én tidligere systemisk behandling. Medicinrådet modtog den foreløbige ansøgning den 10. februar 2020.

2.1 Mycosis fungoides og Sézarys syndrom

Mycosis fungoides (MF) er den hyppigste form af alle kutane T-cellelymfomer (KTCL). KTCL er en heterogen gruppe af sjældne non-Hodgkin lymfomer, hvor MF udgør omkring 50-60 % af alle KTCL. SS er den næstmest almindelige form for KTCL og udgør ca. 3-5 % af alle KTCL[1]. MF viser sig i form af erythematøse patches, plaques og sjældnere tumorer i huden og er almindeligvis langsomt progredierende [2]. MF ses meget sjældent med blodinvolvering. SS er, sammenlignet med MF, en mere aggressiv leukæmisk variant, der primært adskiller sig fra MF ved tilstedeværelsen af høje niveauer af cirkulerende atypiske T-celler (Sézary-celler). Ved SS har patienten omfattende hud erythem og svær kløe. Patienterne er plagede af deres hudsymptomer, som har stor indflydelse på patienternes livskvalitet. For både MF og SS gælder, at forandringerne i huden og den medfølgende immunsuppression gør patienterne udsatte for infektioner, der kan udvikle sig til sepsis.

MF inddeles efter et tumor-, node-, metastases-(TNM) system i stadier fra I-IV efter International Society for Cutaneous Lymphomas/European Organisation for Research and Treatment of Cancer's reviderede kriterier [3]. Stadieinddelingen omfatter normalt blodprøver, en PET-/CT-skanning og en knoglemarvsundersøgelse. Stadierne er forklaret i tabel 1.

Tabel 1. Stadieinddeling for MF

Stadie		
IA	Stadie 1A betyder, at mindre end 10 % af huden er involveret	Lymfomet er begrænset til huden (patches eller plaque)
IB	Stadie 1B betyder, at 10 % eller mere af huden er involveret	
IIA	Stadie 2A betyder, at der er patches eller plaque på huden, og lymfeknuderne er forstørrede, men de indeholder ikke unormale lymfomceller	
IIB	Stadie 2B betyder, at der er en eller flere forhøjede tumores i huden. Lymfeknuderne er eller er ikke forstørrede, men indeholder ikke lymfomceller	
IIIA	Stadie 3A betyder, at der er få eller ingen lymfomceller i blodbanen (erythrodermisk mycosis fungoides)	80 % eller mere af huden er involveret med erythrodermi (diffus rødme, fortykkelse og eventuelt sprækker i huden), hævelse, kløe og undertiden smerte. Lymfeknuderne kan være forstørrede, men indeholder ikke lymfomceller.
IIIB	Stadie 3B betyder, at et moderat antal lymfomceller findes i blodbanen	
IV	Stadie 4A betyder, at der er talrige unormale lymfomceller i blodbanen (Sézarys syndrom), eller lymfeknuderne indeholder lymfomceller Der er lymfom i huden i form af patches, plaques og/eller erythrodermi.	
IV	Stadie 4B betyder, at lymfomet er spredt til andre organer	

Prognosen for MF er stadieafhængig. Stadie IA og IB har en god prognose (medianoverlevelse > 6 år). Omtrent 25 % af patienterne med stadie IA eller IB oplever med tiden progression til mere avancerede sygdomsstadier. Stadie IIB og III har en medianoverlevelse på 4-6 år, mens stadie IV har en

medianoverlevelse på mindre end 4 år. Sygdommen har således et meget varierende forløb med en levelængde på år til dekader. Indtræder der progressiv sygdom, f.eks. når der kan detekteres maligne celler i blodet, forringes prognosen markant. Hos patienter med SS er det sværere at inducere remissioner, og disse patienter har derfor oftest en kortere forventet overlevelse. Den mediane overlevelse for patienter med SS er ca. 3 år, og ca. 25 % er i live efter 5 år [4].

I Danmark lever ca. 400-500 patienter med behandlingskrævende KTCL (lokal såvel som systemisk behandling). Fagudvalget vurderer, at der er ca. 15 patienter, der er kandidater til mogamulizumab (prævalens), og at der vil være en incidens på ca. 5 nye patienter om året.

