Medicinrådet

Bilag til Medicinrådets anbefaling vedrørende brigatinib til førstelinje-behandling af uhelbredelig ALK-positiv ikke-småcellet lungekræft

Vers. 1.0

Bilagsoversigt

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Medicinrådet

Medicinrådets sundheds-økonomiske afrapportering

Brigatinib

Førstelinjebehandling af uhelbredelig ALK-positiv ikke-småcellet lungekræft

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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Indholdsfortegnelse

1. Begreber og forkortelser

AIP	Apotekernes indkøbspris
ALK	Anaplastisk lymfom kinase
BSC	*Best supportive care*
CNS	Centralnervesystemet
DKK	Danske kroner
DRG	Diagnose Relaterede Grupper
EGFR	*Epidermal growth factor receptor*
IPD	*Individual patient data*
MAIC	*Matching Adjusted Indirect Comparison*
NSCLC	Ikke-småcellet lungekræft (*non-small-cell lung cancer*)
OS	Overlevelse
PD	Progredieret overlevelse
PFS	Progressionsfri overlevelse
ROS1	*ROS proto-onkogene 1 receptor tyrosin kinase*
SAIP	Sygehusapotekernes indkøbspriser

2. Konklusion

Inkrementelle omkostninger og budgetkonsekvenser
I det scenarie, Medicinrådet mener er mest sandsynligt, er de inkrementelle omkostninger for brigatinib ca. [redacted] DKK pr. patient sammenlignet med alectinib. Når analysen er udført med apotekernes indkøbspriser (AIP), er de inkrementelle omkostninger til sammenligning ca. -97.000 DKK pr. patient.

De inkrementelle omkostninger er hovedsageligt drevet af lægemiddelomkostningerne, idet alt andet i analysen er antaget som værende identiske for brigatinib og alectinib. Der er dog usikkerhed vedr. denne antagelse, idet den er baseret på en række indirekte sammenligninger af studier, hvor population og studiedesign ikke er sammenlignelige. Fagudvalget har dog i vurderingsrapporten konkluderet, på baggrund af en narrativ sammenligning, at brigatinib og alectinib forekommer lige effektive – og ligestiller foreløbigt de to lægemidler.
Der er ligeledes usikkerhed vedr. spændet mellem den relative dosisintensitet for brigatinib og alectinib. Fagudvalget vurderer, at spændet i dansk klinisk praksis vil være større. Dette svarer til, at patienter i behandling med brigatinib oftere vil blive dosisreduceret, hvilket vil reducere de inkrementelle omkostninger yderligere.

Medicinrådet vurderer, at budgetkonsekvenserne for regionerne ved anbefaling af brigatinib som mulig standardbehandling vil være ca. [redacted] DKK i år 5. Når analysen er udført med AIP, er budgetkonsekvenserne ca. -1,3 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 brigatinib som mulig standardbehandling på danske hospitaler til behandling af voksne patienter med ALK-positiv, fremskreden ikke-små cellet lungekræft (NSCLC), som ikke tidligere er behandlet med en ALK-TKI.

Analysen er udarbejdet, fordi Medicinrådet har modtaget en endelig ansøgning fra Takeda Pharma. Medicinrådet modtog ansøgningen den 25. november 2020.

3.1 Patientpopulation

Omtrent 4.600 danskere diagnosticeres årligt med lungekræft, og dermed er lungekræft en af de hyppigst forekommende kræftsygdomme i Danmark [1,2]. I slutningen af 2016 levede knap 11.151 personer med lungekræft, mens ca. 3.700 personer årligt dør af lungekræft [2].

Af de diagnosticerede patienter med lungekræft har ca. 85-90 % ikke-småcellet lungekræft (non-small-cell lung cancer (NSCLC)) [4]. Behandlingsmålet for patienter med uhelbredelig NSCLC er symptomlindring og levetidsforlængelse. Patienter med uhelbredelig NSCLC får systemisk behandling i form af kemoterapi, immunterapi og såkaldt targeteret behandling med tyrosinkinasehæmmere (tyrosin kinase inhibitor (TKI)). Valg af behandling er afhængig af tumorkarakteristika, hvor tilstedeværelsen af bestemte biomarkører afgør valg af patientens behandling. Hvis en undersøgelse af tumoren viser genetiske eller kromosomale ændringer, som en behandling kan målrettes mod, vil en targeteret behandling være første valg. I dansk klinisk praksis drejer det sig på nuværende tidspunkt om to biomarkører: aktiverende epidermal growth factor receptor (EGFR)-mutationer og anaplastisk lymfomkinase (ALK)-translokationer [5]. Dertil kommer ROS proto-oncogene 1 receptor tyrosine kinase (ROS1) som en mulig tredje biomarkør, hvortil Medicinrådet er ved at vurdere et targeteret lægemiddel. Targeteret behandling er kun relevant for patienter med uhelbredelig NSCLC og ikke for patienter med NSCLC i tidligere stadier, hvor en behandling med sigte på helbredelse er en mulighed.

ALK-positiv NSCLC kendetegnes ved ALK-translokationer i tumorvævet, som aktiverer adskillige signaleringskaskader involveret i tumordannelse. ALK-translokationer forekommer sjældent med en frekvens på under 1 % ud af alle nydiagnosticerede lungekræfttilfælde. I 2018 lå frekvensen på 0,6 % svarende til 30 patienter [3].

Yderligere information om sygdomsområdet kan findes i Medicinrådets vurderingsrapport.

3.1.1 Komparator

Medicinrådet har vurderet den kliniske værdi af brigatinib på baggrund af følgende kliniske spørgsmål:

Klinisk spørgsmål 1:

Hvilken værdi har brigatinib sammenlignet med alectinib i førstelinjebehandling af patienter med uhelbredelig ALK-positiv ikke-småcellet lungekræft?

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 brigatinib sammenlignet med alectinib. Medicinrådet vurderer nedenfor den sundhedsøkonomiske analyse, som ansøger har indsendt.

4.1 Antagelser og forudsætninger for model

Der foreligger ikke et studie, som direkte sammenligner brigatinib med alectinib, hvorfor ansøger har udført en række forskellige indirekte sammenligninger. Dette inkluderer en Buchers indirekte sammenligning, hvor der ikke er justeret for prognostiske faktorer og effektmodifikatorer, en *anchored matching adjusted indirect comparison* (MAIC) via den fælles komparator crizotinib samt en *unachored matching adjusted indirecte comparison (MAIC).* MAIC-analyserne er konstrueret ved at anvende *individual patient data* (IPD) for brigatinib fra ALTA-L1-studiet [6] og de aggregerede data for alectinib fra ALEX-studiet [7,8]. Dette er gjort for at korrigere for heterogenitet i populationerne i de to studier. Disse sammenligninger er både udført for PFS evalueret af en *blinded independent central review committee* og for PFS evalueret af *investigator.* Derudover har ansøger i sammenligningerne baseret på Buchers og *anchored MAIC* præsenteret resultaterne, hvor der er kontrolleret for overkrydsning, da dette var tilladt i ALTA-L1-studiet [6], men ikke i ALEX-studiet [7,8].

[redacted]

Grundet disse insignifikante resultater og heterogenitet i de anvendte populationer vælger ansøger i den sundhedsøkonomiske model at antage, at effekten er identisk på PFS, CNS-PFS og OS for alectinib og brigatinib. Ansøger har dog også inkluderet muligheden for at anvende de enkelte punktestimater for den relative effekt mellem brigatinib og alectinib i den sundhedsøkonomiske model.

4.1.1 Modelbeskrivelse

Ansøger har indsendt en *partitioned survival*-model til at estimere de inkrementelle omkostninger forbundet med behandlingen med brigatinib.

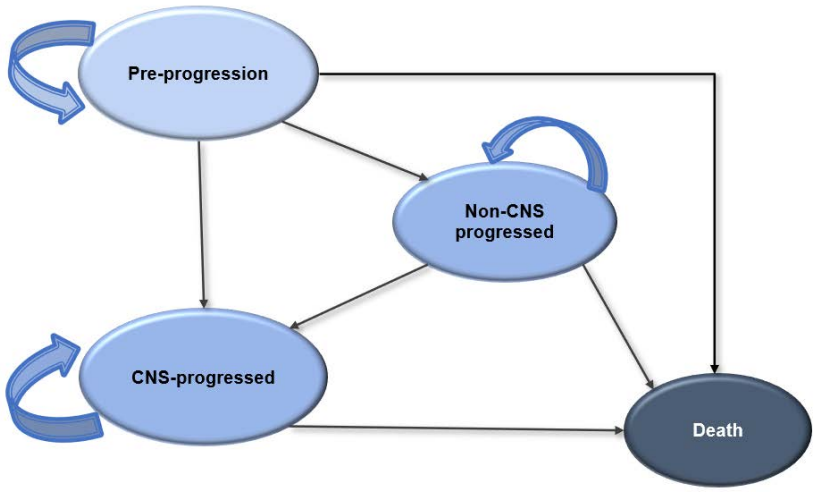
En *partitioned survival*-model indeholder en række sygdomsstadier, som patienterne skifter mellem i takt med sygdomsprogression. Ansøgers model består af fire stadier: præ-progression, post-progression uden CNS-metastaser, post-progression med CNS-metastaser og stadiet død. Se Figur 1 for de forskellige sygdomsstadier, og hvordan patienten kan bevæge sig mellem dem.

Alle patienter starter i sygdomsstadiet præ-progression, hvorfra deres bevægelse gennem modellen bestemmes ud fra ekstrapoleret *time-to-event*-data. Patientens tid i stadiet præ-progression bestemmes ud fra PFS-data fra ALTA-1L-studiet [6] for brigatinib, og det antages, at PFS er identisk for alectinib. Fra præ-progression kan patienten bevæge sig videre til stadiet post-progression uden CNS-metastaser eller post-progression med CNS-metastaser og til stadiet død.

Patienter, der er progredieret, men ikke døde, vil befinde sig i post-progression enten med eller uden CNS-metastaser. Tiden, patienterne befinder sig i dette stadie, estimeres ud fra residualen af patienter, der hverken er i præ-progression eller stadiet død. Fra post-progression kan patienten udelukkende bevæge sig til det absorberende stadie død.

Andelen af patienter i stadiet død bliver estimeret ud fra OS-data fra ALTA-1L-studiet [6] for brigatinib, og det antages, at OS er den samme for alectinib.

Modellen har en cykluslængde på 4 uger.



Figur 1. Beskrivelse af modelstrukturen i omkostningsanalysen

Ansøger modellerer tiden i de forskellige stadier ved at anvende ekstrapolerede Kaplan-Meier (KM)-data for PFS og OS. Dette er nødvendigt, da opfølgningen i ALTA-L1-studiet [6] er kortere end den anvendte tidshorisont.

Ansøger har anvendt en [redacted] funktion til at ekstrapolere PFS for brigatinib og antager, at PFS for alectinib er identisk, se Figur 2. For CNS-PFS har ansøger valgt at ekstrapolere data med en [redacted] funktion for brigatinib og antager, at CNS-PFS for alectinib er identisk, se Figur 3. For OS har ansøger valgt at ekstrapolere data med en [redacted] funktion for brigatinib og antager, at OS for alectinib er identisk, se Figur 4. Disse parametriske funktioner er valgt, da de, jf. AIC- og BIC-værdierne, udviser det bedste statistiske fit.

Figur 2. Ekstrapoleret PFS for brigatinib

Figur 3. Ekstrapoleret CNS-PFS for brigatinib

Figur 4. Ekstrapoleret OS for brigatinib

Ansøger har baseret behandlingsvarighed for brigatinib og alectinib på den gennemsnitlige tid PFS plus 12 uger, da ansøger argumenterer for, at patienter fortsat vil modtage behandling umiddelbart efter progression.

På baggrund af studiedata og ekstrapoleringerne har ansøger estimeret den gennemsnitlige tid, patienten befinder sig i modellens stadier.

Medicinrådets vurdering af ansøgers modelantagelser
Medicinrådet accepterer ansøgers estimater for behandlingsvarighed, PFS og OS samt antagelsen om, at effekten er identisk for alectinib og brigatinib, da der ikke foreligger data, som viser en signifikant forskel på de to lægemidler. Dette er ligeledes i overensstemmelse med vurderingsrapporten, hvor fagudvalget på baggrund af den narrative sammenligning vurderer, at brigatinib og alectinib forekommer lige effektive til førstelinjebehandling af patienter med uhelbredelig ALK-positiv ikke-småcellet lungekræft, og analysen bliver dermed en omkostningsminimeringsanalyse. Dette er dog en streng antagelse, som ikke er dokumenteret, og bidrager derfor med usikkerhed til den sundhedsøkonomiske model.

Estimaterne er præsenteret i Tabel 1.

Tabel 1. Estimeret gennemsnitlig behandlingstid, PFS, PD og OS

Behandling	Behandlingsvarighed [måneder]	PFS [måneder]	Progression uden CNS [måneder]	Progression med CNS [måneder]	OS [måneder]
Brigatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alectinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*Progressionsfri overlevelse (PFS), samlet overlevelse (OS)

Medicinrådet accepterer ansøgers tilgang vedr. modelantagelser.

4.1.2 Analyseperspektiv

I overensstemmelse med metoderne har ansøger valgt et begrænset samfundsperspektiv til sin analyse. Analysen har en tidshorisont på 20 år.

Omkostninger, der ligger efter det første år, er diskonteret med en rate på 4 % pr. år.

Medicinrådets vurdering af ansøgers analyseperspektiv
Medicinrådet accepterer ansøgers valgte tidshorisont, da ansøger argumenterer for, at den gennemsnitlige behandlingslængde (af både første- og andenlinjebehandling) ligger inden for denne tidshorisont. Det betyder ikke, at patienterne modtager behandling med brigatinib eller alectinib i hele tidshorisonten, men at analysen opfanger alle direkte og afledte økonomiske forskelle mellem brigatinib og alectinib set over en tidshorisont på 20 år.

Desuden justeres diskonteringsrenten til 3,5 %, jf. Finansministeriets dokumentationsnotat vedr. den samfundsøkonomiske diskonteringsrente [9]. Denne ændring vurderes at have minimal betydning for analysens resultat.

Medicinrådet accepterer ansøgers valg vedr. analyseperspektiv og tidshorisont, men vælger at justere diskonteringsraten til 3,5 % pr. år.

4.2 Omkostninger

I det følgende er ansøgers antagelser for omkostningerne i den sundhedsøkonomiske analyse af brigatinib sammenlignet med alectinib præsenteret. Ansøger har inkluderet lægemiddelomkostninger, hospitalsomkostninger, bivirkningsomkostninger, patientomkostninger og efterfølgende behandlinger.

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* [10], estimeret lægemiddelomkostninger på baggrund af apotekernes indkøbspris (AIP). Doser anvendt i ansøgers analyse er hentet i de respektive produkters produktresuméer (SPC'er).

Brigatinib: 90 mg én gang dagligt i 7 dage og derefter 180 mg én gang dagligt.

Alectinib: 600 mg to gange dagligt.

Ansøger antager en dosisintensitet på 85,51% for brigatinib baseret på ALTA-1L-studiet [6] og 95,6 % for alectinib baseret på ALEX-studiet [7,8]. Der er i modellen ikke inkluderet omkostninger til spild.

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

Tabel 2. Anvendte lægemiddelpriser, SAIP (april 2021)

Lægemiddel	Styrke	Daglig mg/dosis	Pakkings-størrelse	Pris [DKK]	Kilde
Brigatinib	90 mg	90 mg	7 stk.*	[redacted]	Amgros
	180 mg	180 mg	28 stk.	[redacted]	Amgros
Alectinib	150 mg	1.200 mg	224 stk.	[redacted]	Amgros

*Ansøger anvender ikke Alunbrig Startpakke (brigatinib) med 7 (90 mg) + 21 (180 mg) stk. tabletter til at afspejle indkøringsperioden for dosis i analysen. I stedet anvender ansøger ¼ af prisen på en pakning med 28 stk. tabletter à 90 mg til at estimere lægemiddelomkostningerne for de syv dage, indkøringsperioden varer.

Fagudvalget vurderer, at spændet mellem dosisintensiteten for alectinib og brigatinib potentielt er større end antaget af ansøger. Denne usikkerhed vælger sekretariatet at udforske yderligere i en følsomhedsanalyse, hvor den relative dosisintensitet justeres. Sekretariatet vælger desuden at inkludere lægemiddelspild. Her antages det, at tabletter svarende til én cyklus vil gå til spilde, når en patient progredierer (dvs. én pakke for både brigatinib og alectinib).

Medicinrådet accepterer ansøgers antagelser vedr. lægemiddelomkostninger. Dog fremhæver fagudvalget, at der er usikkerhed vedr. spændet i dosisintensiteten mellem brigatinib og alectinib, og derfor udføres en følsomhedsanalyse vedr. den relative dosisintensitet. Desuden inkluderer sekretariatet omkostninger til lægemiddelspild.

4.2.2 Hospitalsomkostninger

Administrationsomkostninger

Da brigatinib og alectinib administreres oralt, har ansøger ikke inkluderet nogen administrationsomkostninger.

Medicinrådets vurdering af ansøgers antagelser vedr. administrationsomkostninger

Medicinrådet accepterer ansøgers tilgang vedr. administrationsomkostninger.

Monitoreringsomkostning

Ansøger har inkluderet omkostninger til monitorering og opfølgning, hvor ansøger antager, at frekvensen af monitorering afhænger af sygdomsstadie, men er identisk for brigatinib og alectinib. Ansøger antager desuden, at der vil være en ekstra omkostning for patienter med CNS-metastaser, og denne omkostning er ligeledes identisk for alectinib og brigatinib. Ansøger har antaget, at de respektive elementer i monitoreringsomkostningerne kan estimeres i form af DRG-takster.

Medicinrådets vurdering af ansøgers antagelser vedr. monitoreringsomkostninger

Medicinrådet accepterer ansøgers tilgang til estimering af monitoreringsomkostninger, men vælger at ekskludere monitoreringsomkostninger efter progression, da fagudvalget vurderer, at patienterne ikke vil blive monitoreret efter progression. Sekretariatet vælger at erstatte ansøgers antagelse vedr. omkostninger til monitoreringsbesøg hos onkolog

fra 179 DKK til 1.316 DKK, jf. Medicinrådets værdisætning af enhedsomkostninger [11]. Desuden vælger sekretariatet at opdatere de anvendte DRG-takster fra 2020 til 2021.

Anvendte monitoreringsomkostninger kan ses i Tabel 3, mens ekstraomkostningen for patienter med CNS-metastaser kan ses i Tabel 4.

Tabel 3. Omkostninger til opfølgning og monitorering

	Andel patienter [%]	Månedlig frekvens	Omkostning [DKK]	Kilde
PFS – Første cyklus				
Onkologbesøg	100	1	1.316	Medicinrådets værdisætning af enhedsomkostninger
Biokemi/blodprøver	100	1	352	DRG 2021: 04SP01
PFS – Efterfølgende cyklus				
Onkologbesøg	100	1	1.316	Medicinrådets værdisætning af enhedsomkostninger
Biokemi/blodprøver	100	1	2.998	DRG 2021: 04SP01
CT-scanning	100	0,5	2.032	DRG 2021: 30PR06
MR-scanning	100	0,2	2.768	DRG 2021: 30PR02
Røntgen	100	0,3	747	DRG 2021: 30PR17
EKG	100	1	2.737	DRG 2021: 05PR04
Efter progression				
Onkologbesøg	100	1	1.316	Medicinrådets værdisætning af enhedsomkostninger
Biokemi/blodprøver	100	1,5	2.998	DRG 2021: 04SP01
CT-scanning	100	0,75	2.032	DRG 2021: 30PR06
MR-scanning	100	0,5	2.768	DRG 2021: 30PR02
Røntgen	100	0,5	747	DRG 2021: 30PR17

Tabel 4. Omkostninger til opfølgning og monitorering af patienter med CNS-metastaser

	Andel patienter [%]	Maks. antal behandlinger	Omkostning pr. behandling [DKK]	Kilde
Stereotaktisk strålebehandling	50	6	747	DRG 2021: 30PR17

Justering af omkostningerne til onkologbesøg og ekskludering af monitoreringsomkostninger efter progression har ingen betydning for resultatet, da patienter i behandling med alectinib og brigatinib monitoreres med samme frekvens og er antaget til at have samme behandlingslængde.

Medicinrådet bemærker, at ansøger ikke har inkluderet omkostninger forbundet med diagnosticeringstests i analysen. Medicinrådet accepterer dog ekskluderingen af disse omkostninger, idet alle patienter testes for biomarkører, hvorfor omkostningerne ikke påvirker resultatet.

Medicinrådet accepterer ansøgers tilgang vedr. monitoreringsomkostninger, men vælger at ekskludere omkostninger til monitorering efter progression samt at justere omkostningerne til monitorering hos onkolog.

Bivirkningsomkostninger

Ansøger har inkluderet omkostninger forbundet med bivirkninger i analysen. I ansøgers model benyttes frekvenser for uønskede hændelser (AE) af grad 3-4 som mål for bivirkningerne. For brigatinib og alectinib har ansøger benyttet de rapporterede bivirkningsrater fra ALTA-L1-studiet [6] og ALEX-studiet [7,8] og dermed ikke antaget ens bivirkninger, ligesom der er gjort ved effekt. Ressourcerne brugt i forbindelse med de forskellige bivirkninger har ansøger baseret på DRG-takster.

Medicinrådets vurdering af ansøgers antagelser vedr. bivirkningsomkostninger

Medicinrådet accepterer ansøgers tilgang til estimering af bivirkningsomkostninger, men idet fagudvalget vurderer, at behandling med begge lægemidler er forbundet med en række uønskede hændelser, som generelt kan betragtes som sammenlignelig vælger sekretariatet at antage, at bivirkningsprofilen for alectinib er identisk med brigatinib. Fagudvalget bemærker dog, at der i brigatinib-studiet er flere grad 3-4 bivirkninger end i alectinib-studierne, men det vides ikke, om det skyldes forskel i opgørelsen af sikkerhed mellem studierne, forskel i studiepopulationerne eller en reel forskel i bivirkninger. Sekretariatet vælger derfor også at udføre en følsomhedsanalyse, hvor bivirkningsprofilerne fra ALTA-L1-studiet [6] og ALEX-studiet [7,8] bl.a. anvendes.

Sekretariatet vælger desuden, på samme vis som for monitoreringsomkostningerne, at opdatere de anvendte DRG-takster vedr. bivirkninger fra 2020 til 2021.

Bivirkningsfrekvenser og anvendte takster kan ses i Tabel 5.

Tabel 5. Rapporterede bivirkningsfrekvenser ved behandling med brigatinib og alectinib samt enhedsomkostninger for bivirkningerne

	Brigatinib [%]	Alectinib [%] (bruges kun i følsomhedsanalysen)	DRG-kode 2021	Takst [DKK]
Akut nyreskade	0,0 %	1,7 %	11MA01	41.799
Forhøjet amylase	2,9 %	-	07MA14	25.512
Anæmi	0,7 %	3,0 %	16PR02	4.628
Forhøjet kreatinfosfokinase	11,6 %	1,7 %	05MA08	1.837
Diarré	0,4 %	0,0 %	06MA11	5.130
Træthed	0,0 %	0,4 %	01PR02	2.400
Forhøjet gamma-glutamyltransferase	0,4 %	0,4 %	07MA14	25.512
Hypertension	3,6 %	-	05MA11	14.155
Forhøjet alanin-aminotransferase	0,7 %	3,0 %	07MA14	25.512
Forhøjet aspartat-aminotransferase	1,1 %	3,4 %	07MA14	25.512
Forhøjet lipase	6,2 %	-	07MA14	25.512
Kvalme	0,7 %	0,4 %	03MA02	5.091
Pneumoni	0,4 %	1,7 %	04MA13	36.514
Urinvejsinfektion	0,0 %	1,7 %	11MA07	24.431

Medicinrådet accepterer ansøgers tilgang vedr. bivirkningsomkostninger, men vælger at præsentere dem som en del af en følsomhedsanalyse. I hovedanalysen antager sekretariatet, jf. vurderingsrapporten, at bivirkningsprofilerne er identiske for brigatinib og alectinib.

4.2.3 Efterfølgende behandling

Ansøger inkluderer omkostninger til efterfølgende behandling, da OS forventes at afspejle effekten af både førstelinjebehandling og de efterfølgende behandlinger. Som efterfølgende behandling har ansøger antaget, at 5 % af patienterne, som progredierer på enten brigatinib eller alectinib, vil modtage atezolizumab som andenlinjebehandling, mens 90 % vil modtage carboplatin + pemetrexed. Efter disse behandlinger vil 100 % modtage *best supportive care* (BSC). Denne fordeling er baseret på en vurdering af

[redacted]

Ansøger antager, at den gennemsnitlige behandlingsvarighed for efterfølgende behandling er 33 uger for atezolizumab baseret på OAK-studiet [12], 12 uger for carboplatin og 26,9 uger for pemetrexed baseret på ASCEND-studiet [13]. Ansøger antager desuden, at patienter modtager BSC den resterende tid indtil død, svarende til 3,8 år. Efterfølgende behandling antages at være identisk for både brigatinib og alectinib.

Medicinrådets vurdering af ansøgers antagelser vedr. efterfølgende behandling
Medicinrådet vælger at ekskludere omkostninger til efterfølgende behandling fra analysen. Idet ansøger har antaget, at både effekt og efterfølgende behandling er identisk, vil ekskludering af efterfølgende behandling ikke have indflydelse på resultatet, men blot reducere usikkerheden uden at bidrage til beslutningsgrundlaget.

Medicinrådet vælger at ekskludere efterfølgende behandling fra analysen.

4.2.4 Patientomkostninger

Patientomkostninger er estimeret på baggrund af administrations- og monitoreringsbesøg på hospitalet og inkluderer patientens effektive tid på hospitalet, ventetid og transporttid. Ansøger antager, at dette udgør to timer ved hver cyklus (hver 4. uge).

Ansøger anvender en enhedsomkostning for patienttid på 179 DKK pr. time og transportomkostninger på 100 DKK pr. besøg, jf. Medicinrådets *Katalog for værdisætning af enhedsomkostninger.*

Desuden antager ansøger, at der vil være patientomkostninger forbundet med køb af medicin, som ikke udleveres på hospitalet, dvs. co-medicin. Her anvendes frekvenserne for *concomitant medication* fra ALTA-1L-studiet [6] og antages at være identiske for både brigatinib og alectinib.

Medicinrådets vurdering af ansøgers antagelser vedr. patientomkostninger
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 simple følsomhedsanalyser, hvor effekten af variation i forskellige parametre undersøges. Følgende følsomhedsanalyser er udført:

Tabel 6. Følsomhedsanalyser og beskrivelse

Følsomhedsanalyse	Beskrivelse
Ændring af omkostningerne til andenlinjebehandling	Det antages, at omkostningerne til andenlinjebehandling øges med 30 % for hhv. brigatinib og alectinib
Variation i omkostningerne til co-medicinering	Det antages, at omkostningerne til co-medicinering øges med 30 % for hhv. brigatinib og alectinib
Variation i omkostningerne til bivirkninger	Det antages, at omkostningerne til bivirkninger øges med 30 % for hhv. brigatinib og alectinib

Derudover har ansøger inkluderet mulighed for at ændre en række parametre i modellen, som kan bruges til at foretage følsomhedsanalyser. Konkret er fremhævet to scenarier, som ansøger vurderer er de mest informative. Et scenarie, hvor den relative dosisintensitet fra de to studier anvendes, og det samtidig antages, at patienter modtager behandling indtil progression. I det andet scenarie antages det, at andenlinjebehandling er fordelt ligesom i ALTA-1L-studiet [6] for brigatinib og ligesom beskrevet i alectinib-ansøgningen til det britiske HTA-institut NICE. Ansøger har dog ikke redegjort for, hvor data i alectinib-ansøgningen til NICE stammer fra.

Medicinrådets vurdering af ansøgers valg af følsomhedsanalyser
Medicinrådet vælger ikke at præsentere ansøgers følsomhedsanalyser, da de er meget simple og bidrager med begrænset information. Sekretariatet vælger at foretage en følsomhedsanalyse, hvor spændet i den relative dosisintensitet for brigatinib sænkes med 10 %-point, og en følsomhedsanalyse, hvor den relative dosisintensitet sættes til 100 % for både alectinib og brigatinib.

Da effekten er antaget at være identisk for brigatinib og alectinib, vælger sekretariatet også at udføre en følsomhedsanalyse, hvor punktestimaterne for den relative forskel mellem brigatinib og alectinib fra ansøgers indirekte sammenligninger samt bivirkningsfrekvenserne fra ALTA-L1-studiet [6] og ALEX-studiet [7,8] anvendes.