2.2 Mogamulizumab

Mogamulizumab er et humaniseret IgG1 kappa antistof, der selektivt binder sig til C-C kemokinreceptor type 4 (CCR4). Ved at binde til CCR4-antigener på overfladen af T-cellerne induceres en antistofafhængig cellulær cytotoksicitet.

Mogamulizumab har indikation til voksne patienter med MF eller SS, som har modtaget mindst én tidligere systemisk behandling.

Mogamulizumab blev i 2016 betegnet som *orphan drug* til følgende tilstand: Behandling af kutant T-cellelymfom.

Fagudvalget vurderer, at mogamulizumab vil være et relevant behandlingsalternativ til patienter med fremskreden sygdom (MF, stadie II-IV og SS), der i dansk klinisk praksis har været i behandling med mindst to systemiske behandlinger (f.eks. methotrexat, retinoider og interferon-α) eller har kontraindikation for et eller flere af disse systemiske behandlinger. Mogamulizumab bør derfor anvendes på linje med de targeterede behandlinger og pathway inhibitors, som er beskrevet i afsnit 2.3.

Den anbefalede dosis for mogamulizumab er 1 mg/kg som intravenøs infusion over mindst 60 minutter. Administrationen er ugentligt på dag 1, 8, 15 og 22 i den første 28-dages cyklus, efterfulgt af infusioner hver anden uge på dag 1 og 15 i hver af de efterfølgende 28-dages cykler. Behandlingen fortsættes indtil sygdomsprogression eller uacceptabel toksicitet.

2.3 Nuværende behandling

Behandlingen af kutant T-cellelymfom i Danmark varetages af de dermatologiske afdelinger i samarbejde med hæmatologiske og onkologiske afdelinger. Behandlingen følger internationale guidelines fra ESMO og EORTC [5,6]. Der er ingen defineret standardbehandling, da behandlingen individualiseres ud fra det kutane lymfoms karakteristika, sygdommens sværhedsgrad, patientens performancestatus, komorbiditeter, tidligere behandlinger, patientens præferencer mv.

Målet med behandlingen er sygdomskontrol og symptomlindring, idet behandlingen, fraset allogen stamcelletransplantation, ikke er kurativ. Først forsøges tumorbyrden nedbragt, hvorefter sygdommen kontrolleres og følges. Den palliative strategi går således ud på at lindre symptomer, forbedre livskvalitet, inducere remissioner, udskyde progression og undgå betydelig behandlingsrelateret toksicitet. Behandlingsforløbene er oftest af længere varighed (år).

I tidlige stadier af MF (IA-IIA) anvendes topikal behandling i form af f.eks. kortikosteroider i kombination med ultraviolet lysbehandling (smalspektret UVB eller 8-Methoxypsoralen + UV-A (PUVA)) eller mustargenpenslinger (kvælstof-sennepsgas).

I senere, mere fremskredne stadier (IIB-IV) af MF anvendes lavdosis elektronvolts helkropsbestråling, lokal strålebehandling mod tumor eller systemisk medicinsk behandling i form af interferon-α, retinoider (f.eks.

Acitretin og Bexaroten) eller lavdosis methotrexat. Til udvalgte patienter kan anvendes knoglemarvstransplantation, som gives med kurativ intention. De forskellige former for systemisk behandling kombineres ofte og anvendes ofte også i kombination med topikale behandlinger og/eller ultraviolet lysbehandling. Behandlingen, der følger efter de første systemiske behandlinger (interferon-α, retinoider, lavdosis methotrexat) planlægges ved multidisciplinær konference med hæmatologisk afdeling, og der anvendes targeterede behandlinger, pathway inhibitors eller kemoterapi (f.eks. højdosis methotrexat, gemcitabin eller doxorubicin).

De targeterede behandlinger omfatter brentuximab vedotin (anti CD30), og alemtuzumab (anti CD52). og pembrolizumab (PD-1 hæmmer). Pathway inhibitors omfatter histon deacetylase (HDAC)-hæmmeren romidepsin. Disse lægemidler betragtes af fagudvalget som ligeværdige behandlingsalternativer. Behandlingsvalget er individualiseret og guides af patientens markørudtryk. Ingen af de targeterede behandlinger/pathway-hæmmere kan betragtes som standardbehandlinger i Danmark, og kun brentuximab vedotin har indikation til behandling af KTCL, herunder MF/SS. Behandlingen med disse alternativer er derfor afhængig af individuelle ansøgninger til lægemiddelkomitéerne. EMA har tidligere afvist at give markedsføringstilladelse til romidepsin til denne indikation. Behandling med pembrolizumab, alemtuzumab og romidepsin er derfor uden for godkendt indikation (off-label).

I dermatologien anvendes off-label-behandling i ganske stort omfang pga. manglende evidens for behandling til givne hudsygdomme.

SS betragtes per definition som en systemisk sygdom og kræver derfor systemisk behandling. Ekstrakorporal fotoferese (ECP), enten alene eller i kombination med f.eks. interferon-α og/eller retinoider, elektronvolts helkropsbestråling og PUVA er foreslået som initiale behandlingsvalg til SS. Som andenlinjebehandling anvendes targeterede behandlinger/pathway-hæmmere som beskrevet ovenfor og sjældnere allogen stamcelletransplantation.

Ofte anvendes systemiske behandlinger i kombination med lokalbehandling med f.eks. PUVA eller potente topikale steroider som supplerende behandling.

3 Kliniske spørgsmål

Medicinrådet bruger kliniske spørgsmål til vores vurderinger af lægemidlers værdi for patienterne. Til hvert spørgsmål knytter sig en definition af patientgruppen (population), af det lægemiddel vi undersøger (interventionen), af den behandling vi sammenligner med (komparator(er)) og af effektmålene.

Fagudvalget mener, at mogamulizumab i dansk klinisk praksis bør anvendes efter mindst to tidligere systemiske behandlinger (f.eks. methotrexat, interferon-α, retinoider og ECP (kun ved SS)), som er veltolererede, effektive og omkostningseffektive behandlinger, og som ligger før de targeterede behandlinger i behandlingsforløbet. Derfor formulerer fagudvalget det kliniske spørgsmål i henhold til denne population i stedet for til populationen svarende til indikationen (mindst én tidligere systemisk behandling).

3.1 Klinisk spørgsmål 1

Hvilken værdi har mogamulizumab sammenlignet med nuværende behandling for patienter med mycosis fungoides eller Sézarys syndrom, der har fået mindst to tidligere systemiske behandlinger?

Population
Voksne patienter med mycosis fungoides eller Sézarys syndrom stadie II-IV, der har fået mindst to tidligere systemiske behandlinger samt relevant ”skin directed” behandling (topikale steroider, UVB lysbehandling og evt. lavdosis elektronvolts helkropsbestråling) – eller har kontraindikationer (f.eks. tidligere malignt melanom) herfor?

Intervention
Mogamulizumab 1 mg/kg på dag 1, 8, 15 og 22 i den første 28-dages cyklus, efterfulgt af infusioner hver anden uge på dag 1 og 15 i hver af de efterfølgende 28-dages cykler.

Komparator
For at afspejle den danske behandlingspraksis ønsker fagudvalget at sammenligne mogamulizumab med enten en targeteret behandling eller en pathway-hæmmer og herudover kemoterapi. Ansøger bør foretage en sammenligning med mindst én komparator indenfor hver gruppe.

En targeteret behandling eller en pathway-hæmmer, doseret som følger

- Brentuximab vedotin
  1,8 mg/kg (dog højst 180 mg) i.v.-infusion hver 3. uge
  (Ved eGFR < 30 ml/min 1,2 mg/kg, dog højst 120 mg)
- Alemtuzumab
  10 mg s.c. 3 gange ugentligt i 12 uger
- Pembrolizumab
  200 mg i.v.-infusion over 30 minutter hver 3. uge eller 2 mg/kg hver 3. uge
- Romidepsin
  14 mg/m^2 på dag 1, 8 og 15 i serier a 28 dage (til progression)

Kemoterapi, doseret som følger
- Højdosis methotrexat
  60-240 mg/m^2 i.v.-infusion 1-2 gange ugentligt
- Doxorubicin
  20 mg/m^2 i.v. hver fjerde uge eller 20 mg/m^2 hver 3. uge
- Gemcitabin
  1000 mg/m^2 i.v.-infusion over 30 min. på dag 1 og 8 i serier a 21 dage
  Eller 250 mg/m^2 hver uge i 3 uger, herefter 2 ugers pause.