Sekretariatet fremhæver, at den parameter, der har størst indflydelse på resultaterne, er den lægemiddelpris, brigatinib indkøbes til.

Medicinrådet accepterer ansøgers følsomhedsanalyser, men vælger ikke at præsentere dem. Desuden foretages en følsomhedsanalyse, hvor den relative dosisintensitet justeres, og hvor punktestimatet vedr. den relative effekt for brigatinib og alectinib, fra ansøgers indirekte sammenligninger, anvendes.

4.4 Opsummering af basisantagelser

I Tabel 7 opsummeres basisantagelserne i henholdsvis ansøgers og Medicinrådets hovedanalyse.

Tabel 7. Basisantagelser for ansøgers og Medicinrådets hovedanalyse

Basisantagelser	Ansøger	Medicinrådet
Tidshorisont	30 år	30 år
Diskonteringsrate	4 %	3,5 %
Inkluderede omkostninger	Administrationsomkostninger Monitoreringsomkostninger Bivirkningsomkostninger Patient- og transportomkostninger Efterfølgende behandling	Administrationsomkostninger Monitoreringsomkostninger Bivirkningsomkostninger Patient- og transportomkostninger
Dosering	Brigatinib: 90 mg én gang dagligt i 7 dage og derefter 180 mg én gang dagligt Alectinib: 600 mg to gange dagligt	Brigatinib: 90 mg én gang dagligt i 7 dage og derefter 180 mg én gang dagligt Alectinib: 600 mg to gange dagligt
Behandlingslinje	1. linje	1. linje
Behandlingslængder		
Brigatinib:	[redacted]	[redacted]
Alectinib:	[redacted]	[redacted]
Parametriske funktioner for PFS		
Brigatinib:	[redacted]	[redacted]
Alectinib:	Samme kurve som brigatinib	Samme kurve som brigatinib
Parametriske funktioner for OS		
Intervention:	[redacted]	[redacted]
Komparator:	Samme kurve som brigatinib	Samme kurve som brigatinib
Inkludering af spild	Nej	Ja

5. Resultater

5.1 Resultatet af Medicinrådets hovedanalyse

Medicinrådets hovedanalyse bygger på samme antagelser som ansøgers hovedanalyse med undtagelse af de ændringer, som er beskrevet i dette dokument, hvoraf de væsentligste fremgår af Tabel 7.

Den gennemsnitlige inkrementelle omkostning pr. patient bliver ca. [redacted] DKK i Medicinrådets hovedanalyse. Størstedelen af omkostningerne forekommer dog de første 5 år af behandlingsforløbet.

Er analysen udført med AIP, bliver den inkrementelle omkostning pr. patient ca. -97.000 DKK.

Resultaterne fra Medicinrådets hovedanalyse er præsenteret i Tabel 8.

Tabel 8. Resultatet af Medicinrådets hovedanalyse ved sammenligning med alectinib, DKK, diskonterede tal

	Brigatinib	Alectinib	Inkrementelle omkostninger
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Hospitalsomkostninger	465.950	465.950	0
Efterfølgende behandling	0	0	0
Patientomkostninger	46.147	46.147	0
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 9.

Tabel 9. Resultatet af Medicinrådets følsomhedsanalyser sammenlignet med hovedanalysen, DKK

Scenarie	Inkrementelle omkostninger
Resultatet af hovedanalysen	[redacted]
Relativ dosis for brigatinib reduceres med 10 %-point	[redacted]
Relativ dosis for brigatinib sættes til 100 % for begge lægemidler	[redacted]

Scenarie	Inkrementelle omkostninger
Anvendelse af punktestimatet for den relative effekt mellem brigatinib og alectinib fra ansøgers indirekte sammenligning samt bivirkningsfrekvenser fra ALTA-1L og ALEX	[redacted]
Anvendelse af punktestimatet for den relative effekt mellem brigatinib og alectinib fra ansøgers *anchored* MAIC samt bivirkningsfrekvenser fra ALTA-1L og ALEX	[redacted]
Anvendelse af punktestimatet for den relative effekt mellem brigatinib og alectinib fra ansøgers *uanchored* MAIC samt bivirkningsfrekvenser fra ALTA-1L og ALEX	[redacted]

6. Budgetkonsekvenser

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

- Brigatinib bliver anbefalet som mulig standardbehandling af Medicinrådet til indikationen, som denne analyse omhandler.
- Brigatinib 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 anvender forekomsten af ALK-translokationer af alle nydiagnosticerede lungekræfttilfælde til at estimere patientantallet. Ansøger anvender frekvensen angivet i Dansk Lunge Cancer Registers nationale årsrapport, som i 2016 var 0,8 %, svarende til 36 patienter, i 2017 var 0,9 %, svarende til 43 patienter, mens det i 2018 var 0,6 %, svarende til 30 patienter. Baseret på disse tal antager ansøger et årligt patientantal på 35 nye patienter.

Ansøger antager, at brigatinib ved en anbefaling vil opnå et markedsoptag på 15 % i år 1, 35 % i år 2 og 45 % i år 3, hvorefter markedsoptaget vil forblive på 50 % om året de

efterfølgende år. Ansøger antager ikke, at brigatinib vil opnå et markedsoptag, hvis brigatinib ikke anbefales.

Medicinrådets vurdering af ansøgers budgetkonsekvensanalyse
Fagudvalget er blevet konsulteret i forhold til patientantal, hvis brigatinib anbefales som mulig standardbehandling, og hvis ikke brigatinib anbefales. Fagudvalget accepterer ansøgers estimat på 35 patienter pr. år, som forventes at være kandidater til behandling med brigatinib til den pågældende indikation, og vurderer, at ansøgers antagede markedsoptag er plausibelt, se Tabel 10.

Tabel 10. Medicinrådets estimat af antal nye patienter pr. år

	År 1	År 2	År 3	År 4	År 5
			Anbefales		
Brigatinib	5	12	16	18	18
Alectinib	30	23	19	18	18
			Anbefales ikke		
Brigatinib	0	0	0	0	0
Alectinib	35	35	35	35	35

Medicinrådet accepterer ansøgers antagelser vedr. patientantal og markedsoptag.

6.2 Medicinrådets budgetkonsekvensanalyse

Medicinrådet estimerer, at anvendelse af brigatinib vil resultere i budgetkonsekvenser på ca. [redacted] DKK i år 5. Resultatet er præsenteret i Tabel 11.

Er analysen udført med AIP, bliver budgetkonsekvenserne ca. -1,3 mio. DKK i år 5.

Tabel 11. Medicinrådets analyse af totale budgetkonsekvenser, mio. DKK, ikke-diskonterede tal

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

7. Diskussion

Behandling med brigatinib er forbundet med inkrementelle omkostninger på ca. [redacted] DKK sammenlignet med behandling med alectinib. De inkrementelle omkostninger er næsten udelukkende drevet af lægemiddelomkostningerne for brigatinib, da alt er antaget identisk for brigatinib og alectinib på nær bivirkningsomkostningerne, som er en anelse højere for brigatinib end for alectinib.

Den sundhedsøkonomiske model er bygget op omkring antagelsen, at effekten af brigatinib kan ligestilles med alectinib, mens bivirkningsprofilerne ikke er identiske. Denne antagelse er baseret på en række indirekte sammenligninger af studier, hvor populationerne og studiedesign ikke er sammenlignelige, og som ansøger har valgt ikke at inkludere i den kliniske del af ansøgningen. Der er derfor usikkerhed vedr. denne antagelse, men fagudvalget har dog i vurderingsrapporten konkluderet, på baggrund af en narrativ sammenligning, at brigatinib og alectinib forekommer lige effektive – og ligestiller foreløbigt de to lægemidler.

Slutteligt er der usikkerhed vedr. den relative dosisintensitet, idet fagudvalget vurderer, at spændet mellem brigatinib og alectinib potentielt vil være større end antaget af ansøger. Det betyder, at patienter i behandling med brigatinib i større omfang vil blive dosisreduceret end patienter i behandling med alectinib. Dette vil reducere de inkrementelle omkostninger yderligere.

Alle øvrige usikkerheder har ingen eller meget begrænset betydning for resultatet.

8. Referencer

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9. Bilag

9.1 Resultatet af ansøgers hovedanalyse

I ansøgers hovedanalyse bliver den inkrementelle omkostning pr. patient [redacted] DKK over en tidshorisont på 30 år. Resultaterne fra ansøgers hovedanalyse er præsenteret i Tabel 12.

Tabel 12. Resultatet af ansøgers hovedanalyse, DKK, diskonterede tal

	Brigatinib	Alectinib	Inkrementelle omkostninger
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Hospitalsomkostninger	692.432	686.387	6.045
Efterfølgende behandling	293.930	293.930	0
Patientomkostninger	59.536	59.536	0
Totale omkostninger	[redacted]	[redacted]	[redacted]

9.2 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 brigatinib vil resultere i budgetkonsekvenser på ca. [redacted] DKK i år 5. Ansøgers estimat af budgetkonsekvenserne fremgår af Tabel 13.

Tabel 13. Ansøgers hovedanalyse for totale budgetkonsekvenser, mio. DKK, ikke-diskonterede tal

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

Amgros I/S
Dampfærgevej 22
2100 København Ø
Danmark

T +45 88713000
F +45 88713008

Medicin@amgros.dk
www.amgros.dk

Forhandlingsnotat

Dato for behandling i Medicinrådet	28.04.2021
Leverandør	Takeda
Lægemiddel	Alunbrig (brigatinib)
Ansøgt indikation	Brigatinib til behandling af uhelbredelig anaplastisk lymfom kinase (ALK)-positiv ikke-småcellet lungekræft, som ikke er tidligere blevet behandlet med en ALK-TKI (førstelinjebehandling)

Forhandlingsresultat

[redacted]

[redacted]

Amgros har opnået følgende pris på brigatinib:

Lægemiddel	Styrke/dosis	Pakningsstørrelse	AIP (DKK)	Forhandlet SAIP (DKK)	Rabatprocent ift. AIP
Brigatinib	30 mg	28 stk.	9.632,70	[redacted]	[redacted]
Brigatinib	90 mg	28 stk	28.586,83	[redacted]	[redacted]
Brigatinib	180 mg	28 stk	38.017,04	[redacted]	[redacted]
Brigatinib	90 + 180 mg	7 + 21 stk	38.843,37	[redacted]	[redacted]

Kontrakten løber indtil d. 30.09.2021 med mulighed for 2 * 6 måneders forlængelse.

Vurdering af forhandlingsresultatet

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

[redacted]

Konklusion

Amgros vurderer at vi har opnået den bedst mulige pris på brigatinib.

Relation til markedet:

Lægemiddel	Behandlings linje	Dosering	Lægemiddeludgift (SAIP) pr patient pr. år. (DKK)
Brigatinib	Første linje	180 mg	[redacted]
Alectinib	Første linje	600 mg *2	[redacted]
lorlatinib	Anden linje og tredje linje	100 mg	[redacted]
Crizotinib	Første linje - 2. valg i glædende rekommandation	250 mg * 2	[redacted]

Status fra andre lande

Norge: Brigatinib er blevet godkendt d. 15.02.2021 under betingelse af at firmaet byder ind med en konkurrencedygtig pris i det kommende udbud. Brigatinib er blevet direkte indplaceret i en behandlingsvejledning[1].

Sverige: Brigatinib er blevet godkendt i Sverige i september 2020[2] Firmaet skal dog supplere med data om indirekte sammenligning med Alectinib og brigatinib i slutningen af 2021.

UK, Nice: Godkendt d. 27.01.2021[3].

[1] Brigatinib (Alunbrig) - Indikasjon II (nyemetoder.no)
[2] Alunbrig ingår i högkostnadsskyddet med uppföljningsvillkor - Tandvårds- och läkemedelsförmånsverket TLV
[3] Documents | Brigatinib for ALK-positive advanced non-small-cell lung cancer that has not been previously treated with an ALK inhibitor | Guidance | NICE

Høringssvar vedr. den foreløbige merværdikategorisering for brigatinib til 1. linje behandling af ALK+ NSCLC

Takeda takker for muligheden for at indgive et høringssvar vedr. den foreløbige merværdikategorisering for brigatinib behandling til tidligere ubehandlede ALK+ NSLCL patienter i forhold til nuværende dansk standard behandling med alectinib.
Takeda takker yderligere Medicinrådets Sekretariatsmedarbejdere for en god proces karakteriseret af transparens og åbenhjertig ligefrem dialog.

Takeda noterer at det, inden for rammerne af Medicinrådets metoder, ikke har været muligt at placere brigatinib i en merværdikategori, hvorfor den samlede kategori bliver "kan ikke kategoriseres". Dette skyldes forskelle i studiedesign, der vanskeliggøre en formel indirekte sammenligning mellem brigatinib og alectinib vha. den fælles komparator crizotinib.
Takeda finder det beklageligt, at Medicinrådets metoder ikke kan rumme studier fra terapeutiske områder karakteriseret af hurtig udvikling og flere konkurrerende udviklingsprogrammer, der tester nye lægemidler mod hvad der var *standard of care* for blot 2-3 år siden, da studierne blev designet.

Takeda noterer yderligere at Fagudvalget for lungekræft i det konkluderende afsnit samlet vurderer at brigatinib og alectinib "*…forekommer lige effektive til førstelinjebehandling af patienter med uhelbredelig ALK-positiv ikke-småcellet lungekræft.*" [1]
Takeda tilslutter sig denne konklusion da både relative og absolutte effektmål fra de to udviklingsprogrammer, i den udstrækning de kan sammenlignes, fremstår ens, tabel 4 i udkast til Medicinrådets merværdivurdering.

Med venlig hilsen

Anders Bondo Dydensborg
Medical Advisor Oncology

Sigurd Hilborg
Patient Value and Access Manager Oncology

Louise -Herbild
Director Patient Value and Access

[1] Afsnit 5.1.5 Fagudvalgets konklusion, *side 27 i Udkast: Medicinrådets vurdering vedrørende brigatinib til førstelinjebehandling af uhelbredelig ALK-positiv ikke-småcellet lungekræft*.

Medicinrådet

Medicinrådets vurdering vedrørende brigatinib til førstelinjebehandling af uhelbredelig ALK-positiv ikke-småcellet lungekræft

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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1. Medicinrådets konklusion

Medicinrådet finder, at datagrundlaget ikke tillader, at den samlede værdi af brigatinib sammenlignet med alectinib til førstelinjebehandling af ALK-positiv ikke-småcellet lungekræft kan kategoriseres efter Medicinrådets metoder. Der er dog både dokumentation fra kliniske studier og klinisk erfaring fra fagudvalget, hvilket Rådets konklusion er bygget på.

Begge lægemidler er andengenerations ALK-tyrosin kinase inhibitorer og er hver især sammenlignet med crizotinib i randomiserede kliniske studier. Der er forskelle på studierne, som gør, at der ikke er udført en statistisk, indirekte sammenligning. For overlevelse er observationstiden i studiet af brigatinib for kort til at vurdere, om der er forskelle mellem alectinib og brigatinib. På effektmålene sygdomsprogression i centralnervesystemet og progressionsfri overlevelse er der vist en markant bedre effekt af både brigatinib og alectinib end crizotinib. Forskelle i studiepopulation og studiedesign gør, at vi ikke kan drage sikre konklusioner om en eventuel forskel mellem brigatinib og alectinib for disse to effektmål. For livskvalitet viser data, at gennemsnitlig tid til forværring af livskvalitet er sammenlignelig mellem brigatinib og alectinib.

Medicinrådet vurderer, at sikkerhedsprofilerne for de to lægemidler er forskellige, hvor begge lægemidler kan medføre en række uønskede hændelser. På baggrund af det foreliggende datagrundlag samt fagudvalgets kliniske erfaring er der dog ikke grund til at formode, at der er forskel i alvorlige bivirkninger, som kan være af væsentlig betydning for patienterne. Dette understøttes af, at forskellen i bivirkninger mellem brigatinib og alectinib ikke medfører en forskel mellem lægemidlerne, hvad angår livskvalitet.

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 (f.eks. på grund af usikkerheder omkring effektforhold og spinkelt datagrundlag). Medicinrådet konkluderer da, at samlet værdi ikke kan kategoriseres. Medicinrådet vil i disse tilfælde argumentere for, om der er grund til at formode, at det nye lægemiddel er dårligere eller evt. bedre end gældende standardbehandling, eller der ikke er grund til at skelne mellem behandlingerne. Det sker på baggrund af det foreliggende datagrundlag og fagudvalgets kliniske erfaring. Vurderingen er forbundet med større usikkerhed end vurderinger, hvor lægemidlets værdi kan kategoriseres.

MEDICINRÅDET VURDERER KVALITETEN AF DE DATA, DER LIGGER TIL GRUND FOR VURDERINGEN AF LÆGEMIDLET (EVIDENSENS KVALITET), I EN AF FØLGENDE GRADE-KATEGORIER:

- **Høj:** Nye studier vil med meget lav sandsynlighed ændre konklusionen.
- **Moderat:** Nye studier vil med lav sandsynlighed ændre konklusionen.
- **Lav:** Nye studier vil med moderat sandsynlighed ændre konklusionen.
- **Meget lav:** Nye studier vil med høj sandsynlighed ændre konklusionen.

2. Begreber og forkortelser

ALK:	*Anaplastic Lymphoma Kinase*
BIRC:	*Blinded Independent Review Committee*
CI:	Konfidensinterval
CNS:	Centralnervesystemet
EGFR:	*Epidermal Growth Factor Receptor*
EMA:	Det Europæiske Lægemiddelagentur (*European Medicines Agency)*
EORTC:	*European Organisation for Research and Treatment of Cancer*
EPAR:	*European Public Assessment Report*
GRADE:	System til at vurdere evidens (*Grading of Recommendations, Assessment, Development and Evaluation*)
HR:	*Hazard ratio*
IASCL:	*International Association for the Study of Lung Cancer*
IRC:	*Independent Review Committee*
ITT:	*Intention-to-treat*
MKRF:	Mindste klinisk relevante forskel
NMA:	Netværksmetaanalyse
NSCLC:	Ikke-småcellet lungekræft (*Non-small-cell lung cancer)*
OR:	*Odds ratio*
OS:	Samlet overlevelse (*Overall Survival)*
PFS:	Progressionsfri overlevelse (*Progression Free Survival)*
PICO:	Population, intervention, komparator og effektmål (*Population, Intervention, Comparator and Outcome)*
QLQ-C30:	*Quality-of-life Questionnaire-Core 30*
RCT:	Randomiseret kontrolleret studie *(Randomised Controlled Trial)*
RECIST:	*Response Evaluation Criteria in Solid Tumors*
ROS1:	*ROS proto-oncogene 1 receptor tyrosine kinase*
RR:	Relativ risiko

SMD: *Standardized Mean Difference*

TKI: *Tyrosin Kinase Inhibitor*

TNM: System til at klassificere tumorer (*Tumor, Node, Metastasis*)

3. Introduktion

Formålet med Medicinrådets vurdering af brigatinib til førstelinjebehandling af uhelbredelig ALK-positiv ikke-småcellet lungekræft er at vurdere den værdi, lægemidlet har sammenlignet med dansk standardbehandling.

Vurderingen er udarbejdet, fordi Medicinrådet har modtaget en endelig ansøgning fra Takeda. Medicinrådet modtog ansøgningen den 25. november 2020.

Det kliniske spørgsmål er:

Hvilken værdi har brigatinib sammenlignet med alectinib i førstelinjebehandling af patienter med uhelbredelig ALK-positiv ikke-småcellet lungekræft?

3.1 Ikke-småcellet lungekræft

Omtrent 4.600 danskere diagnosticeres årligt med lungekræft, og dermed er lungekræft en af de hyppigst forekommende kræftsygdomme i Danmark [1,2]. I slutningen af 2016 levede knap 11.151 personer med lungekræft, mens ca. 3.700 personer årligt dør af lungekræft [2]. Den seneste årsrapport fra Dansk Lunge Cancer Gruppe & Dansk Lunge Cancer Register viser, at 1-årsoverlevelsesraten for samtlige nydiagnosticerede patienter med lungekræft udredt i 2017 uanset stadie var 51,4 %, mens 5-årsoverlevelsen for patienter udredt i 2013 var 15,9 % [3]. Der er altså tale om en sygdom med en dårlig prognose og kort overlevelse efter diagnosetidspunkt for størstedelen af patienterne.

Af de diagnosticerede patienter med lungekræft har ca. 85-90 % ikke-småcellet lungekræft (*non-small-cell lung cancer* (NSCLC)) [4]. NSCLC inddeles på baggrund af histologi/cytologi i planocellulære og ikke-planocellulære tumorer. Fagudvalget estimerer, at ca. 25 % af patienterne har planocellulære tumorer (svarende til ca. 1.000 patienter), og ca. 75 % af patienterne har ikke-planocellulære tumorer (svarende til ca. 3.000 patienter). Langt de fleste ikke-planocellulære tumorer er såkaldte adenokarcinomer.
Symptomer på lungekræft kan være hoste, åndenød og smerter i brystkassen. Hvis kræften spreder sig til andre organer (f.eks. andre strukturer i brystkassen, knogler eller hjerne), kan patienterne få symptomer fra disse i form af kvalme, opkast, smerter, forvirring og kognitive problemer.

Lungekræft er inddelt i stadier afhængigt af udbredelsesgrad, jf. *International Association for the Study of Lung Cancer* (IASLC) *Tumor, Node, Metastasis* (TNM)-klassifikation for lungekræft. Langt de fleste kliniske studier benytter TNM-version 7 [5], mens man i dansk klinisk praksis i dag anvender version 8 [6]. I henhold til version 7 har patienter med spredning til lymfeknuder svarende til N3-sygdom i stadium IIIB, mens stadium IV betegner metastatisk sygdom. Disse stadier betragtes som udgangspunkt som uhelbredelig NSCLC.

Behandlingsmålet for patienter med uhelbredelig NSCLC er symptomlindring og levetidsforlængelse. Patienter med uhelbredelig NSCLC får systemisk behandling i form af kemoterapi, immunterapi og såkaldt targeteret behandling med tyrosinkinasehæmmere (*Tyrosin Kinase Inhibitor* (TKI)). Valg af behandling er afhængig af tumorkarakteristika, hvor tilstedeværelsen af bestemte biomarkører afgør valg af patientens behandling. Hvis en undersøgelse af tumoren viser genetiske eller kromosomale ændringer, som en behandling kan målrettes mod, vil en targeteret behandling være første valg. I dansk klinisk praksis drejer det sig på nuværende tidspunkt om to biomarkører; aktiverende *Epidermal Growth Factor Receptor* (EGFR)-mutationer samt anaplastisk lymfomkinase (ALK)-translokationer [7]. Dertil kommer ROS proto-oncogene 1 receptor tyrosine kinase (ROS1) som en mulig tredje biomarkør, hvortil Medicinrådet er ved at vurdere et targeteret lægemiddel. Targeteret behandling er aktuelt kun relevant for patienter med uhelbredelig NSCLC og ikke for patienter med NSCLC i tidligere stadier, hvor en behandling med sigte på helbredelse er en mulighed.

ALK-positiv NSCLC kendetegnes ved ALK-translokationer i tumorvævet, som aktiverer adskillige signaleringskaskader involveret i tumordannelse. ALK-translokationer forekommer sjældent med en frekvens på under 1 % ud af alle nydiagnosticerede lungekræfttilfælde. I 2018 lå frekvensen på 0,6 % svarende til 30 patienter [3]. Overlevelsen for patienter med ALK-positiv NSCLC er betydeligt bedre end for den samlede gruppe af patienter med lungekræft, når de behandles med en ALK-TKI. I et klinisk forsøg med ALK-TKI'en alectinib til førstelinjebehandling af uhelbredelig ALK-positiv NSCLC (ALEX-studiet) var der en median progressionsfri overlevelse på mindst 34,8 måneder [8].

Omkring halvdelen af patienter med uhelbredelig ALK-positiv NSCLC vil i deres sygdomsforløb få metastaser til centralnervesystemet (CNS), herefter omtalt som hjernemetastaser. Patienter med hjernemetastaser oplever betydelig morbiditet og reduceret livskvalitet – ofte med neurologiske dysfunktioner og kognitive ændringer [9–11].

3.2 Brigatinib

Brigatinib er en tyrosinkinasehæmmer (TKI) med specifik aktivitet mod ALK, IGF-1R, ROS1 og EGFR. ALK er et af de molekyler, som spiller en afgørende rolle for cellevækst og differentiering. Ved at hæmme ALK reduceres aktiviteten af de signaleringskaskader, der har betydning for cellernes overlevelse og deres evne til at formere sig, og som er særligt aktive i ALK-positiv NSCLC [12]. På den måde mindsker brigatinib tumors vækst og spredning.
Brigatinib har fået en indikationsudvidelse fra Det Europæiske Lægemiddelagentur (*European Medicines Agency* (EMA)). Den nye indikation er:

Brigatinib er indiceret som monoterapi til behandling af voksne patienter med ALK-positiv, fremskreden ikke-småcellet lungekræft (NSCLC), som ikke tidligere er behandlet med en ALK-TKI.

Brigatinib har også følgende EMA-indikation, hvortil det også blev anbefalet af Medicinrådet i september 2019:
Brigatinib er indiceret som monoterapi til behandling af voksne patienter med fremskreden ALK-positiv, ikke-småcellet lungecancer (NSCLC), som tidligere har fået behandling med crizotinib.

Brigatinib administreres oralt som én tablet dagligt. Efter syv dages indkøringsperiode med 90 mg én gang dagligt øges dosis til 180 mg én gang dagligt. Lægemidlet gives indtil sygdomsprogression eller intolerable bivirkninger.

Ifølge fagudvalget vil ca. 43 patienter med uhelbredelig ALK-positiv NSCLC årligt være kandidater til førstelinjebehandling med brigatinib i Danmark.

3.3 Nuværende behandling

Målet med behandling af uhelbredelig NSCLC er livsforlængelse og symptomlindring. For patienter med uhelbredelig NSCLC med en genetisk ændring, hvortil der er en targeteret behandling, vil den targeterede behandling være førstevalg for hovedparten af patienterne i nuværende dansk klinisk praksis. Medicinrådets behandlingsvejledning for førstelinjebehandling af uhelbredelig NSCLC beskriver behandlingen af patienter med ALK-translokation og aktiverende EGFR-mutation [7]. Her er alectinib førstevalg til førstelinjebehandling af patienter med uhelbredelig ALK-positiv NSCLC. Fagudvalget forventer, at langt størstedelen af de danske patienter med ALK-translokation bliver behandlet med alectinib i førstelinje.

4. Metode

Medicinrådets protokol for vurdering vedrørende brigatinib 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. Der blev ikke identificeret nogen direkte sammenligning af brigatinib med alectinib. På baggrund af litteratursøgningen er følgende 5 fuldtekstartikler udvalgt:

- En fuldtekstartikel fra ét randomiseret kontrolleret studie (*Randomised Controlled Trial* (RCT) for brigatinib (ALTA-1L-studiet) [13].
- Tre fuldtekstartikler fra to alectinib-RCT'er (ALEX- og ALESIA-studierne) [14–16].
- En fuldtekstartikel fra én netværksmetaanalyse [17].

Alle fuldtekstartikler, undtagen netværksmetaanalysen, er medtaget i vurderingen. Medicinrådet har desuden valgt at tillægge primær analysen fra ALEX-studiet til vurderingen, Peters et al.-publikationen [18], pga. yderligere data (se tabel 4). Derudover indgår EMAs EPAR og produktresumé for brigatinib [19,20] og alectinib [21,22].

Tabel 1 viser de fuldtekstartikler, der indgår i Medicinrådets vurdering af brigatinib til førstelinjebehandling af uhelbredelig ALK-positiv NSCLC.