Effektmål
De valgte effektmål står i tabel 2.

3.2 Effektmål

Medicinrådet mener, at vurderingen af lægemidlets værdi bliver bedst understøttet af de effektmål, vi har nævnt i tabel 2. For hver effektmål har Medicinrådet fastsat en mindste klinisk relevant forskel (MKRF). I det følgende afsnit argumenterer vi for valget af effektmål og de mindste klinisk relevante forskelle.

Tabel 2. Effektmål.

Effektmål	Vigtighed	Effektmålsgruppe	Måleenhed	Mindste klinisk relevante forskel
Samlet overlevelse (OS)	Kritisk	Dødelighed	Median OS i antal måneder	En forskel på 6 måneder
Livskvalitet	Kritisk	Livskvalitet samt alvorlige symptomer og bivirkninger	Gennemsnitlig ændring over tid Skindex-29 total score - fra baseline til endt opfølgning	Forskel på 10 point

Progressionsfri overlevelse (PFS)	Kritisk	Livskvalitet samt alvorlige symptomer og bivirkninger	Median PFS i antal måneder	En forskel på 4 måneder
Uønskede hændelser	Vigtig	Livskvalitet samt alvorlige symptomer og bivirkninger	Andel af patienter med uønskede hændelser grad 3-4	Forskel på 5 %-point
			Andel af patienter der oplever alvorlige uønskede hændelser (SAE'er)	Forskel på 5 %-point

For alle effektmål ønsker vi data med længst mulig opfølgningstid, med mindre andet er angivet.

3.2.1 Kritiske effektmål

Samlet overlevelse (OS)

OS er et præcist effektmål, der belyser patientens levetid. OS defineres som tiden fra randomisering eller opstart af behandling til død, uanset årsag. Den forventede overlevelse er stadieafhængig og varierer mellem MF og SS. MF/SS er en livsforkortende sygdom, og fagudvalget ønsker at medtage OS i vurderingen for at sikre, at mogamulizumab ikke har en negativ indflydelse på patienters overlevelse. Med udgangspunkt i mediane overlevelser fra 3-6 år til mindre end 2 år i de seneste sygdomsstadier har fagudvalget fastsat den mindste klinisk relevante forskel på median OS til 6 måneder.

Livskvalitet
Livskvalitet fremhæves af fagudvalget som et yderst relevant effektmål, når patienterne lever længe med deres sygdom. Behandlingen er palliativ og patienternes livskvalitet undervejs i behandlingen er derfor afgørende. I vurderingen af mogamulizumab vurderes livskvalitet som et kritisk effektmål. Patienternes livskvalitet er tæt forbundet med deres hudsymptomer, da hudgenerne medfører betydeligt ubehag for patienterne og samtidig en øget infektionsrisiko. Derfor ønskes livskvalitet vurderet ved Skindex-29. Skindex-29 er et selvrapporteret spørgeskema, der er udviklet til at måle dermatologiskspecifik livskvalitet. Spørgeskemaet består af tre underskalaer: hudrelaterede, emotionelle og funktionelle symptomer. Den totale score går fra 29-116 og transformeres i vurderingen af livskvalitet til en lineær skala fra 0-100, hvor en højere score indikerer en dårligere livskvalitet [7]. Fagudvalget er ikke bekendt med studier, som undersøger mindste klinisk relevante forskelle for brugen af Skindex-29 hos patienter med KTCL. Værktøjet er imidlertid generisk i den forstand, at det er beregnet til brug for enhver form for hudlidelse. Der findes studier, som har forsøgt at fastsætte cut-off-værdier for henholdsvis mild, moderat og svær påvirkning af den samlede livskvalitet ved brug af Skindex-29 såvel som de enkelte domæner (hudrelaterede, emotionelle og funktionelle symptomer). Her viser et studie, at en 10-points reduktion i total-score svarer til en ændring fra svær til moderat påvirkning og tilsvarende fra moderat til mild påvirkning [8]. På denne baggrund har fagudvalget valgt 10 point som den mindste klinisk relevante forskel. Som supplement til den gennemsnitlige ændring i total score ønsker fagudvalget en opgørelse af effekten på de enkelte domæner med henblik på en kvalitativ vurdering af effekten på livskvalitet.

Progressionsfri overlevelse
Progressionsfri overlevelse (PFS) er defineret som tiden fra initiering af behandling til progression eller død uafhængigt af årsag. PFS er hos MF- og SS-patienter tæt forbundet med livskvalitet og anvendes i vurderingen af mogamulizumab som et udtryk for længden af sygdomskontrol, som opnås under og efter behandling. Fagudvalget vurderer, at PFS er et kritisk effektmål i vurderingen. Længden af den progressionsfri periode for patienter, der behandles med de nuværende behandlingsmuligheder, varierer fra ca. 6-12 måneder. Baseret på fagudvalgets erfaringer med de nuværende behandlingsmuligheder vurderer fagudvalget, at det nye lægemiddel skal tilbyde en forbedring i median PFS på minimum 4 måneder.

3.2.2 Vigtige effektmål

Uønskede hændelser

Uønskede hændelser grad 3-4

Forekomsten af uønskede hændelser grad 3-4 har stor betydning for den enkelte patients livskvalitet og vilje til at forblive i en behandling over længere tid. Mogamulizumab skal gives til progression, så eventuelle bivirkninger skal tolereres over en lang periode. Fagudvalget betragter en forskel på 5 %-point mellem patientgrupperne som den mindste klinisk relevante forskel.

Alvorlige uønskede hændelser (SAE'er)

Fagudvalget hæfter sig ved, at bivirkningsprofilen skal stå mål med lægemidlets effekt, især i betragtning af at der er tale om en pallierende behandling. Behandlingen bør derfor undgå betydelig alvorlig toksicitet. Fagudvalget betragter en forskel på 5 %-point mellem patientgrupperne som den mindste klinisk relevante forskel.

4 Litteratursøgning

Medicinrådet har på baggrund af den foreløbige ansøgning undersøgt, om der findes en eller flere fuldtekstartikler publiceret i videnskabelige, fagfællebedømte tidsskrifter, hvor mogamulizumab er sammenlignet direkte med en af de listede komparatorer indenfor hver gruppe (targeterede/pathway-hæmmere henholdsvis kemoterapi).

Medicinrådet har ikke fundet fuldtekstartikler, der indeholder en direkte sammenligning mellem mogamulizumab og en af de listede komparatorer. Derfor skal ansøger søge efter artikler, der muliggør en indirekte sammenligning med en eller flere af komparatorerne. Søgestrengen fremgår nedenfor. Derudover skal ansøger konsultere Det Europæiske Lægemiddelagenturs (EMA) European public assessment reports (EPAR) for både det aktuelle lægemiddel og dets komparator(er).

Søgestrenge fremgår af bilag 1.

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.

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.
- Angiv og redegør for forskelle mellem studiepopulation(er) og den danske population beskrevet i det 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.
- Redegør for studiernes indbyrdes sammenlignelighed, f.eks. studiedesign, studiepopulationer mv.
- 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.

- Redegør for studiernes indbyrdes sammenlignelighed, f.eks. studiedesign, studiepopulationer mv.
- 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.
- Redegør for studiernes indbyrdes sammenlignelighed, f.eks. studiedesign, studiepopulationer mv.
- 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 Komparator

Fagudvalget bemærker, at ansøger i deres registreringsstudie har sammenlignet mogamulizumab med HDAC-hæmmeren vorinostat, som ikke er markedsført i Europa, men som anvendes til behandling af kutane T-cellelymfomer i USA. På den baggrund ønsker fagudvalget, at ansøger redegør for, hvordan effekten af vorinostat er i sammenligning med de behandlingsmuligheder, der anvendes i dansk klinisk praksis.