Tabel 1. Oversigt over fuldtekstartikler, der indgår i vurderingen

	ALTA-1L/NCT02737501	ALEX/NCT02075840	ALESIA/ NCT02838420
Publikationer	Camidge DR et al. Brigatinib Versus Crizotinib in Advanced ALK Inhibitor–Naive ALK-Positive Non–Small Cell Lung Cancer: Second Interim Analysis of the Phase III ALTA-1L Trial. J Clin Oncol. 2020;38(31) [13]	Mok T et al. Updated overall survival and final progression-free survival data for patients with treatment-naive advanced ALK-positive non-small-cell lung cancer in the ALEX study. Ann Oncol. 2020;31(8) [15] Gadgeel S et al. Alectinib versus crizotinib in treatment-naive anaplastic lymphoma kinase-positive (ALK+) non-small-cell lung cancer: CNS efficacy results from the ALEX study. Ann Oncol. 2018;29(11) [14] Peters et al. Alectinib versus Crizotinib in Untreated ALK-Positive Non-Small-Cell Lung Cancer. N Engl J Med. 2017;377(9) [18]	Zhou C et al. Alectinib versus crizotinib in untreated Asian patients with anaplastic lymphoma kinase-positive non-small-cell lung cancer (ALESIA): a randomised phase 3 study. Lancet Respir Med [internet]. 2019;7(5):437–46 [16]
Population	Patienter med uhelbredelig (lokalt avanceret (stadie IIIB) eller metastatisk (stadie IV)) ALK-positiv NSCLC, som ikke tidligere havde modtaget en TKI-hæmmer (ALK-naive)	Patienter med uhelbredelig (avanceret/recurrent (stadie III) eller metastatisk (stadie IV)) ALK-positiv NSCLC, som ikke tidligere havde modtaget behandling mod deres avancerede sygdom (behandlingsnaive)	Patienter med uhelbredelig (stadie IIIb eller IV) ALK-positiv NSCLC, som ikke tidligere havde modtaget behandling mod deres avancerede sygdom (behandlingsnaive)
Intervention	Brigatinib vs. crizotinib	Alectinib vs. crizotinib	Alectinib vs. crizotinib
Data	Inklusion fra 98 centre i Nord- og Sydamerika, Europa, Australien og Asien	Inklusion fra 124 centre i Nordamerika, Europa, Australien og Asien	Inklusion fra 21 centre i Kina, Sydkorea og Thailand

Median opfølgningstid	24,9 måneder i brigatinib-armen	48,2 måneder for OS/37,8 måneder for PFS (investigator-vurderet) i alectinib-armen 18,6 måneder for PFS og CNS-progression (IRC-vurderet) i alectinib-armen	16,2 måneder i alectinib-armen
Respons-evaluering	RECIST 1.1; uafhængig komité	RECIST 1.1; investigator og uafhængig komité	RECIST 1.1; investigator og uafhængig komité

Studie- og baselinekarakteristika (tabel 2) for de inkluderede studier beskrives nedenfor.

ALTA-1L [13]: Dette er et randomiseret, ublindet fase 3-studie, der undersøgte effekten og sikkerheden af førstelinjebehandling med brigatinib sammenlignet med crizotinib hos patienter med uhelbredelig ALK-positiv NSCLC, som ikke tidligere havde modtaget en TKI-hæmmer (ALK-naive). Patienterne blev randomiseret 1:1 til brigatinib, 180 mg én gang dagligt (efter syv dages indkøringsperiode med 90 mg én gang dagligt) (n=137), eller crizotinib, 250 mg to gange dagligt (n=138). Randomiseringen var stratificeret efter tilstedeværelsen af CNS-metastaser (ja el. nej) og tidligere kemoterapi (≥ 1 hel cyklus) for lokalt avanceret eller metastatisk sygdom (ja el. nej). Overkrydsning fra crizotinib til brigatinib var tilladt ved progression. De nyeste opdaterede studiedata (anden interim analyse) stammer fra median opfølgningstid på 24,9 måneder i brigatinib-armen sammenlignet med 15,2 måneder i crizotinib-armen (opfølgning stoppede ved overkrydsning). To blindede uafhængige review-komitéer (*Blinded Independent Review Committees* (BIRCs)) vurderede sygdomsprogression; én for general sygdomsprogression (*all disease*) ved brug af *Response Evaluation Criteria in Solid Tumors* (RECIST) 1.1 og én for intrakraniel CNS-progression. Studiets primære endepunkt var BIRC-vurderet progressionsfri overlevelse (*Progression Free Survival* (PFS)). Sekundære endepunkter af relevans for denne vurdering inkluderede BIRC-vurderet objektiv responsrate (ORR), intrakraniel PFS, samlet overlevelse (*Overall Survival* (OS)), sikkerhed og livskvalitet (målt med EORTC-QLQ-C30). Effektanalyser blev opgjort for *intention-to-treat* (ITT)-populationen, og sikkerhedsanalyser blev opgjort for alle patienter, der modtog mindst én studiedosis.

ALEX [14,15]: Dette er et randomiseret, ublindet fase 3-studie, der undersøgte effekten og sikkerheden af førstelinjebehandling med alectinib sammenlignet med crizotinib hos patienter med uhelbredelig ALK-positiv NSCLC, som ikke tidligere havde modtaget behandling mod deres sygdom. Patienterne blev randomiseret 1:1 til alectinib, 600 mg to gange dagligt (n=152), eller crizotinib, 250 mg to gange dagligt (n=151). Randomiseringen var stratificeret efter performance status (PS 0/1 vs. 2), race (asiatisk vs. ikke-asiatisk) og tilstedeværelsen af CNS-metastaser (ja el. nej). Overkrydsning mellem armene var ikke tilladt per-protokol. Efterfølgende behandling ved progression var op til den behandlende læge og kunne inkludere alectinib efter crizotinib i de lande, hvor behandlingen var godkendt. De nyeste opdaterede studiedata (endelige, modne PFS-data og OS/sikkerhedsdata efter 5 års opfølgning) stammer fra median opfølgningstid på 48,2 måneder for OS (37,8 måneder for PFS) i alectinib-armen sammenlignet med 23,3 måneder for OS (23 måneder for PFS) i crizotinib-armen. Sygdomsprogression blev vurderet af investigator eller af en uafhængig review-komité (*Independent Review Committee* (IRC)) ved brug af RECIST 1.1. IRC lavede to vurderinger af sygdomsprogression: én for general sygdomsprogression (*all disease*) og én for CNS-endepunkter – begge ved brug af RECIST 1.1. IRC vurderede alene sygdomsprogression i forbindelse med den primære analyse og ikke ved senere tidspunkter. Studiets primære endepunkt var investigator-vurderet PFS. Sekundære endepunkter inkluderede IRC-vurderet PFS, IRC-vurderet tid til CNS-progression, OS, sikkerhed og livskvalitet (målt med EORTC-QLQ-C30). Effektanalyser blev opgjort for *intention-to-treat* (ITT)-populationen, og sikkerhedsanalyser blev opgjort for alle patienter, der modtog mindst én studiedosis.

ALESIA [16]: Studiet er magen til ALEX-studiet i design, men inkluderede kun asiatiske patienter. Studiets formål var at sammenligne den kliniske effekt af alectinib med crizotinib for at afgøre, om PFS-effekten vil være sammenlignelig med den, der blev rapporteret i ALEX-studiet. Studiebeskrivelsen af ALEX-studiet (se ovenfor) beskriver også ALESIA.

Tabel 2. Baselinekarakteristika for ALTA-1L-, ALEX- og ALESIA-studierne

	ALTA-1L		ALEX		ALESIA	
	Brigatinib (n=137)	**Crizotinib (n=138)**	**Alectinib (n=152)**	**Crizotinib (n=151)**	**Alectinib (n=125)**	**Crizotinib (n=62)**
Medianalder (range)	58 (27-86)	60 (29-89)	58 (25-88)	54 (18-91)	51 (43-59)	49 (41-59)
Kvinder, n (%)	69 (50)	81 (59)	84 (55)	87 (58)	61 (49)	28 (45)
Race, n (%)						
Ikke-asiatisk	78 (57)	89 (64)	83 (55)	82 (54)		
Asiatisk	59 (43)	49 (36)	69 (45)	69 (46)	125 (100)	62 (100)
ECOG, n (%)						
0/1	131 (96)	132 (96)	142 (93)	141 (93)	121 (97)	61 (98)
2	6 (4)	6 (4)	10 (7)	10 (7)	4 (3)	1 (2)
Stadie, n (%)						
IIIB	8 (6)	12 (9)	4 (3)	6 (4)	13 (10)	4 (7)
IV	129 (94)	126 (91)	148 (97)	145 (96)	112 (90)	58 (94)
CNS-metastaser, n (%)	40 (29)	41 (30)	64 (42)	58 (38)	44 (35)	23 (37)
Tidligere strålebehandling af hjernen, n (%)	18 (13)	19 (14)	26 (17)	21 (14)	8 (6)	5 (8)
Tidligere kemoterapi for avanceret sygdom, n (%)	36 (26)	37 (27)	0	0	0*	0*

* 6 % og 15 % af patienterne i henholdsvis alectinib- og crizotinib-armen havde tidligere modtaget kemoterapi mod lokaliseret sygdom.

Alle studierne undersøger effekten af en behandling med en TKI-hæmmer hos patienter med ALK-positiv NSCLC, som ikke tidligere har modtaget en TKI-hæmmer. Fagudvalget bemærker, at der i ALTA-1L og ALEX-studierne primært indgår patienter i PS 0/1 med stadie IV-sygdom. Der var lidt flere ikke-asiatiske patienter end asiatiske patienter i ALTA-1L- og ALEX-studierne, og ALESIA-studiet inkluderede kun asiatiske patienter. Der var færre patienter, der tidligere havde modtaget strålebehandling af hjernen, i ALESIA-studiet.

Der var betydelige forskelle mellem studierne, både hvad angår studiedesign og studiepopulation. De væsentligste forskelle er fremhævet i tabel 3.

Tabel 3. Væsentligste studieforskelle mellem ALTA-1L- og ALEX/ALESIA-studierne

	ALTA-1L	ALEX og ALESIA
Overkrydsning fra kontrolarmen (crizotinib-armen) til intervention ved progression	Tilladt	Ikke tilladt per-protokol. I ALEX-studiet var efterfølgende behandling ved progression op til den behandlende læge og kunne inkludere alectinib i de lande, hvor behandlingen var godkendt.
CNS-metastaser i crizotinib-armen ved baseline*	30 %	38 % i ALEX og 37 % i ALESIA
Patienter, der tidligere havde modtaget kemoterapi§	Tilladt	Ikke tilladt

* CNS-metastaser har en prognostisk betydning for patienter behandlet med crizotinib, da crizotinib har dårligere penetrans til CNS (lavere koncentration af lægemiddel) og dermed ikke er effektiv mod CNS-metastaser [23–25]. Dette er af mindre betydning for brigatinib og alectinib, som har effekt mod CNS-metastaser [13–16]. Derudover har patienter med CNS-metastaser dårligere prognose [26–29].
§ Patienter uden forudgående behandling vil teoretisk have et bedre behandlingsrespons.

Forskellene oplistet i tabel 3 kan potentielt påvirke størrelsesordenen på effektestimaterne mellem studierne og er dermed af betydning for sammenligneligheden af de tre studiepopulationer.

Fagudvalget bemærker, at patienterne i ALEX-studiet er mest sammenlignelige med den danske patientpopulation, da de fleste patienter i Danmark ikke vil have modtaget kemoterapi før behandling med en TKI-hæmmer. Dog er der flere asiatiske patienter inkluderet i studiet, end der forventes i en dansk patientpopulation. Fagudvalget forventer ikke, at der er forskel på effekt eller bivirkninger i forhold til asiatisk/ikke-asiatisk etnicitet. Derudover er der i begge studier meget få patienter i PS2.

5.1.2 Databehandling og analyse

I dette afsnit er ansøgers datagrundlag og databehandling beskrevet.

Ansøger har indsendt en narrativ sammenligning af brigatinib med alectinib på baggrund af ALTA-1L-, ALEX- og ALESIA-studierne. Dette begrundes i de væsentlige forskelle mellem studiedesign og studiepopulationer, jf. tabel 3 i afsnit 5.1.1, hvilket ikke tillader en statistisk indirekte sammenligning. Medicinrådet understreger, at en narrativ sammenligning er lavere i evidenshierarkiet end en direkte eller indirekte analyse.

Udover den narrative sammenligning af de tre studier har ansøger inkluderet data fra en netværksmetaanalyse (NMA) fra Elliot et al. vedr. behandling af ALK-positiv NSCLC med TKI-hæmmere [17]. I studiet indgik der 13 RCT'er, der sammenlignede crizotinib, ceritinib og alectinib med kemoterapi (7 studier) samt alectinib, ceritinib og brigatinib med crizotinib (6 studier). ALTA-1L-, ALEX- og ALESIA-studierne indgik i netværksmetaanalysen. Medicinrådet bemærker, at antagelsen om "joint randomization" er væsentlig for at kunne sammenligne forskellige studier i en NMA. Det

betyder, at man som udgangspunkt skal forvente, at alle patienterne i studierne kunne være randomiseret til de forskellige behandlinger i ét samlet studie. På grund af de forskelle i studiepopulationer, som er beskrevet i tabel 3, mener Medicinrådet ikke, at forudsætningerne for en NMS er opfyldt, og resultaterne af NMA'en skal derfor tolkes med store forbehold. Blandt andet er populationerne forskellige hvad angår tidligere behandlinger, og effektmål er ikke opgjort på samme måde på tværs af studierne.

Medicinrådet vurderer, at NMA'en ikke bidrager med større sikkerhed angående estimaterne eller anden information, som kan ændre konklusionen baseret på den narrative sammenligning. Medicinrådet gør opmærksom på, at hvis det vurderes, at en indirekte sammenligning ikke er forsvarlig, er det heller ikke forsvarligt at bruge en større analyse som en NMA. Derfor er fagudvalgets vurdering af klinisk værdi udelukkende baseret på den narrative sammenligning.

Datagrundlaget for den narrative sammenligning af brigatinib og alectinib er følgende:

- OS- og PFS-data fra ALTA-1L-, ALEX- og ALESIA-studierne. Kun IRC-vurderet PFS-data fra alectinib studierne er medtaget.
- Sikkerheds- (behandlingsophør grundet uønskede hændelser og uønskede hændelser grad 3-4) og livskvalitetsdata fra ALTA-1L-, ALEX- og ALESIA-studierne. I protokollen ønskede Medicinrådet data på gennemsnitlig ændring over tid fra baseline i EORTC-QLQ-C30. Ansøger har kun indsendt data for dette fra ALTA-1L-studiet. Derudover har ansøger indsendt en HR for gennemsnitlig tid til forværring (≥ 10 points) for ALTA-1L- og ALEX-studierne. ALESIA-studiet rapporterer ikke nogen livskvalitetsdata.
- CNS-progression-data fra ALTA-1L-, ALEX- og ALESIA-studierne. I protokollen ønskede Medicinrådet data på median CNS-progression, som også kaldes intrakraniel PFS, hos *intention-to-treat* (ITT)-populationen, dvs. en analyse, der kun omfatter progression i hjernen. CNS-progression er opgjort forskelligt i studierne, og det besværliggør enhver sammenligning. I ALTA-1L-studiet er der data på intrakraniel PFS, men kun opdelt på subpopulationsniveau (patienter med og uden CNS-metastaser ved baseline) [13]. I brigatinibs EPAR er der data fra en *competing risk*-analyse for CNS-progression i ITT-populationen, præsenteret som HR [19]. I ALEX- og ALESIA-studierne er der data på tid til CNS-progression i ITT-populationen, rapporteret som en *cause-specific* HR ved første data cut-off efter median opfølgningstid på 18,6 måneder i alectinib-armen i ALEX-studiet [18] og 16,2 måneder i ALESIA-studiet [16]. Efterfølgende er der publiceret detaljeret CNS-data fra ALEX-studiet, men kun på subpopulationsniveau, og som ikke kan sammenlignes med data på brigatinib pga. forskel i analyserne [14]. I den narrative sammenligning vil HR fra en *competing risk*-analyse for brigatinib og *cause-specific* HR for alectinib indgå i vurderingen.

Jf. Medicinrådets metoder tillader datagrundlaget ikke, at lægemidlet bliver placeret i en specifik kategori vedrørende lægemidlets samlede værdi, men fagudvalget vil vurdere lægemidlet ud fra de nævnte studier i en narrativ sammenligning.

5.1.3 Evidensens kvalitet

Da vurderingen af brigatinib er baseret på en narrativ sammenligning med alectinib, kan Medicinrådet ikke anvende GRADE til at vurdere kvaliteten af evidensen. Medicinrådet har vurderet studierne ved Cochrane risk of bias tool 2.0. Vurdering af risikoen for bias ved de enkelte studier fremgår af bilag 1. Overordnet er det vurderet, at der er lav risiko for bias ved alle tre inkluderede studier.

Samlet vurderer Medicinrådet, at evidensens kvalitet er meget lav, hvilket betyder, at nye studier med høj sandsynlighed kan ændre konklusionen.

5.1.4 Effektestimater og kategorier

Tabel 4 giver et overblik over effektestimaterne fra ALTA-1L-, ALEX- og ALESIA-studierne, som indgår i den narrative sammenligning.

Tabel 4. Effektestimater fra ALTA-1L-, ALEX- og ALESIA-studierne

Effektmål (MKRF)	ALTA-1L[1] (brigatinib vs. crizotinib)		ALEX[2] (alectinib vs. crizotinib)		ALESIA[3] (alectinib vs. crizotinib)		Aggregeret værdi for effektmålet
	Absolut forskel i forhold til crizotinib (95 % CI)	Relativ forskel i forhold til crizotinib (95 % CI)	Absolut forskel i forhold til crizotinib (95 % CI)	Relativ forskel i forhold til crizotinib (95 % CI)	Absolut forskel i forhold til crizotinib (95 % CI)	Relativ forskel i forhold til crizotinib (95 % CI)	
Median OS (MKRF 3 mdr.)	NR	HR = 0,92 (0,57; 1,47)	NR i alectinib 57,4 mdr. i crizotinib	HR = 0,67 (0,46; 0,98)	NR	HR = 0,28 (0,12; 0,68)	Kan ikke kategoriseres
Behandlingsophør grundet uønskede hændelser (MKRF 5 %-point)	4 %-point (-3,57; 11,65)	RR = 1,43 (0,71; 2,87)	-0,1 %-point (-7,93; 8,14)	RR = 1,0 (0,58; 1,73)	-3 %-point (-4,90; 13,48)	RR = 0,72 (0,27; 1,93)	Kan ikke kategoriseres
CNS-progression (MKRF 3 mdr.)	ND	HR = 0,30 (0,17; 0,53)*	ND	HR = 0,16 (0,10; 0,28)**	ND	HR = 0,14 (0,06; 0,30)**	Kan ikke kategoriseres
Median PFS (MKRF 3 mdr.)	13 mdr.†	HR = 0,49 (0,35; 0,68) †	15,3 mdr.‡	HR = 0,50 (0,36; 0,70)‡	NR i alectinib 11,1 mdr. i crizotinib	HR = 0,37 (0,22; 0,61)‡	Kan ikke kategoriseres
Uønskede hændelser grad 3-4 (MKRF 5 %-point)	12 %-point (0,84; 22,74)	RR = 1,19 (1,00; 1,41)	-4,3 %-point (-6,85; 15,30)	RR = 0,94 (0,78; 1,13)	-19 %-point (4,34; 33,17)	RR = 0,60 (0,41; 0,87)	Kan ikke kategoriseres
Livskvalitet (Gennemsnitlig ændring fra baseline i EORTC-QLQ-C30) (MKRF 10 point)	3,1 point (-0,7; 8,0)	ND	ND	ND	ND	ND	Kan ikke kategoriseres

Livskvalitet (Gennemsnitlig tid til forværring i EORTC-QLQ-C30 (≥ 10 point))	18,4 mdr.	HR = 0,70 (0,40; 1,00)	ND	HR = 0,72 (0,38; 1,39)	ND	ND	Kan ikke kategoriseres

Konklusion	
Samlet kategori for lægemidlets værdi	**Kan ikke kategoriseres**. På det foreliggende datagrundlag er det ikke muligt at vurdere, om der er klinisk relevante forskelle på brigatinib og alectinib på de undersøgte effektmål. Samlet vurderer fagudvalget, at brigatinib og alectinib forekommer lige effektive.
Kvalitet af den samlede evidens	Meget lav

CI = Konfidensinterval, HR = Hazard Ratio, RR = Relativ risiko, NR = *Not reached*, ND = *No data*. *HR fra competing risk analyse på ITT-populationen. ***Cause-specific* HR i ITT-populationen. †BIRC-vurderet. ‡IRC-vurderet.
[1] Opfølgningstiden var 24,9 mdr. i brigatinib-armen og 15,2 mdr. i crizotinib-armen for alle effektmål. Overlevelsesdata, behandlingsophør, PFS, uønskede hændelser grad 3-4 og livskvalitet (gennemsnitlig tid til forværring i EORTC-QLQ-C30) fra Camidge et al. [13], CNS-progression og livskvalitet (gennemsnitlig ændring fra baseline i EORTC-QLQ-C30) fra brigatinibs EPAR [19].
[2] Overlevelsesdata, behandlingsophør og uønskede hændelser grad 3-4 er fra Mok et al. [15] med en opfølgningstid på 48,2 mdr. i alectinib-armen og 23,3 mdr. i crizotinib-armen. CNS-progression og PFS er fra Peters et al. [18] med opfølgningstid på 18,6 mdr. i alectinib-armen og 17,6 mdr. i crizotinib-armen. Data på livskvalitet (gennemsnitlig tid til forværring i EORTC-QLQ-C30) stammer fra Medicinrådets vurdering af alectinib [30].
[3] Alle data stammer fra Zhou et al. med opfølgningstid på 16,2 mdr. i alectinib-armen og 15,0 mdr. i crizotinib-armen [16].

Overlevelse
Som beskrevet i protokollen er effektmålet overlevelse kritisk for vurderingen af lægemidlets værdi for patienterne, fordi der er tale om uhelbredelig sygdom, hvor forbedret samlet overlevelse (OS) med mindst mulig toksicitet vurderes afgørende. Der findes mange relevante effektmål for overlevelse, og i denne sammenhæng har fagudvalget vurderet median OS som det mest relevante effektmål. Den mindste klinisk relevante forskel er 3 måneder.

Hverken ALTA-1L-, ALEX- eller ALESIA-studierne har modne OS-data. OS-data fra alle studier skal derfor tolkes med stor forsigtighed.

Efter median opfølgningstid på 24,9 og 15,2 måneder var median OS ikke opnået i henholdsvis brigatinib- og crizotinib-armen i ALTA-1L-studiet [13]. Overlevelseskurven i Camidge et al. [13] viser, at der stadigvæk ikke ses adskillelse af de to arme, hvilket indikerer, at der ikke er forskel mellem behandlingerne. Dette skyldes højst sandsynligt den relativt korte opfølgningstid. OS-raten ved 2 år var 76 % og 74 % i hhv. brigatinib- og crizotinib-armen. HR ligger på 0,92 (0,57; 1,47) og dækker over både positiv eller negativ merværdi (bredt konfidensinterval, hvor den øvre grænse overstiger 1). Det fremhæves desuden, at overkrydsning fra crizotinib til brigatinib ved progression var tilladt i studiet. Det betyder, at OS-data reflekterer effekten af sekventiel behandling med TKI frem for den isolerede effekt af crizotinib alene på overlevelse.

Efter median opfølgningstid på 48,2 måneder var median OS ikke opnået i alectinib-armen i ALEX-studiet [15]. I crizotinib-armen var median OS 57,4 måneder efter median opfølgningstid på 23,3 måneder. Overlevelseskurven i Mok et al. [15] viser, at de to arme adskilles efter ca. 18 måneder og forbliver adskilte. Det indikerer, at der er forskel mellem effekten af de to behandlinger. OS-raten ved 5 år var 62,5 % og 45,5 % i hhv. alectinib- og crizotinib-armen. HR ligger på 0,67 (0,46; 0,98). Efter 48 måneder skal data dog tolkes med forsigtighed pga. mange censureringer. Det indikerer, at den aflæste median OS på 57,4 måneder er behæftet med usikkerhed.

Efter median opfølgningstid på 16,2 og 15,0 måneder var median OS ikke opnået i henholdsvis alectinib- og crizotinib-armen i ALESIA-studiet [16]. HR ligger på 0,28 (0,12; 0,68). Data skal dog tolkes med stor forsigtighed pga. kort opfølgningstid set i lyset af patienternes prognose.

Fagudvalget finder, at en forskel mellem brigatinib og alectinib på effektmålet ikke kan vurderes. Datagrundlaget besværliggør sammenligning af OS-data for brigatinib og alectinib, da data stadigvæk er umodne i alle studier, og der er stor forskel i opfølgningstiden. Derudover er der forskel i studiedesign, hvor overkrydsning var tilladt i ALTA-1L-studiet i modsætning til ALEX-studiet. Dette påvirker OS-data og dermed sammenligneligheden af studierne. Fagudvalget understreger dog, at ALEX-studiet viser, at førstelinjebehandling med alectinib til patienter med ALK-positiv NSCLC er mere effektiv end crizotinib. Sammenlagt kan effekten af brigatinib sammenlignet med alectinib på effektmålet *overlevelse* **ikke kategoriseres**.

Behandlingsophør grundet uønskede hændelser
Som beskrevet i protokollen er effektmålet behandlingsophør grundet uønskede hændelser kritisk for vurderingen af lægemidlets værdi for patienterne, fordi Medicinrådet finder, at ophør med en potentielt effektiv behandling er kritisk for patienterne. For targeterede behandlinger forventes der ikke at være effekt efter ophør med behandlingen (som der evt. kan være for *check point inhibitor*-immunterapi), og patienterne kan risikere hurtig udvikling af sygdommen, hvis behandlingen stoppes (*flare up*). Den mindste klinisk relevante forskel er 5 %.

13 % og 9 % af patienterne ophørte med behandling med hhv. brigatinib og crizotinib i ALTA-1L-studiet [13]. Den relative risiko var 1,43 (0,71; 2,87).

14,5 % og 14,6 % af patienterne ophørte med behandling med hhv. alectinib og crizotinib i ALEX-studiet [15]. Den relative risiko var 1,0 (0,58; 1,73).

I ALESIA-studiet ophørte 7,0 % og 10,0 % af patienterne behandling med hhv. alectinib og crizotinib [16]. Den relative risiko var 0,72 (0,27; 1,93).

For alle studier dækker den relative risiko over både positiv eller negativ merværdi (bredt konfidensinterval, hvor den øvre grænse overstiger 1). Derfor er det på baggrund af den relative risiko ikke muligt at konkludere, om der er forskel mellem brigatinib eller alectinib og den fælles komparator crizotinib hvad angår behandlingsophør.

Pga. den narrative sammenligning kan effekten af brigatinib sammenlignet med alectinib på effektmålet *behandlingsophør grundet uønskede hændelser* **ikke kategoriseres**. Fagudvalget fremhæver, at opfølgningstiden i ALEX-studiet er markant længere end i ALTA-1L- og ALESIA-studierne, hvorfor flere behandlingsophør kan registreres i ALEX-studiet. Fagudvalget finder, at der på det foreliggende datagrundlag ikke kan vurderes, om der er klinisk relevante forskelle mellem brigatinib og alectinib hvad angår dette effektmål.

CNS-progression
Som beskrevet i protokollen er effektmålet CNS-progression vigtigt for vurderingen af lægemidlets værdi for patienterne, fordi patienter med ALK-positiv NSCLC ofte har spredning til hjernen, hvilket medfører betydelig morbiditet. Effektmålet omfatter både CNS-progression hos patienter med hjernemetastaser på inklusionstidspunktet og patienter, der får hjernemetastaser under behandlingen. Den mindste klinisk relevante forskel i median tid til CNS-progression er 3 måneder, når CNS-progression opgøres som et *time-to-event*-effektmål, hvilket foretrækkes.

Data bliver præsenteret som en HR for CNS-progression i ITT-populationen. Pga. forskel i opgørelsen af effektmålet mellem ALTA-1L- og ALEX/ALESIA-studierne, jf. afsnit 5.1.2., er enhver sammenligning af data mellem studierne forbundet med stor usikkerhed.

I ALTA-1L-studiet er der rapporteret en HR på 0,30 (0,17; 0,53) i sammenligningen mellem brigatinib og crizotinib i ITT-populationen [19].

I ALEX-studiet er der rapporteret en HR på 0,16 (0,10; 0,28) i sammenligningen mellem alectinib og crizotinib i ITT-populationen [18].

I ALESIA-studiet er der rapporteret en HR på 0,14 (0,06; 0,30) i sammenligningen mellem alectinib og crizotinib i ITT-populationen [16].

Alle tre studier viser, at både brigatinib og alectinib er markant mere effektive mod CNS-progression end crizotinib, da de i modsætning til crizotinib kan krydse blod-hjerne-barrieren. Da crizotinib ikke er effektiv mod CNS-metastaser [23–25], er frekvensen af CNS-metastaser ved baseline en vigtig prognostisk markør i patienter, der behandles med crizotinib. Patienter behandlet med crizotinib er i højere risiko for at udvikle CNS-metastaser end patienter behandlet med alectinib eller brigatinib, jf. de tre studier. I den sammenhæng er det vigtigt at fremhæve, at flere patienter i crizotinib-armen i alectinib-studierne havde CNS-metastaser ved baseline (38/37 % i ALEX/ALESIA-studierne vs. 30 % i ALTA-1L-studiet). Derudover bemærker fagudvalget, at studierne adskilte sig hvad angår opgørelsen af CNS-progression, hvor strålebehandling af CNS-metastaser i ALTA-1L-studiet blev defineret som progression i modsætning til i ALEX og ALESIA.