7.2 Differentiering af effekt i MF- og SS-patienter

Da der er tale om en heterogen patientpopulation med varierende prognoser, ønsker fagudvalget at se data for effekten på de inkluderede effektmål opgjort i subgrupperne af MF- og SS-patienter, hvis det er muligt.

7.3 Behandlingsvarighed

Fagudvalget ønsker, at ansøger belyser behandlingsvarigheden af mogamulizumab og de relevante komparatorer.

7.4 Efterfølgende behandling

Fagudvalget ønsker informationer, der kan belyse en vurdering af, 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.

7.5 Sundhedsøkonomiske analyser

Ansøger bedes inddrage sammenligninger med alle relevante komparatorer i de sundhedsøkonomiske analyser.

8 Relation til behandlingsvejledning

Der findes ikke en relevant behandlingsvejledning, og fagudvalget vil derfor ikke tage stilling til en foreløbig placering af lægemidlet.

9 Referencer

1. European Medical Agency (EMA). Assessment report - Poteligeo. 2018.
2. Trautinger F, Eder J, Assaf C, Bagot M, Cozzio A, Dummer R, et al. European Organisation for Research and Treatment of Cancer consensus recommendations for the treatment of mycosis fungoides/Sézary syndrome - Update 2017. Eur J Cancer. 2017;77:57–74.
3. Olsen E, Vonderheid E, Pimpinelli N, Willemze R, Kim Y, Knobler R, et al. Revisions to the staging and classification of mycosis fungoides and Sezary syndrome: a proposal of the International Society for Cutaneous Lymphomas (ISCL) and the cutaneous lymphoma task force of the European Organization of Research and Treatment of Ca. Blood. 2007;110(6):1713–22.
4. Agar NS, Wedgeworth E, Crichton S, Mitchell TJ, Cox M, Ferreira S, et al. Survival Outcomes and Prognostic Factors in Mycosis Fungoides/Sézary Syndrome: Validation of the Revised International Society for Cutaneous Lymphomas/European Organisation for Research and Treatment of Cancer Staging Proposal. J Clin Oncol. 2010;28(31):4730–9.
5. Kempf W, Pfaltz K, Vermeer MH, Cozzio A, Ortiz-Romero PL, Bagot M, et al. EORTC, ISCL, and USCLC consensus recommendations for the treatment of primary cutaneous CD30-positive lymphoproliferative disorders: lymphomatoid papulosis and primary cutaneous anaplastic large-cell lymphoma. Blood. 2011;118(15):4024–35.
6. Willemze R, Hodak E, Zinzani PL, Specht L, Ladetto M. Primary cutaneous lymphomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2018;29:iv30-iv40.
7. Chren M-M. The Skindex instruments to measure the effects of skin disease on quality of life. Dermatol Clin. 2012;30(2):231–6, xiii.
8. Prinsen CAC, Lindeboom R, de Korte J. Interpretation of Skindex-29 scores: cutoffs for mild, moderate, and severe impairment of health-related quality of life. J Invest Dermatol. 2011;131(9):1945–7.

10 Sammensætning af fagudvalg og kontaktinformation til Medicinrådet

Medicinrådets fagudvalg vedrørende lymfekræft
Forvaltningslovens § 4, stk. 2, har været anvendt i forbindelse med udpegning af medlemmer til dette fagudvalg

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
Rikke Bech Afdelingslæge, ph.d.	Dansk Dermatologisk Selskab
Maria Rørbæk Kamstrup Reservelæge, ph.d.	Dansk Dermatologisk Selskab

Medicinrådets sekretariat

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11 Versionslog

Version	Dato	Ændring
1.0	15. juli 2020	Godkendt af Medicinrådet.

12 Bilag 1: Søgestrenge

Søgestrenge til PubMed

https://pubmed.ncbi.nlm.nih.gov/advanced/

#	Søgetermer	Kommentar
#1	Lymphoma, T-Cell, Cutaneous[mh]	Søgetermer for indikationen (P)
#2	(cutaneous[tiab] AND t-Cell[tiab] AND lymphom*[tiab]) OR (mycosis[tiab] AND fungoides[tiab]) OR (sezary[tiab] AND (syndrom*[tiab] OR erythroderm*[tiab] OR lymphom*[tiab]))	
#3	#1 OR #2	
#4	mogamulizumab[nm] OR mogamulizumab[tiab] OR Poteligeo*[tiab] OR AMG-761[tiab] OR AMG761[tiab] OR KM-8761[tiab] OR KM8761[tiab] OR KW-0761[tiab] OR KW0761[tiab]	Intervention (I)
#5	Brentuximab Vedotin[mh] OR brentuximab[tiab] OR Adcetris*[tiab] OR SGN-35[tiab] OR cAC10-vcMMAE[tiab]	Komparator (C)
#6	pembrolizumab[nm] OR pembrolizumab[tiab] OR Keytruda*[tiab] OR MK-3475[tiab] OR SCH-900475[tiab] OR lambrolizumab[tiab]	
#7	Alemtuzumab[mh] OR alemtuzumab[tiab] OR Campath*[tiab] OR Lemtrada*[tiab]	
#8	romidepsin[nm] OR romidepsin[tiab] OR Istodax*[tiab] OR FK228[tiab] OR FR-901228[tiab] OR FR901228[tiab]	
#9	Methotrexate[mh] OR methotrexate[tiab] OR amethopterin[tiab] OR MTX[tiab] OR Mexate*[tiab]	
#10	Doxorubicin[mh] OR doxorubicin*[tiab] OR DOX[tiab] OR Adriablastin*[tiab] OR Adriamycin*[tiab] OR Adriblastin*[tiab] OR DOXO-cell*[tiab] OR Myocet*[tiab] OR Rubex*[tiab]	
#11	gemcitabine[nm] OR gemcitabin*[tiab] OR Gemzar*[tiab]	
#12	#5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11	
#13	#3 AND (#4 OR #12)	Kombination af P, I og C
#14	Case Reports[pt] OR Comment[pt] OR Editorial[pt] OR Letter[pt] OR Review[pt] OR Systematic Review[pt]	Eksklusion af specifikke publikationstyper
#15	#13 NOT #14	Linje #15 = endelig søgning

Søgestrenge til CENTRAL – Cochrane Library

https://www.cochranelibrary.com/advanced-search/search-manager

#	**Søgetermer**	**Kommentar**
#1	[mh "Lymphoma, T-Cell, Cutaneous"]	Søgetermer for indikationen (P)
#2	((cutaneous AND t-Cell AND lymphom*) OR mycosis fungoides OR (sezary AND (syndrom* OR erythroderm* OR lymphom*))):ti,ab,kw	
#3	#1 OR #2	
#4	(mogamulizumab OR AMG-761 OR AMG761 OR KM-8761 OR KM8761 OR KW-0761 OR KW0761 OR Poteligeo*):ti,ab,kw	Intervention (I)
#5	[mh "Brentuximab Vedotin"]	Komparator (C)
#6	(brentuximab* OR Adcetris* OR SGN-35):ti,ab,kw	
#7	(pembrolizumab OR Keytruda* OR MK-3475 OR SCH-900475 OR lambrolizumab):ti,ab,kw	
#8	[mh "Alemtuzumab"]	
#9	(alemtuzumab OR Campath* OR Lemtrada*):ti,ab,kw	
#10	(romidepsin OR FK228 OR FR-901228 OR FR901228 OR Istodax*):ti,ab,kw	
#11	[mh "Methotrexate"]	
#12	(methotrexate OR amethopterin OR MTX OR Mexate*):ti,ab,kw	
#13	[mh "Doxorubicin"]	
#14	(doxorubicin* OR DOX OR Adriablastin* OR Adriamycin* OR Adriblastin* OR DOXO-cell* OR Myocet* OR Rubex*):ti,ab,kw	
#15	(gemcitabine OR Gemzar*):ti,ab,kw	
#16	#5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15	
#17	#3 AND (#4 OR #16)	Kombination af P, I og C
#18	(clinicaltrials.gov OR trialsearch):so	Eksklusion af specifikke publikationstyper
#19	"conference abstract":pt	
#20	#18 OR #19	
#21	#17 NOT #20	Linje #21 = endelig søgning [afgrænses til Trials]