Pga. den narrative sammenligning kan værdien af brigatinib sammenlignet med alectinib på effektmålet *CNS-progression* **ikke kategoriseres**. Fagudvalget fremhæver, at pga. forskel i opgørelsen af effektmålet i ALTA-1L-studiet sammenlignet med ALEX/ALESIA-studierne samt forskel i frekvens af patienter med CNS-metastaser ved baseline er enhver sammenligning af data mellem studierne forbundet med stor usikkerhed. Derfor vurderer fagudvalget, at der på det foreliggende datagrundlag ikke kan vurderes, om der er klinisk relevante forskelle mellem brigatinib og alectinib hvad angår effektmålet.

Progressionsfri overlevelse (PFS)
Progressionsfri overlevelse (PFS) bliver anvendt til at vurdere, hvor lang tid der går, inden sygdommen udvikler sig. PFS er defineret som tiden fra randomisering til første dokumentation af progression i henhold til Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 [31] eller dødsfald. Patienter tåler generelt behandling med en TKI godt i sammenligning med andre typer behandling, såsom kemoterapi. Fagudvalget vurderer derfor, at det har stor betydning for patienterne at forblive i behandling med en TKI længst muligt pga. den favorable bivirkningsprofil. I senere behandlingslinjer vil patienterne blive tilbudt platinbaseret kemoterapi, der betragtes som mere bivirkningstungt. Som beskrevet i protokollen er effektmålet PFS vigtigt for vurderingen af lægemidlets værdi for patienterne, fordi det i dette tilfælde afspejler patienternes symptombyrde og varighed af respons og ikke er et surrogat for overlevelse. Den mindste klinisk relevante forskel i median PFS er 3 måneder.

PFS-data i tabel 4 stammer fra vurderinger foretaget af de uafhængige komitéer.

Efter median opfølgningstid på 24,9 og 15,2 måneder var median PFS 24,0 og 11,0 måneder i henholdsvis brigatinib- og crizotinib-armen i ALTA-1L-studiet, som giver en effektforskel på 13 måneder til fordel for brigatinib [13]. HR ligger på 0,49 (0,35; 0,68).

Efter median opfølgningstid på 18,6 og 17,6 måneder var median PFS 25,7 og 10,4 måneder i henholdsvis alectinib- og crizotinib-armen i ALEX-studiet, som giver en effektforskel på 15,3 måneder til fordel for alectinib [18]. HR ligger på 0,50 (0,36; 0,70). I Mok et al. er der rapporteret investigator-vurderet PFS-data efter længere opfølgningstid på 37,8 og 23,0 måneder i hhv. alectinib- og crizotinib-armen. Forskellen mellem armene blev endnu større efter længere opfølgningstid. Her rapporteres en median PFS på 34,8 måneder i alectinib-armen og 10,9 måneder i crizotinib-armen og en HR på 0,43 (0,32; 0,58) [15].

Efter median opfølgningstid på 16,2 og 15,0 måneder var median PFS ikke opnået i alectinib-armen og 10,7 måneder i crizotinib-armen i ALESIA-studiet [16]. HR ligger på 0,37 (0,22; 0,61).

Fagudvalget ønsker at fremhæve nogle studieforskelle, som påvirker PFS-data og dermed enhver sammenligning af studierne. I ALTA-1L-studiet blev strålebehandling af CNS-metastaser defineret som progression i modsætning til ALEX- og ALESIA-studierne, som er af betydning for opgørelsen af PFS. At strålebehandling af CNS-metastaser var undladt i opgørelsen af PFS i ALEX- og ALESIA-studierne kan potentielt øge behandlingseffekten i disse studier sammenlignet med ALTA-1L-studiet. Derudover var inklusion af patienter, der tidligere har modtaget behandling med kemoterapi, tilladt i ALTA-1L-studiet, men ikke i ALEX-studiet. Det kan potentielt påvirke effektestimaterne negativt, da patienter uden forudgående behandling teoretisk har bedre behandlingsrespons, hvilket dermed har indflydelse på sammenligning af PFS-data på tværs af studierne.

Grundet den narrative sammenligning kan effekten af brigatinib sammenlignet med alectinib på effektmålet *progressionsfri overlevelse* **ikke kategoriseres.** Fagudvalget bemærker, at de rapporterede HR er sammenlignelige mellem ALTA-1L- og ALEX-studierne, og dermed indikerer, at der ikke er forskel mellem brigatinib og alectinib hvad angår effektmålet. ALESIA-studiet adskiller sig fra de to andre studier med en lavere HR – muligvis pga. den kortere opfølgningstid, og fordi studiet kun inkluderede asiatiske patienter. Fagudvalget understreger, at forskellen i opgørelsen af effektmålet i ALTA-1L-studiet sammenlignet med ALEX-/ALESIA-studierne og forskellen i inklusion af patienter, der tidligere har modtaget kemoterapi, gør, at enhver sammenligning af data mellem studierne er forbundet med stor usikkerhed. På det foreliggende datagrundlag kan fagudvalget derfor ikke vurdere, om dette er tilfældet, eller om der er klinisk relevante forskelle mellem brigatinib og alectinib hvad angår PFS.

Uønskede hændelser

Som beskrevet i protokollen er effektmålet uønskede hændelser vigtigt for vurderingen af lægemidlets værdi for patienterne, fordi forekomst af uønskede hændelser grad 3-4 er et udtryk for alvorlig toksicitet af lægemidlet [32]. Medicinrådet ønskede data på uønskede hændelser grad 3-4, hvor den mindste klinisk relevante forskel er 5 %-point i andelen af patienter, der får hændelser af grad 3-4. Derudover ønskede Medicinrådet en gennemgang af alle uønskede hændelser, der opstår ved behandling med brigatinib og alectinib, med henblik på at vurdere hændelsernes type, håndterbarhed og reversibilitet. Der ønskes desuden en liste med alle uønskede hændelser, som fører til behandlingsophør, og deres frekvens i både komparator- og interventionsgruppen.

Uønskede hændelser grad 3-4

I ALTA-1L-studiet oplevede 73 % af patienterne i brigatinib-armen uønskede hændelser grad 3-4 sammenlignet med 61 % af patienterne i crizotinib-armen [13]. Den relative risiko var 1,19 (1,00; 1,41).

I ALEX-studiet oplevede 52 % af patienterne i alectinib-armen uønskede hændelser grad 3-4 sammenlignet med 56,3 % af patienterne i crizotinib-armen [13]. Den relative risiko var 0,94 (0,78; 1,13).

I ALESIA-studiet oplevede 29 % af patienterne i alectinib-armen uønskede hændelser grad 3-4 sammenlignet med 48 % af patienterne i crizotinib-armen [13]. Den relative risiko var 0,60 (0,41; 0,87).

Studierne adskiller sig hvad angår opgørelsen af bivirkninger. I ALTA-1L-studiet blev sygdomsprogression opgjort som bivirkning i modsætning til de to andre studier. Dermed er der risiko for, at flere hændelser bliver registeret som bivirkning i ALTA-1L-studiet sammenlignet med ALEX- og ALESIA-studierne. Derudover var der forskel i opfølgningstiden mellem studierne, hvor flere hændelser kunne registreres som bivirkning i ALEX-studiet pga. længere opfølgningstid. Fagudvalget kan heller ikke udelukke, at forskellen mellem studiepopulationerne, hvad angår tidligere behandling med kemoterapi, kan medvirke til den rapporterede forskel i frekvensen af uønskede hændelser mellem studierne.

Pga. den narrative sammenligning kan effekten af brigatinib sammenlignet med alectinib på effektmålet *uønskede hændelser grad 3-4* **ikke kategoriseres.** Fagudvalget bemærker, at frekvensen af grad 3-4 uønskede hændelser er højere ved behandling med brigatinib i ALTA-1L-studiet sammenlignet med alectinib i ALEX-studiet på trods af næsten dobbelt så lang opfølgningstid i ALEX-studiet. Det er dog usikkert, om det skyldes forskellen i opgørelsen af sikkerhed i studierne, forskellen i studiepopulationerne, eller om der er reel forskel i frekvensen af bivirkninger mellem de to lægemidler. Derfor vurderer fagudvalget, at der på det foreliggende datagrundlag ikke kan vurderes, om der er klinisk relevante forskelle mellem brigatinib og alectinib hvad angår effektmålet.

Kvalitativ gennemgang af uønskede hændelser

Gennemgangen af bivirkningsprofilerne tager udgangspunkt i lægemidlernes produktresuméer, hvor bivirkningsprofilerne er sammenlagt fra de underliggende studier [20,21].

For begge lægemidler er de mest almindelige bivirkninger fra mave-tarm-kanalen, hæmatologiske bivirkninger, forhøjede levertal, udslæt og muskelsmerter (myalgi).

I brigatinibs produktresumé er der særlig advarsel og forsigtighedsregler vedr. interstitiel lungesygdom (ILS)/pneumonitis, hypertension, bradykardi, synsforstyrrelser, forhøjet kreatinkinase og pancreasenzymer, levertoksicitet og hyperglykæmi. I ALTA-1L-studiet fik i alt 2,9 % af patienterne en vilkårlig grad (any grade) interstitiel lungesygdom (ILS)/pneumonitis tidligt i behandlingen (inden for 8 dage), heraf grad 3-4 ILS/pneumonitis hos 2,2 % af patienterne. Der var ingen tilfælde af letal ILS/pneumonitis. Desuden fik 3,7 % af patienterne pneumonitis senere i behandlingen.

I alectinibs produktresumé er der særlig advarsel og forsigtighedsregler vedr. ILS/pneumonitis, bradykardi, levertoksicitet, svær myalgi og forhøjet kreatinkinase, gastrointestinal perforation og fotosensitivitet. Frekvensen af ILS/pneumonitis ved behandling med alectinib er lavere end ved brigatinib (0,7 % for alle grader og 0,2 % for grad 3-4 fra de underliggende alectinib-studier).

Fagudvalget vurderer, at behandling med begge lægemidler er forbundet med en række uønskede hændelser, som generelt kan betragtes som sammenlignelige. Fagudvalget understreger dog, at i modsætning til brigatinib er der en del klinisk erfaring på danske klinikker med behandling med alectinib, som har en håndterbar bivirkningsprofil og er veltolereret hos patienterne. Fagudvalget udtrykker en bekymring for, at behandling med brigatinib tilsyneladende er forbundet med en højere frekvens af ILS/pneumonitis og hypertension end alectinib, som muligvis er irreversible. På det foreliggende datagrundlag kan det dog ikke konkluderes, om det skyldes en reel forskel i bivirkningerne ved de to lægemidler, eller om det skyldes den forskel, der er i de underliggende studier, f.eks. tidligere behandling med kemoterapi (der potentielt kan give flere bivirkninger end hos patienter uden forudgående systemisk behandling).

Samlet vurdering af uønskede hændelser

Pga. den narrative sammenligning kan effekten af brigatinib sammenlignet med alectinib på effektmålet uønskede hændelser **ikke kategoriseres**. Fagudvalget bemærker, at der i brigatinib-studiet er flere grad 3-4 bivirkninger end i alectinib-studierne, men det vides ikke, om det skyldes forskel i opgørelsen af sikkerhed mellem studierne, forskel i studiepopulationerne eller en reel forskel i bivirkninger. Gennemgangen af bivirkningsprofilerne viser, at begge lægemidler kan medføre en række uønskede hændelser, hvor fagudvalget særligt udtrykker bekymring for ILS/pneumonitis og hypertension rapporteret ved behandling med brigatinib, og i hvilket omfang de er irreversible.

Livskvalitet

Som beskrevet i protokollen er effektmålet livskvalitet vigtigt for vurderingen af lægemidlets værdi for patienterne. Medicinrådet ønskede data på gennemsnitlig ændring over tid fra baseline i EORTC-QLQ-C30. Den mindste klinisk relevante forskel er ≥ 10 point.

Kun ALTA-1L-studiet opgør data som gennemsnitlig ændring fra baseline. Her var forskellen mellem brigatinib og crizotinib 3,1 point (-0,7; 8,0) til fordel for brigatinib. Der foreligger desuden data på gennemsnitlig tid til forværring i EORTC-QLQ-C30 (≥ 10 point). Her var forskellen mellem brigatinib og crizotinib 18,4 måneder.

Fra både ALTA-1L- og ALEX-studierne foreligger der en HR på gennemsnitlig tid til forværring i EORTC-QLQ-C30 (≥ 10 point). Den er sammenlignelig mellem studierne og ligger på 0,70 (0,49; 1,00) og 0,72 (0,38; 1,39) i hhv. ALTA-1L- og ALEX-studierne.
Pga. den narrative sammenligning kan effekten af brigatinib sammenlignet med alectinib på effektmålet *livskvalitet* **ikke kategoriseres.** Fagudvalget finder, at der på det foreliggende datagrundlag ikke kan vurderes, om der er klinisk relevante forskelle mellem brigatinib og alectinib hvad angår effektmålet.

5.1.5 Fagudvalgets konklusion

Fagudvalget vurderer, at den samlede værdi af brigatinib sammenlignet med alectinib til førstelinjebehandling af patienter med uhelbredelig ALK-positiv ikke-småcellet lungekræft **ikke kan kategoriseres**.

OS-data er endnu ikke modne, og median OS for brigatinib og alectinib er ikke nået i de underliggende studier. For CNS-progression og PFS er der modne data, men på grund af adskillige forskelle mellem studierne, er det ikke muligt at drage konklusioner om en eventuel klinisk forskel mellem brigatinib og alectinib hvad angår effektmålene.

Hvad angår sikkerhedsprofilen vurderer fagudvalget, at begge lægemidler kan medføre en række uønskede hændelser, hvor fagudvalget særligt udtrykker bekymring for ILS/pneumonitis og hypertension rapporteret ved behandling med brigatinib, og i hvilket omfang de er irreversible. På det foreliggende datagrundlag kan det dog ikke konkluderes, om det skyldes en reel forskel i bivirkningerne forbundet med de to lægemidler, eller om det skyldes den forskel, der er i de underliggende studier.

Samlet vurderer fagudvalget på baggrund af den narrative sammenligning, at brigatinib og alectinib forekommer lige effektive til førstelinjebehandling af patienter med uhelbredelig ALK-positiv ikke-småcellet lungekræft. Sikkerhedsprofilerne for de to lægemidler er forskellige, hvor begge lægemidler kan medføre en række uønskede hændelser. På det foreliggende datagrundlag samt fagudvalgets kliniske erfaring kan det dog ikke konkluderes, om forskellen i sikkerhedsprofilerne er af klinisk betydning eller om den ene bivirkningsprofil er mere fordelagtig for patienterne end den anden.

6. Relation til behandlingsvejledning

Fagudvalget formoder ud fra det eksisterende datagrundlag og klinisk erfaring, at brigatinib og alectinib foreløbigt kan betragtes som ligestillede til patienter med uhelbredelig ALK-positiv ikke-småcellet lungekræft.

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8. Sammensætning af fagudvalg og kontaktinformation til Medicinrådet

Medicinrådets fagudvalg vedrørende lungekræft

Sammensætning af fagudvalg	
Formand	**Indstillet af**
Halla Skuladottir *Overlæge*	Lægevidenskabelige Selskaber og Region Midtjylland
Medlemmer	**Udpeget af**
Kan ikke opfylde Medicinrådets habilitetskrav	Region Nordjylland
Lotte Holm Land *Afdelingslæge*	Region Syddanmark
Jeanette Haar Ehlers *Overlæge*	Region Sjælland
Udpegning i gang	Region Hovedstaden
Annie Lorenzen *Klinisk farmaceut*	Dansk Selskab for Sygehusapoteksledelse
Nina Hannover Bjarnason *Overlæge*	Dansk Selskab for Klinisk Farmakologi
Amal Durakovic *Overlæge*	Dansk Lungemedicinsk Selskab
Morten Hiul Suppli *Afdelingslæge*	Dansk Selskab for Klinisk Onkologi
Selskabet ser sig repræsenteret af øvrige medlemmer og ønsker derfor ikke at udpege yderligere medlemmer	Dansk Onkologisk Lungercancer Gruppe
Nille Behrendt *Overlæge*	Dansk Patologiselskab
Selskabet ser sig repræsenteret af øvrige medlemmer og ønsker derfor ikke at udpege yderligere medlemmer	Dansk Lunger Cancer Gruppe

Sammensætning af fagudvalg	
Finn Klausen Patient/patientrepræsentant	Danske Patienter
Tidligere medlemmer, som har bidraget til arbejdet	**Udpeget af**
Stefan Starup Jeppesen *Overlæge*	Region Syddanmark
Lotte Engell-Nørregård *Overlæge*	Region Hovedstaden
Lisbeth Søbæk Hansen Patient/patientrepræsentant	Danske Patienter

Medicinrådets sekretariat

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

9. Versionslog

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

10. Bilag 1: Evidensens kvalitet

10.1 Cochrane – risiko for bias

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

Tabel 5. Vurdering af risiko for bias ALTA-1L, NCT02737501

Bias	Risiko for bias	Uddybning
Risiko for bias i randomiserings-processen	**Lav**	Metode for randomisering er ikke beskrevet, men patienternes baselinekarakteristika i studiet indikerer ikke et problem med randomisering.
Effekt af tildeling til intervention	**Lav**	Open-label-studie, men studieresultaterne indikerer ikke afvigelser i hverken allokering eller adhærence til interventionen, der kan resultere i bias.
Manglende data for effektmål	**Lav**	Der foreligger data for studiets effektmål. Alle data rapporteres for ITT-populationen.
Risiko for bias ved indsamlingen af data	**Lav**	Sygdomsprogression vurderet af to blindede uafhængige review-komitéer.
Risiko for bias ved udvælgelse af resultater, der rapporteres	**Lav**	Data rapporteres i henhold til metodebeskrivelsen.
Overordnet risiko for bias	**Lav**	Den overordnede risiko for bias er lav, da alle domæner har lav risiko for bias

Tabel 6. Vurdering af risiko for bias ALEX, NCT02075840

Bias	Risiko for bias	Uddybning
Risiko for bias i randomiserings-processen	**Lav**	Block-stratificeret randomisering af patienter ved brug af et interaktivt eller web-baseret system.
Effekt af tildeling til intervention	**Lav**	Open-label studie, men studieresultaterne indikerer ikke afvigelser i hverken allokering eller adhærence til interventionen, der kan resultere i bias.
Manglende data for effektmål	**Lav**	Der foreligger data for studiets effektmål. Alle data rapporteres for ITT-populationen.
Risiko for bias ved indsamlingen af data	**Forbehold**	Sygdomsprogression vurderet af investigator og uafhængig review-komité. Da studiet var open-label, kan det potentielt have påvirket vurderingen af studiets endepunkter. Overlevelse vil ikke påvirkes af open-label studiedesign.
Risiko for bias ved udvælgelse af resultater, der rapporteres	**Lav**	Data rapporteres i henhold til metodebeskrivelsen.
Overordnet risiko for bias	**Lav**	Vurderingen af de fleste endepunkter i studiet laves af investigator, som potentiel kan give bias, når der er tale om et open-label studiedesign. Risikoen vurderes dog til at være lav, da studieresultaterne ikke indikerer nogle afvigelser.

Tabel 7. Vurdering af risiko for bias ALESIA, NCT02838420

Bias	Risiko for bias	Uddybning
Risiko for bias i randomiserings-processen	**Lav**	Block-stratificeret randomisering af patienter ved brug af et interaktivt voice- eller web-baseret system.
Effekt af tildeling til intervention	**Lav**	Open-label studie, men studieresultaterne indikerer ikke afvigelser i hverken allokering eller adhærence til interventionen, der kan resultere i bias.
Manglende data for effektmål	**Lav**	Der foreligger data for studiets effektmål. Alle data rapporteres for ITT-populationen.
Risiko for bias ved indsamlingen af data	**Forbehold**	Sygdomsprogression vurderet af investigator og uafhængig review-komité. Da studiet var open-label, kan det potentielt have påvirket vurderingen af studiets endepunkter. Der ses forskel i opgørelsen af PFS mellem investigator og uafhængig komité, men CI overlapper. Overlevelse vil ikke påvirkes af open-label studiedesign.
Risiko for bias ved udvælgelse af resultater, der rapporteres	**Lav**	Data rapporteres i henhold til metodebeskrivelsen.
Overordnet risiko for bias	**Lav**	Vurderingen af de fleste endepunkter i studiet laves af investigator, som potentiel kan give bias, når der er tale om et open-label studiedesign. Risikoen vurderes dog til at være lav, da studieresultaterne ikke indikerer nogle afvigelser.

Medicinrådet

Application for the assessment of Alunbrig for 1st line treatment of ALK+ NSCLC

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1 Basic information

Table 1 Contact information

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

Table 2 Overview of the pharmaceutical

Proprietary name	Alunbrig
Generic name	Brigatinib
Marketing authorization holder in Denmark	Takeda Pharma A/S
ATC code	L01XE43
Pharmacotherapeutic group	Tyrosine-kinase inhibitor
Active substance(s)	brigatinib
Pharmaceutical form(s)	**Alunbrig 30 mg** film-coated tablets Round, white to off-white film-coated tablet of approximately 7 mm in diameter with debossed “U3” on one side and plain on the other side. **Alunbrig 90 mg** film-coated tablets Oval, white to off-white film-coated tablet of approximately 15 mm in length with debossed “U7” on one side and plain on the other side. **Alunbrig 180 mg** film-coated tablets Oval, white to off-white film-coated tablet of approximately 19 mm in length with debossed “U13” on one side and plain on the other side.
Mechanism of action	Cytostatic through selective inhibition of the kinase activity of fusion proteins containing the ALK-kinase domain.
Dosage regimen	180 mg daily with a 7-**day** lead-in of 90 mg daily.
Therapeutic indication relevant for assessment (as defined by the European Medicines Agency, EMA)	Alunbrig is indicated as monotherapy for the treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC) previously not treated with an ALK inhibitor.
Other approved therapeutic indications	Alunbrig is indicated as monotherapy for the treatment of adult patients with ALK-positive advanced NSCLC previously treated with crizotinib.

Will dispensing be restricted to hospitals?	Yes
Combination therapy and/or co-medication	Not Applicable
Packaging – types, sizes/number of units, and concentrations	Brigatinib 30 mg film-coated tablets, 56 tablets Brigatinib 90 mg film-coated tablets, 7 tablets Brigatinib 90 mg film-coated tablets, 28 tablets Brigatinib 180 mg film-coated tablets, 28 tablets
Orphan drug designation	No

2 Abbreviations

ADR: Adverse Drug Reaction
AE: Adverse Event
ALK: Anaplastic large cell Lymphoma Kinase
BIRC: Blinded Independent Review Committee
CI: Confidence Interval
CNS: Central Nervous System
CR: Complete Response
(ECOG) PS: Eastern Cooperative Oncology Group Performance Status
EORTC: European Organisation for Research and Treatment of Cancer
EOT: End-Of-Treatment
HRQoL: Health Related Quality of Life
IRC: Independent Review Committee
ITT: Intention To Treat (Population)
KM: Kaplan-Meier
MedDRA: Medical Dictionary for Regulatory Activities
NA: Not Applicable

NE: Not estimable
NR: Not Reported
NSCLC: Non-Small Cell Lung Cancer
ORR: Objective Response Rate
OS: Overall Survival
PD: Progressive Disease
PR: partial Response
PFS: Progression Free Survival
PK: Pharmacokinetics
PS: (Eastern Cooperative Oncology Group) Performance Status
QD: once daily
RCT: Randomized Clinical Trial
RECIST: Response Evaluation Criteria In Solid Tumors
SAE: Serious Adverse Event
SAP: Statistical Analysis Plan
SD: Stable Disease
SoC: Standard of Care
STD Dev: Standard Deviation
TEAE: Treatment Emergent Adverse Event
TKI: Tyrosine Kinase Inhibitor

3 Summary

This application concerns itself with the pharmaceutical Alunbrig (brigatinib) for patients with advanced ALK+ NSCLC who have not previously received an ALK-TKI.

Alunbrig is compared to current Danish Standard of Care, Alecensa (alectinib).

The comparison is done using the outcome measures stipulated in the protocol forwarded to the applicant (Takeda Pharma A/S) by the Medicines Council. These outcome measures are *Overall Survival* (critical), *Discontinuation due to AEs* (critical), *intracranial Progression Free Survival in the ITT population* (important), Progression Free Survival (important), *rate of AEs* (important), and *Health Related Quality of Life* (important).

A systematic literature search in the databases MEDLINE and CENTRAL was performed to identify published randomized clinical trials, or indirect comparisons, comparing brigatinib with alectinib within the stated patient population (ALK-TKI naïve ALK+ NSLCLC patients).
No RCT comparing brigatinib directly with alectinib was found.
One indirect comparison was found: a network meta-analysis, which compared PFS.
Consequently, the outcome measures were compared indirectly through a naïve narrative synthesis of RCT comparing alectinib and brigatinib with a common comparator, crizotinib.
The analysis was done using one RCT of brigatinib vs. crizotinib; the global ALTA-1L trial. Alectinib was compared to crizotinib in two trials; the global ALEX trial and the regional ALESIA trial conducted in Asia.

The analysis was impacted by underlying differences in the patient populations in the trials investigated:

- The ALTA-1L trial allowed patients who had previously received chemotherapy into the trial, while ALEX and ALESIA did not.
- ALTA-1L allowed cross-over following progression on crizotinib; ALEX and ALSIA did not (affecting OS)
- A larger proportion of patients in ALEX and ALESIA had brain metastasis at baseline than ALTA-1L (affecting intracranial PFS and PFS)
- PFS-events included radiotherapy to the brain in the ALTA-1L study, but not in the ALEX and ALESIA trials (affecting intracranial PFS and PFS)
- Signs and symptoms of progression of the underlying disease was not counted as AEs in the ALEX and ALESIA trial, but counted as AEs in the ALTA-1L trial (affecting Discontinuation due to AEs and rate of AEs)
- The ALESIA trial only enrolled patients of Asian ethnicity, while ALEX and ALTA-1L were global trials.

These differences means that the narrative comparison of relative effect size must be interpreted with caution.

Indeed, based on the indirect naïve comparison, few, if any, differences in efficacy between alectinib or brigatinib were found.

4 Literature search

The literature searches for Clinical Question 1 were conducted according to the specifications in the protocol (table A2a and A2b, appendix 1).

The literature searches were conducted on 20-JUL-2020 using Google Chrome and yielded 263 records. This number was reduced to 5 articles following removal of duplicate records and screening of titles (see PRISMA diagram in appendix, section 8.1.3).

Of the remaining 5 articles, 5 were excluded from an attempt to perform a statistically valid indirect comparison between alectinib and brigatinib, table A, section 4.3, below, in the absences of randomized clinical trials comparing alectinib and brigatinib.

The 5 excluded articles were two meta-analyses and three RCTs (Table A). One of the meta-analysis did not take into consideration underlying differences in definition of PFS in the alectinib and brigatinib development programs, while the second metanalysis summed the efficacy of alectinib at several different doses.

Differences in the protocols and baseline characteristics of the patients in the remaining three RCTs were considered substantial by the applicant and an attempt at performing an indirect comparison was abandoned.

This application is therefore based on a narrative description of the results from the identified studies to delineate the efficacy differences, if any, between alectinib and brigatinib.

The narrative indirect comparison of alectinib and brigatinib is conducted using a total of four articles, table A, below.

Of note, the ALESIA study was conducted in a population consisting solely of Asian patients and thus does not represent a Danish patient population well. It was however, a randomized controlled trial and an argument can therefore be made that the relative efficacy can be of value for an assessment like the current. Takeda has therefore, in accordance with a principle of caution, chosen to present it. However, the results should be interpreted with caution due to the differences in ethnicity of the underlying patient population as well as the comparatively short follow-up time of 16.2 months (Zhou et al. 2019).

4.1 Studies/publications read at full text level.

TABLE A: STUDIES / PUBLICATIONS READ AT FULL TEXT LEVEL.

Reference	Reason for exclusion from indirect comparison of brigatinib and alectinib	Reference
Gadgeel, S., S. Peters, T. Mok, A. T. Shaw, D. W. Kim, S. I. Ou, M. Pérol, A. Wrona, S. Novello, R. Rosell, A. Zeaiter, T. Liu, E. Nüesch, B. Balas and D. R. Camidge (2018). "Alectinib versus crizotinib in treatment-naive anaplastic lymphoma kinase-positive (ALK+) non-small-cell lung cancer: CNS efficacy results from the ALEX study." Ann Oncol 29(11): 2214-2222.	Retained	(Gadgeel et al. 2018)
Camidge, D. R., H. R. Kim, M. J. Ahn, J. C. H. Yang, J. Y. Han, M. J. Hochmair, K. H. Lee, A. Delmonte, M. R. García Campelo, D. W. Kim, F. Griesinger, E. Felip, R. Califano, A. Spira, S. N. Gettinger, M. Tiseo, H. M. Lin, N. Gupta, M. J. Hanley, Q. Ni, P. Zhang and S. Popat (2020). "Brigatinib Versus Crizotinib in Advanced ALK Inhibitor-Naive ALK-Positive Non-Small Cell Lung Cancer: Second Interim Analysis of the Phase III ALTA-1L Trial." J Clin Oncol: Jco2000505.	Retained	(Camidge et al. 2020)
Elliott, J., Z. Bai, S. C. Hsieh, S. E. Kelly, L. Chen, B. Skidmore, S. Yousef, C. Zheng, D. J. Stewart and G. A. Wells (2020). "ALK inhibitors for non-small cell lung cancer: A systematic review and network meta-analysis." PLoS One 15(2): e0229179.	Retained for PFS	(Elliott et al. 2020)
Mok, T., D. R. Camidge, S. M. Gadgeel, R. Rosell, R. Dziadziuszko, D. W. Kim, M. Pérol, S. I. Ou, J. S. Ahn, A. T. Shaw, W. Bordogna, V. Smoljanović, M. Hilton, T. Ruf, J. Noé and S. Peters (2020). "Updated overall survival and final progression-free survival data for patients with treatment-naive advanced ALK-positive non-small-cell lung cancer in the ALEX study." Ann Oncol 31(8): 1056-1064.	Retained	(Mok et al. 2020)
Yang, Y. L., Z. J. Xiang, J. H. Yang, W. J. Wang and R. L. Xiang (2020). "Effect of alectinib versus crizotinib on progression-free survival, central nervous system efficacy and adverse events in ALK-positive non-small cell lung cancer: a systematic review and meta-analysis." Ann Palliat Med 9(4): 1782-1796.	Excluded. Meta-analysis based on several doses of alectinib.	(Yang et al. 2020)
Zhou, C., S. W. Kim, T. Reungwetwattana, J. Zhou, Y. Zhang, J. He, J. J. Yang, Y. Cheng, S. H. Lee, L. Bu, T. Xu, L. Yang, C. Wang, T. Liu, P. N. Morcos, Y. Lu and L. Zhang	Retained	(Zhou et al. 2019)

(2019). "Alectinib versus crizotinib in untreated Asian patients with anaplastic lymphoma kinase-positive non-small-cell lung cancer (ALESIA): a randomised phase 3 study." Lancet Respir Med 7(5): 437-446.		

TABLE B. RELEVANT STUDIES/PUBLICATIONS INCLUDED IN THE ASSESSMENT.

Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)	Relevant for clinical question 1
Brigatinib Versus Crizotinib in Advanced ALK Inhibitor-Naive ALK-Positive Non-Small Cell Lung Cancer: Second Interim Analysis of the Phase III ALTA-1L Trial. Camidge DR, Kim HR, Ahn MJ, Yang JCH, Han JY, Hochmair MJ, et al. Journal of Clinical Oncology, 2020.	ALTA-1L	NCT02737501	Start: May 26th, 2016 Estimated End: October 15th, 2020	Yes
Updated overall survival and final progression-free survival data for patients with treatment-naive advanced ALK-positive non-small-cell lung cancer in the ALEX study. Mok T, Camidge DR, Gadgeel SM, Rosell R, Dziadziuszko R, Kim DW, et al. Annals of Oncology, 2020.	ALEX	NCT02075840	Start: August 19th, 2014 Estimated End: September 29th, 2022	Yes
Alectinib versus crizotinib in treatment-naive anaplastic lymphoma kinase-positive (ALK+) non-small-cell lung cancer: CNS efficacy results from the ALEX study. Gadgeel S, Peters S, Mok T, Shaw AT, Kim DW, Ou SI, et al. Annals of Oncology, 2018.	ALEX	NCT02075840	Start: August 19th, 2014 Estimated End: September 29th, 2022	Yes
Alectinib versus crizotinib in untreated Asian patients with anaplastic lymphoma kinase-positive non-small-cell lung cancer (ALESIA): a randomised phase 3 study. Zhou, C., S. W. Kim, T. Reungwetwattana, J. Zhou, Y. Zhang, J. He, J. J. Yang, Y. Cheng, S. H. Lee, L. Bu, T. Xu, L. Yang, C. Wang, T. Liu, P. N. Morcos, Y. Lu and L. Zhang (2019). Lancet Respir Med **7**(5): 437-446.	ALESIA	NCT02838420	*Study Start:* August 3rd, 2016 Study End: December 6th, 2019	

4.2 Main characteristics of included studies

In total three RCTs and one Network Meta-Analysis were included in the current application:

- ALK inhibitors for non-small cell lung cancer: A systematic review and network meta-analysis
- ALEX: a global open-label randomized phase 3 trial of alectinib vs. crizotinib in previously untreated ALK+ NSCLC patients (RCT)
- ALESIA: a regional (ASIA) open-label randomized phase 3 trial of alectinib vs. crizotinib in previously untreated ALK+ NSCLC patients (RCT)
- ALTA-1L: a global open-label randomized phase 3 trial of brigatinib vs. crizotinib in ALK-inhibitor naïve ALK+ NSCLC patients (RCT)

A detailed description of the individual RCT are presented in table A2a-c.

5 Clinical questions

5.1 What is the clinical value of brigatinib compared to alectinib in first line treatment of patients with incurable ALK+ NSCLC?

5.1.1 Presentation of relevant studies

ALK inhibitors for non-small cell lung cancer: A systematic review and network meta-analysis

This meta-analysis published in 2020 used network meta-analysis to analyze rates of treatment related death, OS, PFS and SAEs among four ALK TKIs (crizotinib, ceritinib, alectinib, and brigatinib) and chemotherapy (Elliott et al. 2020).

From the methods section

We first performed pair-wise meta-analysis to explore the class effect of treatment with any ALK inhibitor versus chemotherapy, followed by NMA to explore the effect of individual ALK inhibitors. Base-case analyses involving all participants were performed for all outcomes (treatment-related death, overall survival, progression-free survival, SAEs) as were subgroup analyses based on treatment experience. Complete case analyses were performed for dichotomous outcomes (treatment-related deaths, SAEs). For all other outcomes, analyses involved HRs reported by study authors, which accounted for participants censored from the study. Analyses were stratified by treatment experience (naive or experienced) for all meta-analyses and NMAs; no additional subgroup analyses were performed. Bayesian meta-analyses and NMA were performed by use of WinBUGS (v.1.4.3; MRC Biostatistics Unit). Chemotherapy was selected as the reference group for the MA and NMA comparisons. We assessed heterogeneity by use of the I_2 value, with I_2 values above 75% considered to represent high heterogeneity; data were not pooled if the I_2 value exceeded this threshold. We also considered clinical heterogeneity across RCTs by evaluating the similarity of included participants. Additionally, we assessed the model fit (fixed versus random effects) based on the deviance information criterion (DIC) and by comparing the residual deviance to the number of unconstrained data points for each analysis.
In the Bayesian MA and NMAs, a normal likelihood with identity link model was applied for the time-to-event outcomes (overall survival, progression-free survival) using study-level summary measures (log HRs and their standard errors). A binomial likelihood model with logit link was used for the Bayesian MA and NMAs for the dichotomous outcomes (treatmentrelated death, SAEs) to estimate relative risk (RR) and risk difference (RD). Point estimates (odds ratios [ORs], RR, RD for dichotomous outcomes, HRs for time-to-event outcome) and 95% credible intervals (CrIs) were estimated using Markov Chain Monte Carlo methods. For dichotomous outcomes, the RR was estimated based on the OR and the mean proportion of patients who experience the outcome in the reference group of the included studies. The conversion of OR to RR was based on the incidence of the event in the reference group. Vague priors (N (0, 100_2)) were assigned for basic parameters of the treatment effect in the model. Informative priors (Log normal (-3.02, 1.85_2)) were applied for the between-study variance parameter in the random-effect binomial likelihood model for dichotomous outcomes to improve precision and reduce heterogeneity between studies.[13] Model convergence was assessed by use of model diagnostics (trace plots, Brooks–Gelman–Rubin statistic). Three chains were fit into WinBUGS for each analysis, each employing ≥ 10,000 iterations, with a burn-in of ⩾ 10,000 iterations. Inconsistency between direct evidence and indirect evidence was formally assessed using the posterior mean deviance of the individual data points in the inconsistency model plotted against their posterior mean deviance in the consistency model if there were closed loops in the networks. For networks without a closed loop, we assessed exchangeability by comparing the study and patient characteristics to ensure that they satisfied the assumption that all patients were equally likely to receive a given treatment in the network.
All network diagrams were constructed using NodeXL (Social Media Research Foundation).

In total this study included 13 RCTs comparing crizotinib, ceritinib, and alectinib to chemotherapy as well as alectinib, ceritinib and brigatinib against crizotinib.

The comparisons of PFS and OS between alectinib and brigatinib were conducted as part of NMAs including ceritinib, chemotherapy, alectinib, and brigatinib, figure A. The relevant trials included in the analysis is ALEX and ALESIA (alectinib 600 BD vs. crizotinib 250 BD) and ALTA 1L (brigatinib 180 QD vs. crizotinib 250 BD). The NMA is based on treatment naïve patients, and thus only use a subset of the patients from ALTA-1L.

The data cuts used are the primary data cuts with the shortest follow-up; no attempt is made to differentiate between investigator (ALEX and ALESIA) and blinded independent review committee (ALTA-1l) assessed PFS.

ALEX: a global open-label randomized phase 3 trial of alectinib vs. crizotinib in previously untreated ALK+ NSCLC) patients

Patients aged > 18 years with previously untreated stage III/IV ALK-positive NSCLC were randomized 1 : 1 to receive twice-daily alectinib 600 mg or crizotinib 250 mg until PD, toxicity, withdrawal or death.
Randomization was stratified according to ECOG performance status (0/1 versus 2), race (Asian versus non-Asian) and the presence or absence of CNS metastases at baseline.
Crossover between treatment arms was not permitted before PD. Further lines of therapy after PD were at the physician's discretion and based on treatment availability.
Patients with asymptomatic brain or leptomeningeal metastases were eligible for enrolment.
The primary end point was investigator-assessed PFS. Secondary end points included IRC-assessed PFS, objective response rate, OS and safety. End points that were assessed by the IRC were only undertaken for the primary analysis and were not repeated at later data cuts.
For the most updated publication, investigator assessed whole body and intracranial PFS was based on a data-cut with 37.8 months of follow-up, while all other endpoints (OS, AEs, HRQoL) were based on a data-cut with 48.2 months of follow-up (Mok et al. 2020).

ALESIA: a regional (ASIA) open-label randomized phase 3 trial of alectinib vs. crizotinib in previously untreated ALK+ NSCLC patients (RCT)

The primary objective of this study was to show consistency with the data from the ALEX study in an Asian population. Thus ALESIA was a randomised, open-label, phase 3 study done at 21 investigational sites in China, South Korea, and Thailand.
As the trial aimed to confirm and extend already established data from ALEX to a specific population, the randomization was done 2:1 (alectinib:crizotinib) and solely in an Asian patient population
Otherwise the trial was identical to the ALEX trial; follow-up time was though comparatively short at 18.6 and 17.6 months for alectinib and crizotinib, respectively.

ALTA-1L: a global open-label randomized phase 3 trial of brigatinib vs. crizotinib in ALK-inhibitor naïve ALK+ NSCLC patients (RCT)

ALTA-1L was a global phase 3, open-label randomized study conducted in 20 countries.
Patients were adults with locally advanced/metastatic NSCLC and ≥ 1 measurable lesion per RECIST version 1.1 who had not received prior ALK-targeted therapy. Asymptomatic or stable CNS metastases (defined as neurologically stable, without increasing doses of corticosteroids or anticonvulsant use for 7 days before randomization) were permitted.
Patients were stratified by presence/absence of brain metastases and completion of ≥ 1 cycle of chemotherapy for locally advanced/metastatic disease (yes/no) and then randomly assigned (1:1) to brigatinib 180 mg once daily (with 7-day lead-in at 90 mg once daily) or crizotinib 250 mg twice daily.
Patients continued treatment until progression, intolerable toxicity, or another discontinuation criterion.
Crossover from crizotinib to brigatinib was offered after BIRC-assessed progression.
The primary end point was BIRC-assessed PFS. Secondary end points included BIRC-assessed confirmed objective response rate (ORR), confirmed intracranial ORR, intracranial PFS, overall survival (OS), duration of response, safety, and change from baseline in GHS/QoL (per EORTC QLQ-C30).
Exploratory end points included BIRC-assessed PFS and confirmed ORR on brigatinib in patients who crossed over after BIRC-confirmed disease progression on crizotinib, and relationship between PFS and AUC.
Investigator assessments of PFS were also analyzed.

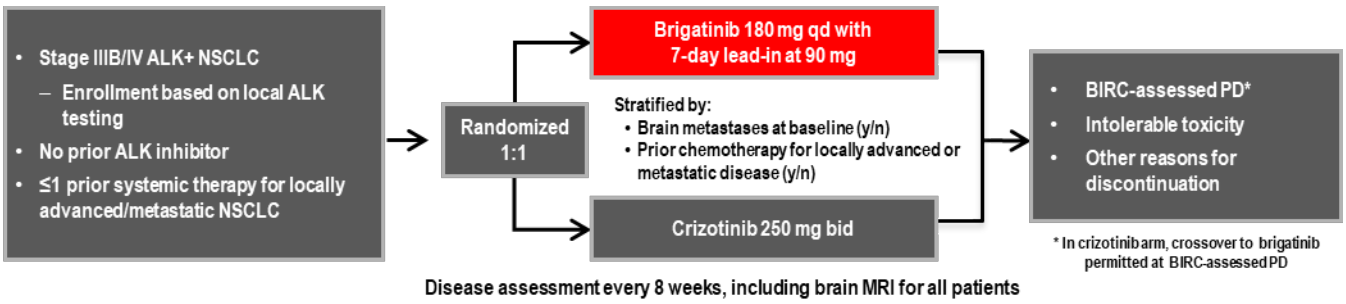

FIGURE B: OVERVIEW OF THE ALTA-1L TRIAL.

Similarities and differences

Within this section, the key differences between the ALTA-1L and the ALEX/ALESIA trials in terms of design and patient baseliane characteristics are considered. These include whether crossover was permitted, the definition of the progression endpoints and follow-up times reported in the publications as outlined in table C below.

Table C: Key trial differences

Design	ALTA-1L	ALEX/ALESIA
Inclusion of patients who had prior chemotherapy for advanced disease	Permitted per protocol	Not permitted per protocol
Treatment crossover after disease progression	Permitted per protocol	Not permitted per protocol
Stratification factors	Presence of baseline brain metastases (yes or no) Completion of at least one full cycle of chemotherapy for locally advanced or metastatic disease (yes or no)	Presence or absence of CNS metastases at baseline ECOG performance status (0 or 1 vs. 2) Race (Asian vs. non- Asian)
Primary endpoint	BIRC-assessed PFS	Investigator-assessed PFS
Definition of disease progression	Progressive disease Death Local radiotherapy for CNS lesions	Progressive disease Death
Median follow-up time (months)	IA1-11.0 (brigatinib arm.) IA2 - 24.9 (brigatinib arm.)	Primary - 18.6 (alectinib arm ALEX) – BIRC Assessed PFS Final - 37.8 (alectinib arm ALEX) – INV assessed PFS Primary – 16.2 (alectinib arm, ALESIA) – BIRC and INV assessed PFS
ALK testing	Local test to enroll patients	Central lab test to enroll patients

ALK, anaplastic lymphoma kinase; BIRC, blinded independent review committee; CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group; IA, interim analysis; PFS, progression-free survival

For an overview of the baseline patient characteristics for the intervention arm, please refer to table D.
The regional ALESIA trial stands out as different from the global ALEX and ALTA-1L trials in relation to age (younger), ethnicity (Asian) and prior radiotherapy to the brain (less).
The two global trials appear quite homogenous, except for inclusion of patients previously treated with chemotherapy in the ALTA-1L trial and the higher proportion of patients in the ALEX (and ALESIA) trial(s) with brain metastasis at baseline.
Given the prognostic importance of baseline brain metastasis in crizotinib treated patients (Gadgeel et al.

2018; Zhou et al. 2019; Camidge et al. 2020; Mok et al. 2020), this imbalance between the trials is potentially quite significant. The imbalance will be addressed in relevant sections below.

TABLE D: COMPARISON OF BASELINE CHARACTERISTICS OF THE PATIENTS IN THE INTERVENTION ARMS.

	Brigatinib	Alectinib	
Study	ALTA-1L	ALEX	ALESIA
No. of patients	137	151	125
Age			
Median	58	53.8	50.5
Range	27-86	18-91	43-59
Gender, N (%)			
Male	NR (50)	64 (42.0)	64 (51)
Female	NR (50)	87 (58.0)	61 (49)
Race			
Asian	(43)	69 (46)	125 (100)
Non-Asian	(55)	82 (54)	0 (0)
Unknown	(1)	NR	NR
ECOG PS			
0	(39)	NR	NR
1	(55)	NR	NR
0 or 1	(95)	141 (93)	121 (97)
2	(5)	10 (7)	4 (3)
Disease stage at study entry			
IIIB	(6)	6 (4)	12 (10)
IV	(94)	145 (96)	112 (90)
Metastatic sites, N (%)			
Brain	(29)	58 (38)	44 (35)

Prior radiotherapy to brain, N (%)	18 (13)	21 (14)	8 (6)
Prior Chemotherapy, %	26	0	0

5.1.2 Results per study

ALK inhibitors for non-small cell lung cancer: A systematic review and network meta-analysis

OVERALL SURVIVAL

A network meta-analysis of the ALEX and ALESIA trials vs. ALTA-1L found an OS HR of 1.55 (95% CI: 0.72; 3.34) (Elliott et al. 2020).

PROGRESSION FREE SURVIVAL

A network meta-analysis of the ALEX and ALESIA trials vs. ALTA-1L found a PFS HR of 1.07 (95% CI: 0.66; 1.75) (Elliott et al. 2020).

Differences in cross-over

This analysis did not take into consideration that cross-over was allowed in the ALTA-1L study, while it was not allowed in the ALEX and ALESIA trials,

Differences in PFS assessment

This analysis did not take differences in PFS assessment into consideration. Thus, the HR of PFS was based on investigator assessed PFS for ALEX and ALESIA, while it was assessed by a blinded independent review committee in the ALTA-1L publication.

ALTA-1L

ANALYSIS POPULATION

For efficacy outcomes, all analysis were performed in the ITT population; safety was analyzed in the safety population defined as all patients who had received at least one dose of study drug (Takeda 2015).

OVERALL SURVIVAL

Definition and Operationalisation of endpoint:

Overall Survival is a precise endpoint that captures the survival of the patients either at a predefined time-point or as a median survival.

OS was a time-to-event outcome and was therefore estimated using Kaplan-Meier methodology (Takeda 2015).

Cross-over from the crizotinib arm to brigatinib was allowed at progression.

Results

At a median follow-up of 24.9 (0-34-1) and 15.2 (0.1-36.0) months in the brigatinib and crizotinib arms, respectively, the median OS was not reached for either treatment arm (Camidge et al. 2020).

The KM derived hazard-ratio was 0.92 (95% CI: 0.57; 1.47, P=0.771), figure C.

The protocol of ALTA-1L allowed for cross-over of the patients in the crizotinib arm at progression.[1]

[redacted]

[redacted]

DISCONTINUATION DUE TO ADVERSE EVENTS

Definition and Operationalisation of endpoint:

All adverse events (AEs) starting/worsening on or after the first dose of study treatment and no later than 30 days after the last dose date were considered as treatment-emergent.

Treatment-emergent AEs were summarized by action taken on study treatment, including dose modifications, interruptions and discontinuations. There is thus no causal relationship between study treatment and adverse events leading to treatment discontinuation.

AEs were coded in MedDRA.

Worsening of signs and symptoms associated with progression of the underlying disease was considered Adverse Events.

Results:

13% and 9% of the patients discontinued brigatinib and crizotinib due to AEs, respectively (Camidge et al. 2020).

[1] Confidential Data on file.

The associated RR was 1.43 (95% CI: 0.71; 2.87, P=0.320).

CNS-Progression (CNS-PFS)

Definition and Operationalisation of endpoint:
The scientific expert committee (Fagudvalget) has requested median intracranial PFS values for the ITT population. To the knowledge of the applicant this analysis does not exist in the public domain for alectinib and has not been made for brigatinib.
Data presented will thus be results of competing risk analyses of intracranial progression, where the time to cause-specific event is defined as time from randomization to the first cause-specific event. Thus, patients with other prior competing events were no longer at risk for the cause-specific event and were censored at the time of these competing events. Patients without any events were censored at the last assessment timepoint.
As competing risk analyses are performed in the ITT population it is estimated that these analysis are the analyses that comes closest to address the question of intracranial efficacy in the ITT population.
The applicant will supplement the above analysis with a intracranial PFS analysis from the patient population with baseline CNS metastasis from the ALTA-1L trial. A similar analysis is not available from the ALEX/ALESIA trials.
See appendix five for a detailed description of the analysis present in the public domain.

Results
The Hazard Ratio of a competing risk analysis for intracranial progression in the ITT population was 0.302, 95% CI: 0.17; 0.53, P<0.0001 (CHMP 2020).
Patients with brain metastasis at baseline had median intracranial PFS of 24.0 months (95% CI: 12.9; NR) and 5.6 months (95% CI: 3.7; 7.5) (absolute difference 18.4 months) for brigatinib and crizotinib, respectively (Camidge et al. 2020).
The KM-curves separates almost immediately after 1 month, figure D.

Progression Free Survival (PFS)

Definition and Operationalisation of endpoint:
PFS was defined as progression (according to RECIST 1.1), death or use of radiotherapy to the brain, whichever occurred first.
To ensure stringency, and consistency, PFS was assessed by a blinded independent review committee (BIRC) (Takeda 2015).

Results

BIRC assessed median PFS was 24.0 months (95% CI: 18.5; NR) and 11.0 months (95% CI: 9.2-12.9) for brigatinib and crizotinib, respectively (Camidge et al. 2020).
The associated hazard ratio was 0.49, 95% CI: 0.25; 0.68, P<0.0001.
The KM-curves separates after 3 months, figure DE.

Rate of Grade 3-4 AEs

Definition and Operationalisation of endpoint:
All adverse events (AEs) starting/worsening on or after the first dose of study treatment and no later than 30 days after the last dose date were considered as treatment-emergent.
Adverse Events captures all events experienced during the study. There is therefore no causality assessment associated with AEs.
AEs were coded in MedDRA.
Worsening of signs and symptoms associated with progression of the underlying disease was considered Adverse Events.

Results
The rate of grade 3-4 AEs were 73% and 61% for brigatinib and crizotinib, respectively.

Quality of Life

Definition and Operationalisation of endpoint:
Quality of Life was measured using the EORTC QCQ 30 instrument.
The HRQoL analysis focus on time to worsening of Quality of Life by 10 points, as this analysis captures the positive effect of treatment as well as the temporal aspect of the positive effect (Camidge et al. 2020).
A publication reporting extensive PRO data and it analysis is in preparation.
The below analysis are the results of the only PRO data currently available in the public domain.

Results
The difference in mean change from baseline was 3.1 points in favor of brigatinib (95% CI: -0.8; 7.0) (CHMP 2020).

Median time to worsening (10 points decrease) of HRQoL was 26.7 months (95% CI: 8.3; NR) and 8.3 months (95% CI: 5.7; 13.5) for brigatinib and crizotinib, respectively (Camidge et al. 2020).
The associated HR was 0.70, 95% CI: 0.49; 1.00, P= 0.049, figure F, left panel (Camidge et al. 2020).

The median duration of improvement (10 point increase from baseline) was NR (95% CI: NR; NR) and 12.0 (95% CI: 7.7; 17.5) months for brigatinib and crizotinib, respectively (Camidge et al. 2020).
The associated HR was 0.27 (95% CI: 0.14; 0.49, P<0.0001), figure F, right panel (Camidge et al. 2020).

ALEX

ANALYSIS POPULATION

For efficacy outcomes, all analysis were performed in the ITT population; safety was analyzed in the safety population defined as all patients who had received at least one dose of study drug (Takeda 2015).

OVERALL SURVIVAL

Definition and Operationalisation of endpoint:
Overall survival was defined as the time from randomization to death for any cause.
Cross-over from crizotinib to alectinib at progression was not allowed; in contrast with the ALTA-1L trial.

Results
Median Overall Survival was NR and 57.4 months for alectinib and crizotinib, respectively (Mok et al. 2020).
The associated HR was O.67 (95% CI: 0.46; 0.98), P=0.0376, figure G.
Median follow-up time was 48.2 months (Mok et al. 2020).

DISCONTINUATION DUE TO AES

Definition and Operationalisation of endpoint:
As opposed to the ALTA-1L trial, worsening of signs and symptoms associated with progression of the underlying disease was not considered Adverse Events (Ltd 2019), in contrast to the reporting of AEs in the ALTA-1L trial.

Results
14.5% and 14.6% of patients treated with alectinib and crizotinib, respectively, discontinued due to AEs (Mok et al. 2020).
The associated RR was 1.0066 (95% CI: 0.58; 1.73, P=0.98).
Median follow-up time was 48.2 months (Mok et al. 2020).

CNS-PROGRESSION (CNS-PFS)

Definition and Operationalisation of endpoint:
The below result are a competing risk analysis of intracranial progression, where the time to cause-specific event is defined as time from randomization to the first cause-specific event. Thus, patients with other prior competing events were no longer at risk for the cause-specific event and were censored at the time of these competing events. Patients without any events were censored at the last assessment timepoint.

Results
The Hazard Ratio of a competing risk analysis for intracranial progression in the ITT population was 0.16, 95% CI: 0.10; 0.28, P<0.0001 (CHMP 2020).

Progression Free Survival (PFS)

Definition and Operationalisation of endpoint:
PFS was defined as progression (according to RECIST 1.1) or death, whichever occurred first.
To ensure stringency, and consistency, the reported PFS was assessed by an unblinded independent review committee (BIRC) (Ltd 2019).

Results
The blinded independent review committee assessed median PFS was 25.7 months (95% CI: 19.9; NE) and 10.4 months (95% CI: 7.7; 14.6) for alectinib and crizotinib, respectively (CHMP 2017).
The associated HR was 0.50 (95% CI: 0.36; 0.70, P<0.0001) (CHMP 2017).
The KM-curves of the BIRC PFS shows curves that separate after roughly 5 months, figure H.

Rate of Grade 3-4 AEs

Definition and Operationalisation of endpoint:
As opposed to the ALTA-1L trial, worsening of signs and symptoms associated with progression of the underlying disease was not considered Adverse Events.

Results
The rate of grade 3-4 AEs were 52.0% and 56.4% for alectinib and crizotinib, respectively (Mok et al. 2020).
The associated Relative Risk was 0.94 (95% CI: 0.78; 1.13, P=0.49).

Quality of Life

Definition and Operationalisation of endpoint:
Quality of Life was measured using the EORTC QCQ 30 instrument.

Results
Median time to worsening (10 points decrease) of HRQoL was not reached in either treatment arm.
The associated HR was 0.72, 95% CI: 0.38; 1.39, P= Not reported (Medicinrådet 2018).

ALESIA

Analysis Population

For efficacy outcomes, all analysis were performed in the ITT population; safety was analyzed in the safety population defined as all patients who had received at least one dose of study drug (Zhou et al. 2019).

Overall Survival

Definition and Operationalisation of endpoint:
Overall survival was defined as the time from randomization to death for any cause.
Cross-over from crizotinib to alectinib at progression was not allowed.

Results
Median Overall Survival was immature and not reported in the primary publication.
The associated HR was O.28 (95% CI: 0.12; 0.68).

Discontinuation due to AEs

Definition and Operationalisation of endpoint:
As opposed to the ALTA-1L trial, worsening of signs and symptoms associated with progression of the underlying disease was not considered Adverse Events (Ltd 2019).

Results
7% and 10% of patients treated with alectinib and crizotinib, respectively, discontinued due to AEs (Zhou et al. 2019).
The associated RR was 0.72 (95% CI: 0.27; 1.93, P=0.51).

CNS-Progression (CNS-PFS)

Definition and Operationalisation of endpoint:
The below result are a competing risk analysis of intracranial progression, where the time to cause-specific event is defined as time from randomization to the first cause-specific event. Thus, patients with other prior competing events were no longer at risk for the cause-specific event and were censored at the time of these competing events. Patients without any events were censored at the last assessment timepoint.

Results
The Hazard Ratio of a competing risk analysis for intracranial progression in the ITT population was 0.14, 95% CI: 0.06; 0.30, P<0.0001 (Zhou et al. 2019).

Progression Free Survival (PFS)

Definition and Operationalisation of endpoint:
PFS was defined as progression (according to RECIST 1.1), death or use of radiotherapy to the brain, whichever occurred first.
To ensure stringency, and consistency, the reported PFS was assessed by a blinded independent review committee (BIRC) (Ltd 2019).

Results
The blinded independent review committee assessed median PFS was NE (95% CI: 16.7; NE) and 10.7 months (95% CI: 7.4; NE) for alectinib and crizotinib, respectively (Zhou et al. 2019).
The associated HR was 0.37 (95% CI: 0.22; 0.61, P<0.0001) (Zhou et al. 2019).

Rate of Grade 3-4 AEs

Definition and Operationalisation of endpoint:
As opposed to the ALTA-1L trial, worsening of signs and symptoms associated with progression of the underlying disease was not considered Adverse Events.

Results
The rate of grade 3-4 AEs were 29% and 48% for alectinib and crizotinib, respectively (Zhou et al. 2019).
The associated Relative Risk was 0.66 (95% CI: 0.41; 0.87, P=0.007).

Quality of Life

Quality of Life data was not reported (Zhou et al. 2019).

5.1.3 Comparative analyses

DATA SOURCES FOR COMPARATIVE ANALYSIS

A comparative analysis is complicated by the fact that no head-to-head trials were identified in the literature search.

Consequently, a **narrative analysis within the current text, will compare the data**.

In this narrative analysis, the term "naïve analysis" will be taken to mean a direct comparison of data from independent trials.

As all three trials were conducted as randomized trials with the same active comparator, crizotinib, a comparison of Hazard Ratios or Relative Risk between the experimental arm and the control arm will be emphasized over absolute values outcome measures (OS, PFS, AEs etc). In case specific differences in study protocols precludes such a comparison, the text will call attention to the specific caveats associated with this approach.

OVERALL SURVIVAL, OS

Of the three trials identified, none have reported mature OS data
The ALEX trial reported an OS HR of 0.67 (95% CI: 0.46; 0.98, P=0.0376) (Mok et al. 2020).
ALESIA reported an OS HR of 0.28 (95% CI: 0.12; 0.68) (Zhou et al. 2019).
As compared to these data, the ALTA-1L trial reported an OS HR of 0.92 (95% CI: 0.57; 1.47, P=0.771) (Camidge et al. 2020).

The Network Meta-Analysis reported by Elliott et al. (Elliott et al. 2020) compared the ALEX and ALESIA trials with the ALTA-1 trial along with several other trials that included ceritinib and chemotherapy.
This comparison found a HR of 1.55 (95% CI: 0.72; 3.34) between brigatinib and alectinib (Elliott et al. 2020).
This analysis did not take into account that patients in the ALTA-1L trial could have received chemotherapy prior to brigatinib, while patients from ALEX/ALESIA could not.

Crossover and subsequent therapies

In the ALTA-1L study, at the discretion of the investigator and with the sponsor's medical monitor approval, patients randomised to crizotinib who experienced progression as assessed by the blinded independent review committee (BIRC) or received radiotherapy to the brain were permitted to cross over to brigatinib in line with the pre-defined trial protocol.

[redacted]

[redacted]

Due to high rates of crossover and subsequent use of ALK TKIs in the ALTA-1L study, the OS data is thus confounded in the crizotinib arm. Hence, the isolated effect on survival associated with frontline crizotinib treatment alone is not observed in the OS data, but rather the OS data reflects the effects of a pathway of sequential TKIs.

Discontinuation due to AEs

The rates of discontinuation due to AEs and the associated relative risks are summarized in table E.

Table E: Rates of Discontinuation due to AEs and corresponding RR.

Study, Reference	Discontinuation of brigatinib, %	Discontinuation of crizotinib, %	Relative risk (95% CI), P	Median Follow-Up, Months
ALTA-1L (Camidge et al. 2020)	13.0	9.0	1.43 (0.71; 2.87), P=0.320	24.9 (brigatinib) 15.2 (crizotinib)
Study, Reference	**Discontinuation of alectinib, %**	**Discontinuation of crizotinib, %**	**Relative risk (95% CI), P**	**Median Follow Up, Months**
ALEX (Mok et al. 2020)	14.5	14.6	1.01 (0.58; 73), P=0.98	48.2 (alectinib) 23.3 (crizotinib)
ALESIA (Zhou et al. 2019)	7	10	0.72 (0.27; 1.93), P=0.51	16.2 (alectinib) 15.0 (crizotinib)

None of the three studies have demonstrated a statistically significant difference in relative risk of discontinuation due to AE; the HR 95% CIs of all three trials overlap (table E).

Numerically, the ALTA-1L and ALEX trial show comparable discontinuation rates between brigatinib and alectinib, while the ALESIA trial stand out with a very low discontinuation rate of alectinib. This is likely to

[2] A small proportion (6.6%; n=10) of patients randomized to crizotinib in the ALEX trial received alectinib as a subsequent therapy after progression (National Institute for Health and Care Excellence 2018).
[3] Confidential Data on file
[4] Data from the ALEX study is based on published information on the website of NICE and hence may not coincide with the latest available data on subsequent therapy used after alectinib.

change when the exposure time of the alectinib patients in the ALESIA study increases with longer follow-up.

For all three studies the longer treatment duration of the experimental drug as compared to crizotinib should be taken into consideration.

Sign and symptoms of progression of the underlying disease as AEs

In the ALTA-1L trial "Worsening of signs and symptoms of the malignancy under study" should be reported as AEs.

In contrast, in the ALEX trial events that were "clearly consistent with the expected pattern of progression of the underlying disease" were not recorded as AEs (Ltd 2016).

Given this difference in AE collection, a naïve comparison of the numeric discontinuation rates should be interpreted with caution.

CNS-Progression (CNS-PFS)

The competing risk analysis are summarized below in table F.

It is seen that the 95% CI of all three trials overlap considerably.

Table F. Summary of the Competing Risk Analysis for intracranial progression.

Study, Reference	Competing risk HR (95% CI), P
ALTA-1L, (Camidge et al. 2020)	0.302 (0.17; 0.53), <0.0001
ALEX, (CHMP 2017; Medicinrådet 2018)	0.16 (0.10; 0.28), <0.0001
ALESIA, (Zhou et al. 2019)	0.14 (0.06; 0.30), <0.0001

Proportion of patients with brain metastases at baseline

Table G summarize the proportion of patients with brain metastasis at baseline.

Table G: Summary of proportion of patients with brain metastasis at baseline.

Study, Reference	ALTA-1L, (Camidge et al. 2020)		ALEX, (Mok et al. 2020)		ALESIA, (Zhou et al. 2019)	
	Brigatinib (N = 137)	Crizotinib (N = 138)	Alectinib (N = 152)	Crizotinib (N = 151)	Alectinib (N = 125)	Crizotinib (N = 62)
Brain metastases at baseline N (%)	40 (29%)	41 (30%)	64 (42%)	58 (38%)	44 (35)	23 (37)

It is seen from table G that a higher proportion of patients in the ALEX and ALESIA trials had CNS involvement at baseline for both the alectinib and crizotinib arms compared with those seen in the ALTA-1L trial.

The proportion of patients with baseline brain metastases in the real-world DK setting is difficult to determine as many centrs do not routinely scan for CNS involvement at baseline. The BRIGALK study - one of the few publications reporting real-world baseline brain metastases at diagnosis - considered retrospective outcomes from patients treated with brigatinib in a French early access program. In this study the proportion of patients with baseline CNS involvement was 28.9% (Descourt et al. 2019) which more closely aligns with the ALTA-1L than the ALEX and ALESIA trials.

Patients on crizotinib frequently experience brain metastases due to its poor penetration of the blood-brain barrier (Solomon et al. 2014; Camidge et al. 2018; Costa et al. 2011; Takeda, Okamoto, and Nakagawa 2013). As a result of the poor CNS penetrance of crizotinib, the presence of brain metastases at baseline is recognized as a critical important prognostic factor for patients treated with crizotinib, and patients with baseline brain metastasis treated with crizotinib is much more likely to progress in the CNS as opposed to a patient treated with a second generation ALK TKI such as alectinib or brigatinib (Gadgeel et al. 2018; Camidge et al. 2020).

It follows from the poor CNS penetrance of crizotinib, that the higher the proportion of patients with baseline CNS metastasis in a patient population, the higher the proportion of patients will be at increased risk of CNS progression *when treated with crizotinib.*

The imbalance of patients with baseline brain metastases observed in ALTA-1L and ALEX/ALESIA, is thus particularly important when the CNS data are considered in indirect comparisons. Indeed, the higher proportion of patients with baseline CNS metastasis in the ALEX and ALESIA trials are likely to favor the Hazard Ratio of CNS-PFS in the ITT in these two trials.

In conclusion, the ALEX and ALESIA trials included roughly 30% more patients with baseline brain metastasis compared to ALTA-1L, and a comparison of the trials at the relative level must be interpreted with caution due to the poor prognostic impact of brain metastasis for crizotinib treated patients and the imbalance in patients with baseline CNS metastasis between the ALEX/ALESIA and ALTA-1L trials.

Progression Free Survival (PFS)

The Network Meta-Analysis reported by Elliott et al. (Elliott et al. 2020) compared the ALEX and ALESIA trials with the ALTA-1 trial along with several other trials that included ceritinib and chemotherapy.
This comparison found a HR of 1.07 (95% CI: 0.66; 1.75) between brigatinib and alectinib (Elliott et al. 2020).
This analysis did not take into account that patients in the ALTA-1L trial could have received chemotherapy prior to brigatinib, while patients from ALEX/ALESIA could not.

Table H summarizes the BIRC assessed PFS data from the three RCTs for a naïve comparison.
While the 95% CI from the ALESIA trial is not reported, it is clear that the HR 95% Confidence Intervals overlap between the ALEX and ALTA-1L trials.
ALESIA differ from ALEX and ALTA-1L in that the HR at 0.37 appears lower than the HR for ALEX and ALTA-1L (0.50 and 0.49, respectively). However, all patients in the ALESI trial were of Asian ethnicity – see below

paragraph "Asian Patient Population" for an analysis of the efficacy of brigatininb vs. crizotinib in Asian patients.

TABLE H: SUMMARY OF BIRC ASSESSED MEDIAN PFS AND HR OF BRIGATINIB VS. CRIZOTINIB.

Study, Reference	Median BIRC PFS brigatinib, Months	Median BIRC PFS crizotinib, Months	Hazard Ratio (95% CI), P
ALTA-1L, (Camidge et al. 2020)	24.0	11.0	0.49 (0.35; 0.68), <0.0001
Study	**Median BIRC PFS Alectinib, Months**	**Median BIRC PFS crizotinib, Months**	**Hazard Ratio (95% CI), P**
ALEX, (Peters et al. 2017)	25.7	10.4	0.50 (0.36; 0.70), <0.0001
ALESIA, (Zhou et al. 2019)	Not Reached	10.7	0.37 (not reported), <0.0001

Definition of disease progression

The ALTA-1L study defines disease progression as a RECIST progression, radiotherapy for brain metastases or death, whichever occurs first. In contrast, the ALEX and ALESIA trials defined a PFS event as a RECIST progression or death, whichever occurs first. The variation in the definition of the primary outcome impacts the following endpoints: BIRC-assessed PFS, investigator assessed PFS and BIRC-assessed intracranial PFS outcomes. Feedback obtained during a Takeda organized Nordic medical advisory board in June 2020 indicated that clinicians preferred the ALTA-1L definition of progression and considered it more reflective of real-world clinical practice.

Radiotherapy for brain metastases was considered by clinicians as a proxy for progression hence the exclusion of patients receiving radiotherapy to the brain from the primary efficacy measure (PFS) is thought to potentially augment the treatment effect in ALEX.
Indeed, 6 out of 7 advisors estimated the added clinical benefit of radiotherapy to the brain during first line therapy to be between 6 and 12 months (the final advisor estimated the benefit to > 12 months). Of the same advisors 3, 3, and 1 advisors estimated that 11%-20%, 21-30%, and 31%-40% of ALK+ NSCLC patients respectively would receive radiotherapy to the brain during first line therapy and thus draw added clinical benefit (Takeda 2020a).
While it is unknown to Takeda how many of the patients in the ALEX and ALESIA trials received radiotherapy to the brain, it remains an important methodical difference between the trials.

Prior chemotherapy
In the ALTA-1L study, 26% and 27% in the brigatinib and crizotinib arms, respectively received at least one full cycle of prior chemotherapy whilst the ALEX and ALESIA trials did not permit inclusion of patients who had prior chemotherapy. The relevance and receipt of prior chemotherapy in ALK-positive advanced NSCLC patients is highly dependent on local practice. Discussions with clinical experts indicates that, while very rare, some centres may sometimes initiate chemotherapy prior to receiving molecular test results, for reasons such as clinical need (e.g. to control worrying symptoms). This indicates that assessing the efficacy of ALK inhibitors following chemotherapy remains a clinically relevant unmet need addressed by the ALTA-1L study.

For the purpose of an indirect comparison the BIRC assessed HR of patients having not received prior chemotherapy was 0.52 (95% CI: 0.35; 0.88) and 0.50 (95% CI: 0.36; 0.70) in the ALTA-1L and ALEX trials, respectively (Peters et al. 2017; Camidge et al. 2020).

Asian patient population

The ALESIA trial was conducted solely in an Asian patient population and found a HR of 0.37, P=0.0001 (95% CI was not reported).

A post-hoc analysis of the ALTA-1L trial elucidating the treatment effect specifically in the Asian subpopulation found that the BIRC assessed PFS HR in the Asian population was 0.38 (95% CI: 0.22; 0.65, P=0.0006) (Myung-Ju Ahn et al. 2020).

Conclusion

Given the differences in definition of PFS (allowing therapeutic benefit of radiotherapy to the brain without counting this as a PFS event, or not) and prior use of chemotherapy in the ALTA-1L patient population, an indirect comparison of absolute median PFS should be interpreted with caution.

Rate of Grade 3-4 AEs

Table I summarizes the rate of Grade 3-4 AE – For ALTA-1L the rates are summarized at two different data cuts to illustrate the impact of longer follow-up.

Table I: rates of grade 3-4 AEs

Study, Reference	Grade 3-4 AEs brigatinib, %	Grade 3-4 AEs crizotinib, %	Relative Risk (95% CI), P	Median Follow-Up, Months
ALTA -1L, (Camidge et al. 2020)	73	61	1.19 (1.00; 1.41), 0.047	24.9 (brigatinib) 15.2 (crizotinib)
ALTA-1L, (Camidge et al. 2018)	61	55	1.10 (0.90; 1.34), 0.35	11.0 (brigatinib) 9.3 (crizotinib)
Study	**Grade 3-4 AEs alectinib, %**	**Grade 3-4 AEs crizotinib, %**	**Relative Risk (95% CI), P**	**Median Follow Up, Months**
ALEX, (Mok et al. 2020)	52.0	56.3	0.94 (0.78; 1.13), 0.49	48.2 (alectinib) 23.3 (crizotinib)
ALESIA, (Zhou et al. 2019)	29	48	0.60 (0.41; 0.87), 0.007	16.2 (alectinib) 15.0 (crizotinib)

A naïve comparison of the relative risk rates of grade 3-4 AEs across the three trials is complicated as:

1. The treatment duration between on the one hand alectinib/brigatinib and on the other crizotinib is quite different. Several types of AEs can occur after long exposure, and the AE-rates and corresponding relative risk rates should therefore ideally be normalized to exposure days to take

this into account. An example of this, is the relative risk between brigatinib and crizotinib, which change from 1.10 to 1.19 with increasing exposure predominantly to the brigatinib patients.

2. The follow-up time of the three trials is quite different.
3. Most importantly, differences in collection of signs and symptoms of progression of the underlying disease as AEs were present between the three trials (see above comparison of discontinuation rates due to AEs), which by default would lead to a higher number of reported AEs amongst patients in the ALTA trial relative to the ALEX and ALESIA trials

Given the above, a naïve comparison of the numeric AE rates and associated relative risk should be interpreted with caution

Qualitative Comparison of Adverse Drug Reactions

Table J compiles the known Adverse Drug Reactions associated with alectinib and brigatinib.
Adverse Drug Reactions are distinct from Adverse Events in so far a causal relationship is considered to exist between the indigestion of the drug and the occurrence of the Adverse Drug Reaction.

Table J: Adverse Drug Reactions of brigatinib and alectinib, as reported in the SPCs

	Brigatinib			Alectinib		
System organ class	**Frequency category**	**Adverse reactions† all grades**	**Adverse reactions Grade 3-4**	**Frequency category**	**Adverse reactions† all grades**	**Adverse reactions Grade 3-4**
Infections and infestations	Very common	Pneumonia[a] Upper respiratory tract infection		Very common		
	Common		Pneumonia[a]	Common		
Blood and lymphatic system disorders	Very common	Anaemia Lymphocyte count decreased APTT increased White blood cell count decreased Neutrophil count decreased	Lymphocyte count decreased	Very common	Anemia[1)] (17%)	Anemia[1)] (3.0%)
	Common	Decreased platelet count	APTT increased Anaemia	Common		

	Brigatinib			Alectinib		
System organ class	**Frequency category**	**Adverse reactions† all grades**	**Adverse reactions Grade 3-4**	**Frequency category**	**Adverse reactions† all grades**	**Adverse reactions Grade 3-4**
	Uncommon		Neutrophil count decreased			
Metabolism and nutrition disorders	Very common	Hyperglycaemia Hyperinsulinaemia[b] Hypophosphataemia Hypokalaemia Hypomagnesaemia Hyponatraemia Hypercalcaemia Decreased appetite		Very common		
	Common		Hypophosphataemia Hyperglycaemia Hyponatraemia Hypokalaemia Decreased appetite	Common		
Psychiatric disorders	Very common	Insomnia		Very common		
Nervous system disorders	Very common	Headache[c] Peripheral neuropathy[d] Dizziness		Very common		
	Common	Memory impairment Dysgeusia	Peripheral neuropathy[d] Headache[c]	Common	Dysgeusia[2)] (5.2%)	Dysgeusia[2)] (0.2%)
Eye disorders	Very common	Visual disturbance[s]		Very common		
	Common		Visual disturbances	Common	Vision Disorder[3)] (8.6%)	
Cardiac disorders	Common	Tachycardia[f] Electrocardiogram QT prolonged Bradycardia Palpitations	Electrocardiogram QT prolonged	Common	Bradycardia[4)] (8.9 %)	

	Brigatinib			Alectinib		
System organ class	Frequency category	Adverse reactions† all grades	Adverse reactions Grade 3-4	Frequency category	Adverse reactions† all grades	Adverse reactions Grade 3-4
	Uncommon		Bradycardia	Uncommon		
Vascular disorders	Very Common	Hypertension	Hypertension	Very Common		
Respiratory, thoracic and mediastinal disorders	Very Common	Cough Dyspnoea[h]		Very Common		
	Common	Pneumonitis[i]	Pneumonitis[i] Dyspnoea[h]	Common		
	Uncommon			Uncommon	Interstitial lung disease / pneumonitis – (0.7%)	Interstitial lung disease / pneumonitis (0.2%)
Gastrointestinal disorders	Very common	Lipase increased Nausea Diarrhoea[j] Amylase increased Vomiting Constipation Abdominal pain[k] Stomatitis[l]	Lipase increased	Very common	Constipation (35%) Nausea (19%) Diarrhoea (16%) Vomiting (11%)	Nausea (0.5%) Diarrhoea (0.7%) Vomiting (0.2%)
	Common	Dyspepsia Flatulence Dry mouth	Amylase increased Abdominal pain[k] Nausea Diarrhoea	Common	Stomatitis[5)] (3.0%)	
	Uncommon	Pancreatitis	Vomiting Stomatitis Dyspepsia Pancreatitis	Uncommon		

	Brigatinib			Alectinib		
System organ class	**Frequency category**	**Adverse reactions† all grades**	**Adverse reactions Grade 3-4**	**Frequency category**	**Adverse reactions† all grades**	**Adverse reactions Grade 3-4**
Hepatobiliary disorders	Very common	AST increased ALT increased Alkaline phosphatase increased		Very common	Bilirubin increase[6)] (18%) AST increased (15%) ALT increased – (14%)	Bilirubin increase[6)], (3.2%) AST increased, (3.7%) ALT increased, (3,7%)
	Common	Blood LDH increased Hyperbilirubinaemia	ALT increased AST increased Alkaline phosphatase increased	Common	Alkaline phosphatase increased**, (6.2%)	Alkaline phosphatase increased**, (0.2%) Drug-induced liver injury[7)], (0.7%)
	Uncommon		Hyperbilirubinaemia		Drug-induced liver injury[7)], (0.7%)	Drug-induced liver injury[7)], (0.7%)
Skin and subcutaneous tissue disorders	Very Common	Rash[m] Pruritus		Very Common	Rash[8)], (18%)	Rash[8)], (0.5%)
	Common	Dry skin Photosensitivity reaction	Rash[m] Photosensitivity reaction	Common	Photosensitivity, (9.1%)	Photosensitivity (0.2%)
	Uncommon		Dry skin	Uncommon		
Musculoskeletal and connective tissue disorders	Very common	Blood CPK increased Myalgia[n] Arthralgia	Blood CPK increased	Very common	Myalgia[9)], (28%) Blood CPK increased, (10%)	Blood CPK increased, (3.2%) Myalgia[9)], (0.7%)

	Brigatinib			Alectinib		
System organ class	**Frequency category**	**Adverse reactions† all grades**	**Adverse reactions Grade 3-4**	**Frequency category**	**Adverse reactions† all grades**	**Adverse reactions Grade 3-4**
	Common	Pain in extremity Musculoskeletal stiffness Musculoskeletal chest pain		Common		
	Uncommon		Pain in extremity Musculoskeletal chest pain, Myalgia[n]	Uncommon		
Renal and urinary disorders	Very common	Blood creatinine increased		Very common		
	Common			Common	Blood creatinine increased, (7.2%) Acute Kidney injury*, (1.0%)	Blood creatinine increased*, (0.7%) Acute Kidney injury*, (1.0%)
General disorders and administration site conditions	Very common	Fatigue[o] Oedema[p] Pyrexia		Very common	Oedema[10)], (30%)	Oedema[10)], (0.7%)
	Common	Pain Non-cardiac chest pain Chest discomfort	Fatigue[o]	Common		
	Uncommon		Non-cardiac chest pain Pyrexia Oedema	Uncommon		
Investigations	Very common			Very common	Weight increased, (12%)	Weight increased, (0.7%)
	Common	Weight decreased Blood cholesterol Increased		Common		
	Uncommon		Weight decreased	Uncommon		

	Brigatinib			Alectinib		
System organ class	Frequency category	Adverse reactions† all grades	Adverse reactions Grade 3-4	Frequency category	Adverse reactions† all grades	Adverse reactions Grade 3-4

[a] Includes atypical pneumonia, pneumonia, pneumonia aspiration, pneumonia pseudomonal, lower respiratory tract infection, lower respiratory tract infection viral, lung infection

[b] Grade not applicable

[c] Includes headache, sinus headache, head discomfort, migraine, tension headache

[d] Includes paraesthesia, peripheral sensory neuropathy, dysaesthesia, hyperaesthesia, hypoaesthesia, neuralgia, neuropathy peripheral, neurotoxicity, peripheral motor neuropathy, polyneuropathy

[e] Includes altered visual depth perception, asthenopia, cataract, colour blindness acquired, diplopia, glaucoma, intraocular pressure increased, macular oedema, photophobia, photopsia, retinal oedema, vision blurred, visual acuity reduced, visual field defect, visual impairment, vitreous detachment, vitreous floaters, amaurosis fugax

[f] Includes sinus tachycardia, tachycardia

[g] Includes bradycardia, sinus bradycardia

[h] Includes dyspnoea, dyspnoea exertional

[i] Includes interstitial lung disease, pneumonitis

[j] Includes diarrhoea, diarrhoea infectious

[k] Includes abdominal discomfort, abdominal distension, abdominal pain, abdominal pain lower, abdominal pain upper, epigastric discomfort

[l] Includes aphthous stomatitis, stomatitis, aphthous ulcer, mouth ulceration, oral mucosal blistering

[m] Includes dermatitis acneiform, erythema, exfoliative rash, rash, rash erythematous, rash macular, rash maculo-papular, rash papular, rash pruritic, rash pustular, dermatitis, dermatitis allergic, generalised erythema, rash follicular, urticaria

[n] Includes musculoskeletal pain, myalgia, muscle spasms, muscle tightness, muscle twitching, musculoskeletal discomfort

[o] Includes asthenia, fatigue.

[p] Includes eyelid oedema, face oedema, localised oedema, oedema peripheral, periorbital oedema, swelling face, generalised oedema, peripheral swelling

[†] The frequencies for ADR terms associated with chemistry and haematology laboratory changes were determined based on the frequency of abnormal laboratory shifts from baseline.

*Includes one Grade 5 event

** Increased alkaline phosphatase was reported in the post-marketing period and in pivotal phase II and phase III clinical trials.

1) includes cases of anaemia and haemoglobin decreased

2) includes cases of dysgeusia and hypogeusia

3) includes cases of blurred vision, visual impairment, vitreous floaters, reduced visual acuity, asthenopia, and diplopia

4) includes cases of bradycardia and sinus bradycardia

5) includes cases of stomatitis and mouth ulceration

6) includes cases of blood bilirubin increased, hyperbilirubinaemia and bilirubin conjugated increased

7) includes two patients with reported MedDRA term of drug-induced liver injury as well as one patient with reported Grade 4 increased AST and ALT who had documented drug-induced liver injury by liver biopsy

8) includes cases of rash, rash maculopapular, dermatitis acneiform, erythema, rash generalised, rash papular, rash pruritic, rash macular and exfoliative rash

9) includes cases of myalgia and musculoskeletal pain

10) includes cases of oedema peripheral, oedema, generalised oedema, eyelid oedema, periorbital oedema, face oedema and localised oedema.

QUALITY OF LIFE

The ALESIA publication did not report any Quality of Life data.

For brigatinib and alectinib the HR of worsening of Global HRQoL was 0.70 (95% CI: 0.49; 1.00, P= 0.049) and 0.72 (95% CI: 0.38; 1.39, P not reported), respectively.
There thus appear to be little (if any) difference in the impact on the Global HRQoL.

A detailed analysis of the symptom domains from the EORTC Lung Cancer 13 instrument from the ALEX and ALTA-1L trials does however, show differences in the Quality of Life with-in one specific, and lung cancer relevant, domain: dyspnea.

Dyspnea
The dyspnea domain of the EORTC LC13 instrument is composed of three questions scored on a four point scale ranging from "not at all" (1) to "very much" (4). The three questions are "where you short of breath when you" 1) "rested?", 2) "walked?", and 3) "climbed stairs?"

[redacted] is consistent with the longer PFS and its associated hazard ratio of 0.49 (Camidge et al. 2020).
On the other hand, the hazard ratio of *time to deterioration of dyspnea* was 1.76 (95% CI: 1.05; 2.92) in the ALEX trial (Pérol et al. 2019) in contrast to the PFS HR of 0.50 (Peters et al. 2017). An explanation for this observation is not provided by the authors, but may be found in the rate of anemia associated with alectinib usage (all grade 17%, grade > 3: 3.0%).

Danish and Nordic oncologist specialized in treatment of lung cancer has on two independent advisory boards described dyspnea as a "core symptom" of lung cancer.
Correspondingly, the experience of dyspnea has been associated with weakness, suffocaction, tightness, congestion, pain, anxiety and panic in lung cancer patients (Smith et al. 2001). Dyspnea thus drives a series of disease related ailments and negative psychological consequences of the disease.

However, such a consequence is unlikely to be captured in a "global" quality of life analysis which include assessments of side effects to chemotherapy, which ALK+ NSCLC patients are not exposed to.

The above difference in patient reported experience of dyspnea thus remain as a significant uncaptured difference between alectinib and brigatinib which have potential implications for the quality of life of patients treated with alectinib and brigatinib.

[5] Confidential Data

CONCLUSION

An indirect comparison of efficacy between brigatinib and alectinib should be interpreted with caution for the following reasons:

Outcome	Reason for caution
OS	Substantial cross-over in ALTA-1l – no cross-over permitted in ALEX and ALESIA.
Discontinuation due to AEs	No capture of signs and symptoms of disease progression as AEs is likely to eliminate symptoms associated with disease progression from the tally of *discontinuation due to* AEs in ALEX and ALESIA.
CNS-PFS	Differences in baseline proportion of patients with brain metastasis is likely to lead to differences in relative CNS effect as crizotinib treated patients are susceptible to progress in the CNS first.
PFS	Differences in definition of PFS is likely to result in patients in ALEX and ALESIA receiving clinical benefit of radiotherapy and extended PFS, while patients in ALTA-1L were scored as progressed upon receipt of radiotherapy.
AEs	No capture of signs and symptoms of disease progression as AEs is likely to eliminate symptoms associated with disease progression from the tally of AEs in ALEX and ALESIA.
HRQoL	Not Applicable

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7 Appendices

Literature search

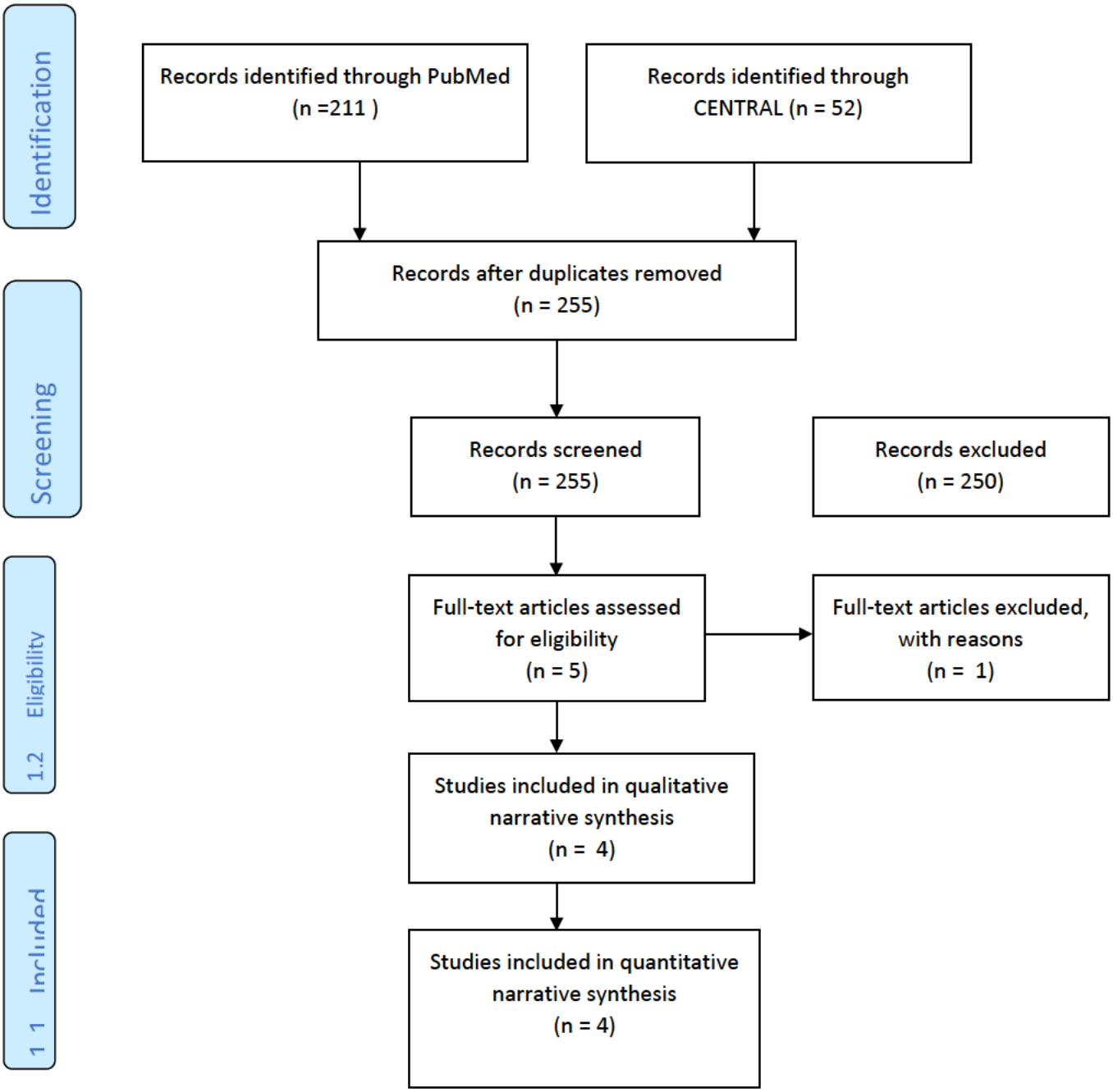
Søgestreng til PubMed:

#	Query PubMed	Hits	Kommentar
1	brigatinib[nm] OR brigatinib[tiab] OR Alunbrig*[tiab] OR AP26113[tiab]	170	Søgetermer for lægemidler
2	alectinib[nm] OR alectinib[tiab] OR Alecensa*[tiab] OR CH5424802[tiab] OR RO5424802[tiab]	503	
3	NSCLC[tiab]	42279	Søgetermer for ALK-positiv NSCLC
4	Carcinoma, Non-Small-Cell Lung[mh]	52312	
5	Adenocarcinoma of Lung[mh]	8227	
6	(nonsmall cell[tiab] or non-small cell[tiab] or squamous cell[tiab] or large cell[tiab]) AND lung[tiab] AND (cancer[tiab] or carcinoma[tiab] or carcinomas[tiab] OR adenocarcinoma*[tiab])	75742	
7	Anaplastic Lymphoma Kinase[mh]	3163	
8	(anaplastic lymphoma kinase[tiab] or ALK[tiab]) AND (mutat*[tiab] OR mutant*[tiab] OR translocat*[tiab] OR rearrange*[tiab] OR positiv*[tiab] OR fused[tiab])	6326	
9	"ALK+"[tiab] OR ALK-R[tiab]	8943	
10	(#1 OR #2) AND (#3 OR #4 OR #5 OR #6) AND (#7 OR #8 OR #9)	448	Kombination af lægemidler og indikation
11	case report[ti] OR review of the literature[tiab] OR retrospective[ti] OR observational[ti]	424792	Eksklusion af specifikke publikationstyper
12	Case Reports[pt] OR Comment[pt] OR Editorial[pt] OR Guideline[pt] OR Letter[pt] OR (Review[pt] NOT (Systematic Review[pt] OR Meta-Analysis[pt]))	6121165	
13	Animals[mh] NOT Humans[mh]	4698496	
14	#10 NOT (#11 OR #12 OR #13)	211	Endeligt resultat

Søgestreng til CENTRAL:

#	Query CENTRAL	Hits	Kommentar
1	(brigatinib or Alunbrig* or AP26113):ti,ab,kw	73	Søgetermer for lægemidler
2	(alectinib or Alecensa* or CH5424802 or RO5424802):ti,ab,kw	107	
3	NSCLC:ti,ab	8742	Søgetermer for ALK-positiv NSCLC
4	("Carcinoma, Non-Small-Cell Lung" or "non small cell lung cancer" or "Adenocarcinoma of Lung" or "large cell lung carcinoma" or "lung adenocarcinoma" or "squamous cell lung carcinoma"):kw	4415	
5	(("nonsmall cell" or "non small cell" or "squamous cell" or "large cell") NEAR/2 lung NEAR/2 (cancer or carcinoma* or adenocarcinoma*)):ti,ab	10909	
6	(lung NEAR/2 adenocarcinoma):ti,ab	324	
7	("anaplastic lymphoma kinase"):kw	92	
8	(("anaplastic lymphoma kinase" or ALK*) and (mutat* or mutant* or translocat* or rearrange* or positiv*)):ti,ab	1424	
9	ALK-R:ti,ab	0	
10	(#1 or #2) and (#3 or #4 or #5 or #6) and (#7 or #8 or #9)	113	Kombination af lægemidler og indikation
11	(clinicaltrials.gov or trialsearch):so	326336	Eksklusion af specifikke publikationstyper
12	review:pt or erratum:ti	19556	
13	#10 not (#11 or #12)	79	
14	embase:an not pubmed:an	337060	Eksklusion af resultater, der kommer fra PubMed
15	#13 and #14 in Trials	52	Endeligt resultat

Prisma Flow Diagram of article selection for Clinical Question 1



Main characteristics of included studies

Study characteristics

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

Trial name	A Phase 3 Multicenter Open-label Study of Brigatinib (AP26113) versus Crizotinib in Patients with ALK-positive Advanced Lung Cancer
NCT number	NCT02737501
Objective	To compare the efficacy of brigatinib to that of crizotinib in ALK+ locally advanced or metastatic NSCLC patients naive to ALK inhibitors..
Publications – title, author, journal, year	Camidge DR, Kim HR, Ahn MJ, Yang JC, Han JY, Lee JS, et al. Brigatinib versus Crizotinib in ALK-Positive Non-Small-Cell Lung Cancer. N Engl J Med. 2018;379(21):2027-39.
Study type and design	Open-label randomized active comparator phase III trial. Enrolled patients were randomly assigned 1:1. Stratification was conducted on the basis of intracranial CNS metastasis at baseline (yes/no) & prior chemotherapy use for locally advanced or metastatic disease (yes/no). For the purposes of stratification, prior chemotherapy is defined as completion of ≥1 full cycle of chemotherapy in the locally advanced or metastatic setting. Cross-over to experimental arm was allowed at progression from control arm.
Follow-up time	Median Follow-Up for brigatinib arm: 24.9 months Median Follow-Up for crizotinib arm: 15.2 months – follow-up for the crizotinib arm was stopped at crossover to brigatinib treatment following progression on crizotinib.
Population (inclusion and exclusion criteria)	**Key Inclusion Criteria** All patients were required to meet all the following eligibility criteria for study entry: • Had histologically or cytologically confirmed Stage IIIB (locally advanced or recurrent and was not a candidate for definitive multimodality therapy) or Stage IV NSCLC. • Met one of the following criteria: –Documented ALK rearrangement by a positive result from the Vysis ALK Break-Apart fluorescence in situ hybridization (FISH) Probe Kit (Abbott Molecular) or the Ventana ALK (D5F3) companion diagnostic assay. The test had to be performed according to the product's instructions for use. –Documented ALK rearrangement by a different test and adequate tissue available for central laboratory testing by an FDA-approved test. Confirmation of central test positivity was not required before randomization. • Had a least 1 measurable (i.e., target) lesion per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. **Key Exclusion Criteria** Patients meeting any of the criteria below were ineligible for the study: • Received a prior investigational antineoplastic agent for NSCLC. • Previously received any prior TKI, including ALK-targeted TKIs. • Previously received more than 1 regimen of systemic anticancer therapy for locally advanced or metastatic disease. • Had major surgery within 30 days of the first dose of study drug. • Had symptomatic CNS metastases (parenchymal or leptomeningeal) at screening or asymptomatic disease requiring an increasing dose of corticosteroids to control symptoms within 7 days before randomization. • Presence or history of pulmonary interstitial disease, drug-related pneumonitis, or radiation pneumonitis.

<table>
<tr><td>Intervention</td><td>Brigatinib was administered as oral tablets at a dose of 180 mg QD after a 7-day lead-in at 90 mg QD, N = 137.
Crizotinib was administered at the approved dose of 250 mg twice daily (BID), N = 138.</td></tr>
<tr><td>Baseline characteristics</td><td>
<table>
<tr><th></th><th></th><th>Brigatinib n=137</th><th>Crizotinib n=138</th><th>Total N=275</th></tr>
<tr><td>Median age, y (range)</td><td></td><td>58 (27–86)</td><td>60 (29–89)</td><td>59 (27–89)</td></tr>
<tr><td>Sex, %</td><td>Female</td><td>50</td><td>59</td><td>55</td></tr>
<tr><td>Race, %</td><td>White,
Asian,
unknown</td><td>55
43
1</td><td>62
36
1</td><td>59
39
1</td></tr>
<tr><td>ECOG performance status, %</td><td>0, 1, 2</td><td>39, 55, 5</td><td>38, 57, 5</td><td>39, 56, 5</td></tr>
<tr><td>Stage of disease at study entry, %</td><td>IIIB, IV</td><td>6, 94</td><td>9, 91</td><td>7, 93</td></tr>
<tr><td>Median time since advanced/metastatic NSCLC diagnosis, mo (range)</td><td></td><td>3.2 (0.3–73.2)</td><td>3.5 (0.4–86.0)</td><td>3.5 (0.3–86.0)</td></tr>
<tr><td>ALK status assessed locally by FDA-approved test, %a</td><td></td><td>90</td><td>81</td><td>86</td></tr>
<tr><td>Brain metastases at baseline, %b</td><td></td><td>29</td><td>30</td><td>29</td></tr>
<tr><td>Prior radiotherapy to the brain, %</td><td>WBRT, SRS</td><td>11, 3</td><td>9, 6</td><td>10, 4</td></tr>
<tr><td>Prior chemotherapy in the locally advanced or metastatic setting, %c</td><td></td><td>26</td><td>27</td><td>27</td></tr>
</table>
</td></tr>
<tr><td>Primary and secondary endpoints</td><td>Primary Endpoint
The primary endpoint for this study is PFS, as assessed by the BIRC, per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. A PFS event in the primary analysis is defined as death, BIRC-determined RECIST progression or receiving radiotherapy for CNS metastases. Radiological scans for the assessment of disease progression and tumor response were scheduled to be performed every 8 weeks, and unscheduled scans could be performed at other times.

Secondary Endpoints
1. Confirmed ORR, as assessed by the BIRC, per RECIST v1.1
2. Confirmed intracranial ORR, as assessed by the BIRC
3. Intracranial PFS, as assessed by the BIRC
4. OS
The first four endpoints above will be evaluated in a closed testing procedure.
5. Duration of response, as assessed by the BIRC
6. Time to response, as assessed by the BIRC
7. Disease control rate, as assessed by the BIRC
8. Safety and tolerability
9. Change from baseline scores in global health status/quality of life (QOL) assessed with the EORTC QLQ-C30 (v3.0), and time-to-deterioration in dyspnea</td></tr>
</table>

	assessed with the EORTC QLQ-LC13 (v3.0) **Exploratory Endpoints** 1. Confirmed ORR for brigatinib, as assessed by the BIRC, per RECIST v1.1, in patients who crossover from Arm B (crizotinib) 2. PFS from the first dose of brigatinib, as assessed by the BIRC, per RECIST v1.1, in patients who crossover from Arm B (crizotinib) 3. Correlation of brigatinib plasma pharmacokinetics with both efficacy and safety 4. Molecular determinants of efficacy and safety with brigatinib and crizotinib
Method of analysis	The following text is based on the statistical analysis plan of study AP26113 (TAKEDA 2019). The primary analysis was based on the ITT population. The ITT population includes all subjects randomized to either regimen. **PFS and OS** The primary analysis of the primary endpoint (PFS) and the secondary endpoint OS were performed using a 2-sided stratified log-rank test (stratification factors: presence of iCNS metastases at baseline [Yes versus No], and prior chemotherapy for locally advanced or metastatic disease [Yes versus No]) to compare the BIRC-assessed PFS of subjects randomized to brigatinib with the BIRC-assessed PFS of subjects randomized to crizotinib. The overall (2-sided) Type I error rate were controlled at 0.05. Median PFS and OS and their associated 95% confidence intervals were estimated for each treatment arm using the Kaplan-Meier method. Additionally, hazard ratios were estimated using the Cox regression model with the stratification factors as covariates. **Confirmed ORR and Confirmed intracranial ORR** Confirmed ORR and Confirmed intracranial ORR were analyzed with the Mantel-Haenszel test (using the stratification factors) on 1) the ITT population (confirmed ORR), 2) the measurable iCNS disease population (confirmed intracranial ORR), 3) the non-measurable iCNS disease population (confirmed intracranial ORR), and 4) the all iCNS disease population (confirmed intracranial ORR). Analysis will differ in that the iCNS ORR will be analyzed with the Mantel-Haenszel test using only the stratification factor of prior chemotherapy. **Duration of response** The analysis of response duration will only include ITT subjects with confirmed CR or PR. An additional analysis of duration of response will be performed using disease assessment performed by the investigator. Median values and 2-sided 95% confidence intervals will be estimated using Kaplan-Meier (KM) method in the ITT population. The KM-estimated PFS rates and OS rates at 12 and 24 months and the associated 2-sided 95% confidence intervals will be computed. Duration of response will also be summarized with descriptive statistics for subjects with confirmed CR or PR and the Kaplan-Meier method in which follow-up for subjects without PFS events will be censored.

	Disease control rate, as assessed by the BIRC Disease control rate will be analyzed with the Mantel-Hanzel test (using the stratification factors) on the ITT population to compare the proportion of subjects achieving disease control. **Intracranial PFS, as assessed by the BIRC** Intracranial PFS will be defined and analyzed in the same manner as for PFS used in the primary endpoint with the exceptions that the progression events used will come from the iCNS BIRC and the analysis will be restricted to subjects identified as having brain metastases at baseline in the randomization. The primary evaluation of iCNS PFS will be performed in the all iCNS disease population, with a sensitivity analysis in the active iCNS disease population. Additional analyses will be performed in the no iCNS disease population, in which case PFS events would consist of either the appearance of new brain metastases or death. iCNS PFS will also be analyzed in the measurable iCNS disease population with a sensitivity analysis in the active measurable iCNS disease population. The treated population for each regimen includes all subjects receiving at least one dose of study drug. Safety were analyzed using the treated population.
Subgroup analyses	The following text is based on the statistical analysis plan of study AP26113 (TAKEDA 2019); as such all subgroups were prespecified **All iCNS Disease Population** The all iCNS disease population will consist of those subjects in the ITT population who were determined by the iCNS BIRC to have iCNS metastases at baseline regardless of whether they had at least one lesion that qualified as a target lesion in their baseline assessment. **No iCNS Disease Population** The no iCNS disease population will consist of those subjects in the ITT population who were not determined by the iCNS BIRC to have iCNS metastases at baseline. **Measurable iCNS Disease Population** Measurability of lesions is a core component definition of a potential target lesion in the RECIST v1.1 process and is retained in the modified RECIST used for iCNS disease assessment (Section 3.4.1.2). Therefore the measurable iCNS disease population will consist of those subjects in the all iCNS Disease population who were determined by the iCNS BIRC to have had at least one target lesion in their baseline assessment **Non-Measurable iCNS Disease Population** The non-measurable iCNS disease population is intended to characterize subjects who were determined to have iCNS disease at baseline but did not have measurable lesions. This means that subjects with both measurable and non-measurable lesions at baseline will not be included in this population. Therefore the non-measurable iCNS disease population will consist of all subjects in the all iCNS disease population who are not included in the measurable iCNS disease population. **Active iCNS Disease Population**

	An active brain lesion is defined for the purpose of this study as meeting either of the following criteria: 1) A lesion that has not previously been irradiated 2) Having had prior radiation treatment but then having definitely progressed, as assessed by the investigator, after being irradiated. However, the independence between disease assessments performed by the BIRC and those performed by the investigators requires limits on the amount and types of information transferred between sites and the central reading process. Information as to whether any radiotherapy to the brain prior to study entry was made available to the BIRC readers, but this did not include whether the therapy was targeted at individual lesions or whether any irradiated lesions subsequently progressed. Therefore, assessment as to whether iCNS lesions are active cannot be done using BIRC time point responses. It can, however, be determined using the RECIST v1.1 assessment performed at baseline by the investigator since those assessments include lesion-level data on radiotherapy and subsequent progression. Therefore the active iCNS disease population is defined as including all subjects in the all iCNS disease population who have one active iCNS lesion in their baseline RECIST v1.1 scan performed by the investigator. Analysis of efficacy in the active iCNS disease population will still be performed using data from the modified RECIST assessments performed by the BIRC. **Active Measurable iCNS Disease Population** The active measurable iCNS disease population is defined as all subjects included in both the measurable iCNS disease population and the active iCNS disease population. **Active Non-Measurable iCNS Disease Population** The active measurable iCNS disease population is defined as all subjects included in both the non-measurable iCNS disease population and the active iCNS disease population. PFS in the iCNS population was analyzed using the same method as the primary endpoint Patients with CNS lesions requiring local radiotherapy such as stereotactic radiosurgery (SRS) were allowed to continue study drug after appropriate interruption, as determined by the investigator with sponsor agreement; however, for analysis purposes, these patients were considered to have PD.

Trial name	Randomized, Multicenter, Phase III, Open-Label Study of Alectinib Versus Crizotinib in Treatment-Naive Anaplastic Lymphoma Kinase-Positive Advanced Non-Small Cell Lung Cancer
NCT number	NCT02075840
Objective	Comparing Alectinib With Crizotinib in Treatment-Naive Anaplastic Lymphoma Kinase-Positive Advanced Non-Small Cell Lung Cancer Participants
Publications – title, author, journal, year	Updated overall survival and final progression-free survival data for patients with treatment-naive advanced ALK-positive non-small-cell lung cancer in the ALEX study. Mok T, Camidge DR, Gadgeel SM, Rosell R, Dziadziuszko R, Kim DW, et al. Annals of Oncology, 2020. Alectinib versus crizotinib in treatment-naive anaplastic lymphoma kinase-positive (ALK+) non-small-cell lung cancer: CNS efficacy results from the ALEX study. Gadgeel S, Peters S, Mok T, Shaw AT, Kim DW, Ou SI, et al. Annals of Oncology, 2018.
Study type and design	Global open label, randomized, multicenter phase III study. Patients were randomized 1:1 to receive alectinib or crizotinib. Randomisation was done centrally via an interactive voice or web response system, with stratification by ECOG PS (0 or 1 vs 2) and baseline CNS metastases (yes vs no). Cross-over was not allowed.
Follow-up time	Median follow-up: Alectinib arm: 48.2 months. Crizotinib arm: 23.3 months.
Population (inclusion and exclusion criteria)	**Inclusion Criteria:** 1. Histologically or cytologically confirmed diagnosis of advanced or recurrent (Stage IIIB not amenable for multimodality treatment) or metastatic (Stage IV) NSCLC that is ALK-positive as assessed by the Ventana immunohistochemistry (IHC) test 2. Life expectancy of at least 12 weeks 3. Eastern cooperative oncology group performance status (ECOG PS) of 0-2 4. Participants with no prior systemic treatment for advanced or recurrent (Stage IIIB not amenable for multimodality treatment) or metastatic (Stage IV) NSCLC 5. Adequate renal, and hematologic function 6. Participants must have recovered from effects of any major surgery or significant traumatic injury at least 28 days before the first dose of study treatment

	7. Measurable disease by response evaluation criteria in solid tumors (RECIST) version 1.1 (v1.1) prior to the administration of study treatment 8. Prior brain or leptomeningeal metastases allowed if asymptomatic (e.g., diagnosed incidentally at study baseline) 9. Negative pregnancy test for all females of child bearing potential 10. Use of highly effective contraception as defined by the study protocol **Exclusion Criteria:** 1. Participants with a previous malignancy within the past 3 years 2. Any gastrointestinal (GI) disorder or liver disease 3. National cancer institute common terminology criteria for adverse events (NCI CTCAE) (version 4.0) Grade 3 or higher toxicities due to any prior therapy (e.g., radiotherapy) (excluding alopecia) 4. History of organ transplant 5. Co-administration of anti-cancer therapies other than those administered in this study 6. Participants with baseline QTc greater than (>) 470 milliseconds or symptomatic bradycardia 7. Recipient of strong/potent cytochrome P4503A inhibitors or inducers within 14 days prior to the first dose until the end of study treatment 8. Recipient of any drug with potential QT interval prolonging effects within 14 days prior to the first dose for all participants and while on treatment through the end of the study for crizotinib-treated participants only 9. History of hypersensitivity to any of the additives in the alectinib and crizotinib drug formulation 10. Pregnancy or lactation 11. Any clinically significant disease or condition (or history of) that could interfere with, or for which the treatment might interfere with, the conduct of the study or the absorption of oral medications or that would, in the opinion of the principal investigator, pose an unacceptable risk to the participant in this study 12. Any psychological, familial, sociological, or geographical condition potentially hampering compliance with the study protocol requirements and/or follow-up procedures; those conditions should be discussed with the participant before trial entry

Intervention	Experimental: Alectinib, 600 mg (4x150 mg) BID, from day 0 until progression, death, withdrawal of consent, or intolerable toxicity. N= 152 Active Comparator: Crizotinib Crizotinib capsules orally at a dose of 250 mg BID with or without food until disease progression, unacceptable toxicity withdrawal of consent, or death.
Baseline characteristics	

Characteristic	Crizotinib (N= 151)	Alectinib (N= 152)
Age — yr		
Mean	53.8±13.5	**56.3±12.0**
Median	54.0	**58.0**
Range	18–91	**25–88**
Sex — no. (%)		
Male	64 (42)	**68 (45)**
Female	87 (58)	**84 (55)**
Race — no. (%)†‡		
Asian	69 (46)	**69 (45)**
Non-Asian	82 (54)	**83 (55)**
ECOG performance status — no. (%)†		
0 or 1	141 (93)	**142 (93)**
2	10 (7)	**10 (7)**
Smoking status — no. (%)		
Active smoker	5 (3)	**12 (8)**
Former smoker	48 (32)	**48 (32)**
Nonsmoker	98 (65)	**92 (61)**
Current stage of disease — no. (%)		
IIIB	6 (4)	**4 (3)**
IV	145 (96)	**148 (97)**
Histologic type — no. (%)		
Adenocarcinoma	142 (94)	**137 (90)**
Large-cell carcinoma	3 (2)	**0**
Mixed with predominantly adeno- carcinoma component	1 (1)	**0**
Squamous-cell carcinoma	2 (1)	**5 (3)**
Undifferentiated	0	**4 (3)**
Other	3 (2)	**6 (4)**
CNS metastases — no. (%)†§		
Yes	58 (38)	**64 (42)**
No	93 (62)	**88 (58)**
Treatment for CNS metastases — no./total no. (%)		
Brain surgery	1/22 (5)	**1/27 (4)**
Radiosurgery	4/22 (18)	**5/27 (19)**
Whole-brain radiotherapy	16/22 (73)	**17/27 (63)**
Other¶	1/22 (5)	**4/27 (15)**
Previous brain radiation — no. (%)		
Yes	21 (14)	**26 (17)**

	No: 130 (86) / 126 (83)
Primary and secondary endpoints	**Primary endpoints** 1. Progression-Free Survival (PFS) by Investigator Assessment [Time Frame: Randomization to first documented disease progression or death, whichever occurs first (assessed every 8 weeks up to 33 months)] 2. Percentage of Participants With PFS Event by Investigator Assessment [Time Frame: Randomization to first documented disease progression or death, whichever occurs first (assessed every 8 weeks up to 33 months)] PFS was assessed percentage of participants with disease progression or death whichever occurred first by investigator assessment using Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 (v1.1) Criteria. As per RECIST v1.1, disease progression is a 20% increase in the sum of the diameters of target lesions, an increase in size of measurable lesions by at least 5 millimeter (mm) and the appearance of new lesions. **Secondary endpoints** 1. PFS Independent Review Committee (IRC)-Assessed [Time Frame: Randomization to first documented disease progression or death, whichever occurs first (assessed every 8 weeks up to 33 months)] 2. Percentage of Participants With PFS Event by IRC [Time Frame: Randomization to first documented disease progression or death, whichever occurs first (assessed every 8 weeks up to 33 months)] PFS was assessed as percentage of participants with disease progression or death whichever occurred first by IRC assessment using Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 (v1.1) Criteria. As per RECIST v1.1, disease progression is a 20% increase in the sum of the diameters of target lesions, an increase in size of measurable lesions by at least 5 mm and the appearance of new lesions. 3. Percentage of Participants With Central Nervous System (CNS) Progression as Determined by IRC Using RECIST V1.1 Criteria [Time Frame: Randomization to CNS PD as first occurrence of disease progression (assessed every 8 weeks up to 33 months)] 4. Percentage of Participants With Central Nervous System (CNS) Progression as Determined by IRC Using Revised Assessment in Neuro

	Oncology (RANO) Criteria [Time Frame: Randomization to the first occurrence of disease progression in the CNS (assessed every 8 weeks up to 33 months)] CNS progression was assessed as percentage of participants with event defined as time from randomization until first radiographic evidence of CNS progression by IRC. The risk for a CNS progression without a prior non-CNS progression with alectinib compared with crizotinib. 5. Percentage of Participants With Objective Response Rate (ORR) of Complete Response (CR) or Partial Response (PR) as Determined by The Investigators According to RECIST V1.1 Criteria [Time Frame: Randomization to first documented disease progression or death, whichever occurs first (assessed every 8 weeks up to 33 months)] ORR was defined as the percentage of participants who attained CR or PR. As per RECIST v1.1, CR: Disappearance of all target lesions and any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm, PR: At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum of diameters. 6. Duration of Response (DOR) According to RECIST V1.1 Criteria as Assessed by the Investigators [Time Frame: First occurrence of objective response to first documented disease progression or death, whichever occurs first (assessed every 8 weeks up to 33 months)] DOR was defined as the time from when response (CR or PR) was first documented to first documented disease progression or death, whichever occurred first. DOR was evaluated for participants who had a best overall response (BOR) of CR or PR. 7. Overall Survival (OS) [Time Frame: From randomization until death (up to 43 months)] Overall survival (OS) was defined as the time from randomization to death from any cause. 8. Percentage of Participants With OS Event [Time Frame: From randomization until death (up to 43 months)] Overall survival (OS) was defined as the time from randomization to death from any cause. 9. Percentage of Participants With CNS ORR of CR or PR IRC-assessed According to RECIST v1.1 Criteria [Time Frame: Randomization to first

	documented disease progression or death, whichever occurs first (assessed every 8 weeks up to 33 months)] CNS ORR was defined as the percentage of participants who attained CR or PR and had measurable/non-measurable CNS lesions at baseline. As per RECIST v1.1, CR: Disappearance of all target lesions and any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm, PR: At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum of diameters. 10. CNS DOR IRC-assessed According to RECIST v1.1 Criteria [Time Frame: First occurrence of CNS objective response to first documented disease progression or death, whichever occurs first (assessed every 8 weeks up to 33 months)] CNS DOR was defined as the time from when response (CR or PR) was first documented to first documented disease progression or death, whichever occurred first. DOR was evaluated for participants who had a best overall response (BOR) of CR or PR. 11. Percentage of Participants With Adverse Events [Time Frame: Baseline up to 28 months in the crizotinib arm and up to 30 months in the alectinib arm] An adverse event (AE) is any untoward medical occurrence in a participant, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. 12. Area Under The Concentration-Time Curve (AUC) of Alectinib [Time Frame: Pre-dose (within 2 hours before alectinib) (baseline), 1, 2, 4, 6, and 8 hours post-dose at Visit 0 (first dosing day) and Week 4; Pre-dose (within 2 hours) at Week 8, then every 8 weeks until disease progression or death/withdrawal (up to 33 months)] 13. Maximum Concentration (Cmax) of Alectinib [Time Frame: Pre-dose (within 2 hours before alectinib), 1, 2, 4, 6, and 8 hours post-dose at baseline and Week 4; Pre-dose (within 2 hours before alectinib) at Week 8, then every 8 weeks until disease progression or death/withdrawal from study (up to 33 months)] 14. Time to Reach Cmax (Tmax) of Alectinib [Time Frame: Pre-dose (within 2 hours before alectinib), 1, 2, 4, 6, and 8 hours post-dose at baseline and Week 4; Pre-dose (within 2 hours before alectinib) at Week 8, then every 8 weeks until disease progression or death/withdrawal from study (up to 33 months)]

	15. AUC of Alectinib Metabolite [Time Frame: Pre-dose (within 2 hours before alectinib) (baseline), 1, 2, 4, 6, and 8 hours post-dose at Visit 0 (first dosing day) and Week 4; Pre-dose (within 2 hours) at Week 8, then every 8 weeks until disease progression or death/withdrawal (up to 33 months)] 16. Cmax of Alectinib Metabolite [Time Frame: Pre-dose (within 2 hours before alectinib), 1, 2, 4, 6, and 8 hours post-dose at baseline and Week 4; Pre-dose (within 2 hours before alectinib) at Week 8, then every 8 weeks until disease progression or death/withdrawal from study (up to 33 months)] 17. Tmax of Alectinib Metabolite [Time Frame: Pre-dose (within 2 hours before alectinib), 1, 2, 4, 6, and 8 hours post-dose at baseline and Week 4; Pre-dose (within 2 hours before alectinib) at Week 8, then every 8 weeks until disease progression or death/withdrawal from study (up to 33 months)] 18. Time to Deterioration by European Organization for The Research And Treatment of Cancer (EORTC) Quality Of Life Questionnaire Core 30 (C30) [Time Frame: Baseline, every 4 weeks until disease progression (up to 33 months)] 19. Percentage of Participants With Deterioration by EORTC Quality Of Life Questionnaire Core 30 (C30) [Time Frame: Baseline, every 4 weeks until disease progression (up to 33 months)] 20. Time to Deterioration by EORTC Quality of Life Questionnaire Lung Cancer Module 13 (LC13) [Time Frame: Baseline, every 4 weeks until disease progression (up to 33 months)] 21. Percentage of Participants With Deterioration by EORTC Quality of Life Questionnaire Lung Cancer Module 13 (LC13) [Time Frame: Baseline, every 4 weeks until disease progression (up to 33 months)] The EORTC QLQ-LC13 module generated one multiple-item scale score assessing dyspnea and a series of single item scores assessing chest pain, arm/shoulder pain, pain in other parts, coughing, sore mouth, dysphagia, peripheral neuropathy, alopecia, and hemoptysis. All the scales and single-item scores were linearly transformed so that each score ranged from 0 to 100. A higher score on the global health and functioning subscales is indicative of better functioning. Confirmed clinically meaningful deterioration in lung cancer symptoms is defined as a >or=10-point increase from baseline in a symptom score that must be held for at least two consecutive assessments or an initial >or=10-point increase above baseline followed by death within 5 weeks from the last assessment. 22. Health-Related Quality of Life (HRQoL) by EORTC Quality of Life Questionnaire C30 Score [Time Frame: Baseline, every 4 weeks until disease progression (up to 33 months)]

	23. HRQoL by EORTC Quality of Life Questionnaire LC13 Score Coughing [Time Frame: Baseline, every 4 weeks until disease progression (up to 33 months)] 24. HRQoL by EORTC Quality of Life Questionnaire LC13 Score Dyspnoea [Time Frame: Baseline, every 4 weeks until disease progression (up to 33 months)] 25. HRQoL by EORTC Quality of Life Questionnaire LC13 Score Pain in Chest [Time Frame: Baseline, every 4 weeks until disease progression (up to 33 months)] 26. HRQoL by EORTC Quality of Life Questionnaire LC13 Score Pain in Arm and Shoulder [Time Frame: Baseline, every 4 weeks until disease progression (up to 33 months)] The EORTC QLQ-LC13 module generated one multiple-item scale score assessing dyspnea and a series of single item scores assessing chest pain, arm/shoulder pain, pain in other parts, coughing, sore mouth, dysphagia, peripheral neuropathy, alopecia, and hemoptysis. All the scales and single-item scores were linearly transformed so that each score ranged from 0 to 100. A higher score on the global health and functioning subscales is indicative of better functioning.
Method of analysis	**From the Statistical Analysis Plan of ALEX (Ltd 2019):** The primary analysis population for efficacy is the intent-to-treat (ITT) population, defined as all randomized patients. The primary analysis population for safety is the Safety Population, defined as all patients who received at least one dose of study medication. Patients will be assigned to treatment groups as treated, and all patients who received any dose of alectinib will be included in the alectinib treatment arm. The treatment comparison of PFS will be based on a stratified log-rank test at the 5% level of significance (two-sided). The randomization stratification factors are ECOG PS (0/1 vs. 2) and race (Asian vs. non-Asian), as recorded on the eCRF, and CNS metastases at baseline (yes vs. no). The Kaplan-Meier method will be used to estimate the median PFS for each treatment arm with 95% confidence limits. A stratified Cox proportional hazard regresision model will be used including treatment in order to provide an estimate of the treatment effect expressed as an HR, as well as a 95% CI. If the primary endpoint of investigator-assessed PFS is statistically significant at a two-sided 5% significance level based on the stratified log-rank test, the following secondary endpoints will be tested in the following sequential order (O'Neill 1997), each at a two-sided 5% significance level:

	• PFS by IRC • Time to CNS progression by IRC RECIST criteria • Objective response rate (ORR) by investigator assessment • OS All tests in the sequence will be based on a stratified log-rank test at the 5% level of significance (two-sided). The stratification factors included and the analysis population will be the same as for the primary hypothesis test. Results from unstratified tests will also be presented as supportive analyses. OS will be analyzed using the same methodology as specified for the primary endpoint Time to CNS progression is defined as the time from randomization until first radiographic evidence of CNS progression by independent review. An independent central radiological review will be performed for all patients, and the analysis of CNS progression will be based on the data from the independent review. All patients in the ITT population will be included in the analysis regardless of their baseline status of CNS metastases. CNS progression is defined as progression due to newly developed CNS lesions and/or progression of preexisting baseline CNS lesions. On the basis of RECIST v1.1, this is defined as a new post-baseline CNS/brain lesion(s) and/or an increase of □ 20% in the sum of longest diameters of the measurable baseline CNS lesions compared with nadir and/or unequivocal progression of non-measurable baseline CNS lesions. In order to account for the competing risks inherent in the comparison of CNS progression between alectinib and crizotinib, a stratified two-sided log-rank test will be computed on the basis of a cause-specific hazard function. The probability of CNS progression, non-CNS progression, and death by treatment group with 95% CIs will each be estimated using cumulative incidence functions. Gray's test to compare the risk of CNS progression between alectinib and crizotinib will also be performed as a supportive analysis. All safety analyses will be performed on the Safety Population; that is, all patients who receive any dose of study medication by treatment arm with all patients who received any dose of alectinib will be included in the alectinib treatment arm. Time to deterioration (TTD) analyses of Patient Reported Outcomes will be performed on lung cancer symptom scores, global health status scores, and cognitive function scale scores in the ITT population and will include all data collected through disease progression and survival follow-up.

	TTD is defined as the time from randomization until the first confirmed clinically meaningful deterioration. Confirmed clinically meaningful deterioration in lung cancer symptoms is defined as a ≥ 10-point increase from baseline in a symptom score that must be held for at least two consecutive assessments or an initial ≥ 10-point increase above baseline followed by death within 5 weeks from the last assessment. Conversely, confirmed clinically meaningful deterioration in global health status or function is defined as a ≥ 10-point decrease from baseline in a symptom score that must be held for at least two consecutive assessments or an initial ≥ 10-point decrease from baseline followed by death within 5 weeks from the last assessment.
Subgroup analyses	From the Statistical Analysis Plan of ALEX (Ltd 2019): PFS by investigator and IRC assessments will be presented separately for important subgroups including age (< 65, > 65), sex, race (Asian, non-Asian), and smoking status and baseline prognostic characteristics including baseline ECOG PS, CNS metastases at baseline as determined by IRC, and prior brain radiation (in patients with CNS metastases at baseline). The HR including a 95% CI will be presented separately for each level of the categorical variables.

Trial name	ALESIA - Randomized, Multicenter, Phase III, Open-Label Study of Alectinib Versus Crizotinib in Asian Patients With Treatment-Naive Anaplastic Lymphoma Kinase-Positive Advanced Non-Small Cell Lung CancerA Study to Evaluate and Compare the Efficacy and Safety of Alectinib Versus Crizotinib and to Evaluate the Pharmacokinetics of Alectinib in Asian Participants With Treatment-Naive Anaplastic Lymphoma Kinase (ALK)-Positive Advanced Non-Small Cell Lung Cancer (NSCLC)
NCT number	NCT02838420
Objective	To Evaluate and Compare the Efficacy and Safety of Alectinib Versus Crizotinib and to Evaluate the Pharmacokinetics of Alectinib in Asian Participants With Treatment-Naive Anaplastic Lymphoma Kinase (ALK)-Positive Advanced Non-Small Cell Lung Cancer (NSCLC)
Publications – title, author, journal, year	Alectinib versus crizotinib in untreated Asian patients with anaplastic lymphoma kinase-positive non-small-cell lung cancer (ALESIA): a randomised phase 3 study. Zhou, C., S. W. Kim, T. Reungwetwattana, J. Zhou, Y. Zhang, J. He, J. J. Yang, Y. Cheng, S. H. Lee, L. Bu, T. Xu, L. Yang, C. Wang, T. Liu, P. N. Morcos, Y. Lu and L. Zhang. Lancet Respir Med **7**(5): 437-446, 2019.
Study type and design	Open label, randomized, multicenter phase III study conducted in Thailand, China and South Korea. Patients were randomized 2:1 to receive alectinib or crizotinib. Randomisation was done centrally via an interactive voice or web response system, with stratification by ECOG PS (0 or 1 vs 2) and baseline CNS metastases (yes vs no). Cross-over was not allowed.
Follow-up time	The median duration of follow-up was 16.2 months (IQR 13.7–17.6) in the alectinib group and 15.0 months (12.5–17.3) in the crizotinib group.
Population (inclusion and exclusion criteria)	**Inclusion Criteria:** • Histologically or cytologically confirmed diagnosis of advanced or recurrent (Stage IIIB not amenable for multimodality treatment) or metastatic (Stage IV) NSCLC that is ALK-positive as assessed by the Ventana immunohistochemistry (IHC) test. Sufficient tumor tissue available to perform ALK IHC is required. Ventana IHC testing will be performed at the designated central laboratory • Life expectancy of at least 12 weeks • Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0-2 • No history of receiving systemic treatment for advanced, recurrent (Stage IIIB not amenable for multimodality treatment) or metastatic (Stage IV) NSCLC • Adequate hematologic function: Platelet count greater than equal to (>=) 100×10^9 per liter (/L); absolute neutrophil count (ANC) >=1500

	cells per microliter (cells/mcL); hemoglobin>=9.0 grams per deciliter (g/dL) • Adequate renal function: an estimated glomerular filtration rate (eGFR) calculated using the Modification of Diet in Renal Disease (MDRD) formula of >=45 milliliters per minute per 1.73 square meter • Participants must have recovered from effects of any major surgery or significant traumatic injury at least 28 days before receiving the first dose of study treatment • Measurable disease (by Response Evaluation Criteria in Solid Tumors version 1.1 [RECIST v1.1]) before administration of study treatment • Previous brain or leptomeningeal metastases are allowed if the participant is asymptomatic (e.g., diagnosed incidentally at study baseline). Asymptomatic central nervous system (CNS) lesions may be treated at the discretion of the investigator as per local clinical practice. If participant has neurological symptoms or signs because of CNS metastasis, the participant must complete whole-brain radiation or gamma knife irradiation treatment. In all cases, radiation treatment must be completed >=14 days before enrollment and disease must be clinically stable • For all females of childbearing potential, a negative serum pregnancy test result must be obtained within 3 days prior to starting study treatment • For women who are not postmenopausal (>=12 months of non-therapy-induced amenorrhea) or surgically sterile (absence of ovaries and/or uterus), agreement to remain abstinent or use single or combined contraceptive methods that result in a failure rate of <1% per year during the treatment period and for at least 3 months after the last dose of study drug. Abstinence is acceptable only if it is in line with the preferred and usual lifestyle of the participant. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception. Examples of contraceptive methods with a failure rate of <1% per year include tubal ligation, male sterilization, hormonal implants, established, proper use of combined oral or injected hormonal contraceptives, and certain intrauterine devices. Alternatively, two methods (e.g., two barrier methods such as a condom and a cervical cap) may be combined to achieve a failure rate of <1% per year. Barrier methods must always be supplemented with the use of a spermicide • For men, agreement to remain abstinent or use a condom plus an additional contraceptive method that together result in a failure rate of <1% per year during the treatment period and for at least 3 months after the last dose of study drug. Abstinence is acceptable only if it is in line with the preferred and usual lifestyle of the participant. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception **Exclusion Criteria:**

	• A malignancy within the previous 3 years (other than curatively treated basal cell carcinoma of the skin, early gastrointestinal (GI) cancer by endoscopic resection, in situ carcinoma of the cervix, or any cured cancer that is considered to have no impact in progression-free survival (PFS) or overall survival (OS) for the current NSCLC) • Any GI disorder that may affect absorption of oral medications, such as malabsorption syndrome or status post-major bowel resection • Liver disease characterized by: • Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) greater than (>) 3× the upper limit of normal (ULN; >=5×ULN for participants with concurrent liver metastases) confirmed on two consecutive measurements; or • Impaired excretory function (e.g., hyperbilirubinemia), synthetic function, or other conditions of decompensated liver disease such as coagulopathy, hepatic encephalopathy, hypoalbuminemia, ascites, and bleeding from esophageal varices; or • Acute viral or active autoimmune, alcoholic, or other types of hepatitis • National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0 Grade 3 or higher toxicities because of any previous therapy (e.g., radiotherapy) (excluding alopecia), which have not shown improvement and are strictly considered to interfere with current study medication • History of organ transplant • Co-administration of anti-cancer therapies other than those administered in this study • Baseline QTc >470 ms or symptomatic bradycardia • Administration of strong/potent cytochrome P4503A inhibitors or inducers within 14 days prior to the receiving the first dose of study treatment and during treatment with alectinib or crizotinib • Administration of agents with potential QT interval prolonging effects within 14 days prior to receiving the first dose of study drug • History of hypersensitivity to any of the additives in the alectinib or crizotinib drug formulation • Pregnant or lactating • Known human immunodeficiency virus (HIV-positivity or acquired immunodeficiency syndrome (AIDS)-related illness • Any clinically significant concomitant disease or condition that could interfere with, or for which the treatment might interfere with, the conduct of the study or the absorption of oral medications or that would, in the opinion of the Principal Investigator, pose an unacceptable risk to the participant in this study • Any psychological, familial, sociological, or geographical condition that potentially hampers compliance with the study protocol requirements or follow-up procedures; those conditions should be discussed with the participant before study entry
Intervention	Experimental: Alectinib Alectinib capsules orally at a dose of 600 mg BID with food until disease progression, unacceptable toxicity withdrawal of consent, or death.

<table>
<tr><td></td><td>Active Comparator: Crizotinib
Crizotinib capsules orally at a dose of 250 mg BID with or without food until disease progression, unacceptable toxicity withdrawal of consent, or death.</td></tr>
<tr><td>Baseline characteristics</td><td>
<table>
<tr><td>Age, years
Mean
Median</td><td>51.1 (12.6)
49 (41-59)</td><td>50.5 (11.3)
51 (43-59)</td></tr>
<tr><td>Sex
Male
Female</td><td>
34 (55%)
28 (45%)</td><td>
64 (51%)
61 (49%)</td></tr>
<tr><td>ECOG PS
0–1
2</td><td>
61 (98%)
1 (2%)</td><td>
121 (97%)
4 (3%)</td></tr>
<tr><td colspan="3">Smoking status</td></tr>
<tr><td>Active smoker</td><td>3 (5%)</td><td>4 (3%)</td></tr>
<tr><td>Non-smoker</td><td>45 (73%)</td><td>84 (67%)</td></tr>
<tr><td>Former smoker</td><td>14 (23%)</td><td>37 (30%)</td></tr>
<tr><td>Adenocarcinoma histology</td><td>59 (97%)</td><td>117 (94%)</td></tr>
<tr><td>Previous chemotherapy for localised disease</td><td>9 (15%)</td><td>7 (6%)</td></tr>
<tr><td>Previous brain radiation</td><td>5 (8%)</td><td>8 (6%)</td></tr>
<tr><td>CNS metastases (IRC)</td><td>23 (37%)</td><td>44 (35%)</td></tr>
<tr><td>CNS metastases (investigator)</td><td>20 (32%)</td><td>42 (34%)</td></tr>
<tr><td>Mean target lesion size at baseline (IRC), mm</td><td>72·9
(42·2)</td><td>78·0 (43·9)</td></tr>
<tr><td>Mean target lesion size at baseline (investigator), mm</td><td>65·5
(43·8)</td><td>61·4 (36·2)</td></tr>
<tr><td>Disease stage at baseline
3B
4</td><td>
4 (7%)
58 (94%)</td><td>
13 (10%)
112 (90%)</td></tr>
</table>
</td></tr>
<tr><td>Primary and secondary endpoints</td><td><u>Primary Outcome</u>
1. Progression-Free Survival (PFS) as Determined by Investigator Using Response Evaluation Criteria in Solid Tumor (RECIST) v1.1
[Time Frame: From the date of randomization to the date of the first documented disease progression or death, whichever occurred first (up to overall period of approximately 40 months)]

PFS was defined as the time (in months) from randomization to the first documentation of disease progression, as determined by the investigators, or to death from any cause, whichever occurred first.

<u>Secondary Outcomes</u>:
1. PFS as Determined by Independent Review Committee (IRC) Using RECIST v1.1 [Time Frame: Baseline, Week 8, thereafter every 8 weeks until disease progression, death or withdrawal from the study and 4 weeks after permanent discontinuation (up to overall period of approximately 40 months)]</td></tr>
</table>

	PFS was defined as the time (in months) from randomization to the first documentation of disease progression, as determined by an independent review committee, or to death from any cause, whichever occurred first. 2. Percentage of Participants With Objective Response of Complete Response (CR) or Partial Response (PR) as Determined by Investigator Using RECIST v1.1 [Time Frame: Baseline, Week 8, thereafter every 8 weeks until disease progression, death or withdrawal from the study and 4 weeks after permanent discontinuation (up to overall period of approximately 40 months)] 3. Time to Progression of Disease in the CNS as Determined by IRC Using RECIST v1.1 [Time Frame: Baseline, Week 8, thereafter every 8 weeks until disease progression, death or withdrawal from the study and 4 weeks after permanent discontinuation (up to overall period of approximately 40 months)] 4. Time to Progression of Disease in the CNS as Determined by IRC Using Response Assessment in Neuro-Oncology (RANO) [Time Frame: Baseline, Week 8, thereafter every 8 weeks until disease progression, death or withdrawal from the study and 4 weeks after permanent discontinuation (up to overall period of approximately 40 months)] 5. Duration of Response (DOR) Assessed by Investigator Using RECIST v1.1 [Time Frame: Baseline, Week 8, thereafter every 8 weeks until disease progression, death or withdrawal from the study and 4 weeks after permanent discontinuation (up to overall period of approximately 40 months)] 6. Overall Survival Time [Time Frame: Baseline, until death (up to overall period of approximately 40 months)] 7. Percentage of Participants With Non-serious Adverse Events and Serious Adverse Events [Time Frame: Up to overall period of approximately 40 months] An adverse event is any untoward medical occurrence in a participant administered a pharmaceutical product and which does not necessarily have to have a causal relationship with the treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a pharmaceutical product, whether or not considered related to the pharmaceutical product. Preexisting conditions which worsen during a study are also considered as adverse events. 8. Time to Deterioration Assessed Using EORTC Quality of Life Questionnaire-Core (QLQ-C30) Score [Time Frame: Baseline, Week 4, thereafter every 4 weeks until disease progression, death or

	withdrawal from the study and 4 weeks after permanent discontinuation (up to overall period of approximately 40 months)] 9. Time to Deterioration Assessed Using EORTC Quality of Life Questionnaire-Lung Cancer Module (QLQ-LC13) Score [Time Frame: Baseline, Week 4, thereafter every 4 weeks until disease progression, death or withdrawal from the study and 4 weeks after permanent discontinuation (up to overall period of approximately 40 months)] 10. Area Under the Plasma Concentration-time Curve (AUC) of Alectinib and Its Metabolite [Time Frame: Baseline and Week 4 predose (within 2 hours before administration of study drug)] AUC was collected for both alectinib and its major metabolite, M4, and was based on their concentrations in plasma over time. 11. Maximum Plasma Concentration Observed (Cmax) of Alectinib and Its Metabolite [Time Frame: Baseline and Week 4 predose (within 2 hours before administration of study drug)] Cmax was collected for both alectinib and its major metabolite, M4, and was based on their concentrations in plasma over time. 12. Time to Cmax (Tmax) of Alectinib and Its Metabolite [Time Frame: Baseline and Week 4 predose (within 2 hours before administration of study drug)] Tmax was collected for both alectinib and its major metabolite, M4, and was based on their concentrations in plasma over time
Method of analysis	The primary objective of this study was to show consistency with the progression-free survival benefit of alectinib seen in ALEX. The primary endpoint of investigator-assessed progression-free survival was used to determine the sample size. Consistency was defined as maintaining at least 50% risk reduction compared with ALEX. Based on the assumption of a progression-free survival HR of 0.65 as in ALEX, 97 progression-free survival events were required to achieve approximately 87% probability to show consistency; hence, a sample size of 183 patients in a 2:1 randomised allocation was determined. As the ALEX results were better than expected, with a progression-free survival HR of 0・47, the primary analysis of ALESIA was done earlier than originally planned—ie, when at least 60 progression-free survival events (ie, disease progression or patient death) had occurred. As the HR for investigator assessed progression-free survival for ALEX was 0.47 (53% risk reduction), if the point estimate of the HR from ALESIA was less than 0.735, the primary objective to determine consistency with ALEX would be met. Kaplan–Meier methodology was used to estimate the

	median progression-free survival, overall survival, and duration of response for each treatment group with corresponding 95% CI. A stratified Cox proportional hazards regression model was used to estimate the treatment effect expressed as a HR, with corresponding 95% CI. Stratification factors for this model were the same as the randomisation stratification factors. Non-CNSprogression without previous CNS progression, and death without previous CNS or non-CNS progression, were regarded as competing risks for CNS progression. To account for competing risks in the time to CNS progression analysis, HRs were computed on the basis of cause-specific hazard functions. The probability of CNS disease progression, non-CNS disease progression, and death were each estimated with the use of CI functions. The Clopper–Pearson method was used to estimate the proportion of patients who achieved an objective response with corresponding 95% CI. Proportions of responses were compared using a Mantel-Haenszel test based on the stratification factors. The p-values presented for the efficacy endpoints are descriptive only.
Subgroup analyses	PFS by investigator and IRC assessments will be presented separately for important subgroups including age (< 65, > 65), sex, race (Asian, non-Asian), and smoking status and baseline prognostic characteristics including baseline ECOG PS, CNS metastases at baseline as determined by IRC, and prior brain radiation (in patients with CNS metastases at baseline). The HR including a 95% CI will be presented separately for each level of the categorical variables.

Results per study

Table A3a Results of study ALTA

Trial name:	**Study AP26113-13-301: A Phase 3 Multicenter Open-label Study of Brigatinib (AP26113) versus Crizotinib in Patients with ALK-positive Advanced Lung Cancer**										
NCT number:	NCT02737501										
				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 OS, Months	Brigatinib Crizotinib	137 138	NR NR	NE	NE	NA	HR: 0.92	0.57; 1.47	0.771	Hazard ratios were estimated using the Cox regression model with the stratification factors as covariates. Log-Rank Test were used for P-value calculations	(Camidge et al. 2020)
Discontinuation due to AEs, %	Brigatinib Crizotinib	136 137	13 9	4	-3,57; 11,65	0,29	RR: 1.43	0.71; 2.87	0.320	Relative Risk was computed according to Altman 1991. CI on absolute difference was calculated according to Altman, 2000.	(Camidge et al. 2020)
CNS Progression, Competing Risk	Brigatinib Crizotinib	137 138					HR: 0.302	0.17; 0.53	<0.0001	Time to cause-specific event is defined as time from randomization to the first cause-specific event. Patients with other prior competing events were no longer at risk for the cause-specific event and were censored at the time of these	(CHMP 2020)

										competing events. Patients without any events will be censored at the last assessment timepoint. The hazard ratio and associated p-value were obtained using a Cox proportional hazards model with randomization stratification factors (current) as covariates.	
Median PFS by BIRC assessment, Months	Brigatinib Crizotinib	137 138	24.0 (18.5-NE) months 11.0 (9.2-12.9) months	13.0		<0.0001	HR: 0.49	0.35; 0.68	<0.0001	The median PFS is based on the Kaplan–Meier estimator. The HR is based on a Cox proportional hazards model with adjustment for stratification (baseline intracranial CNS mets and prior chemotherapy).	(Camidge et al. 2020)
Rate of grade 3-4 AEs	Brigatinib Crizotinib	136 137	73 61	12	0,84; 22,74	0,035	RR: 1.19	1.00; 1.41	0.047	Relative Risk was computed according to Altman 1991. CI on absolute difference was calculated according to Altman, 2000.	(Camidge et al. 2020)
HRQoL Mean change from baseline	Brigatinib Crizotinib	137 138	Not Reported Not Reported	3.1	-0.8; 7.0						(CHMP 2020)
HRQOL Time to worsening	Brigatinib Crizotinib	137 138	26.7 (8.3; NE) 8.3 (5.7; 13.5)	18.4			0.70	0.49; 1.00	0.049	Groups were compared using a 2-sided stratified log-rank test.	(Camidge et al. 2020)

(10 point), Months			HRs and Cis were estimated using a Cox proportional hazard model with baseline brain metastasis and prior chemotherapy as covariates.	

NR: Not Reported

Table A3b Results of study ALEX

Trial name:	*ALEX*										
NCT number:											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Hazard/Odds/ Risk ratio	95% CI	*P* value		
Median OS, Months	Alectinib	152	Not Reached	NE	NE	NA	HR: 0.67	0.46; 0.98	0.0376	OS is based on the Kaplan–Meier estimator. The HR is based on a Cox proportional hazards model.	*(Mok et al. 2020)*
	Crizotinib	151	57.4								
Discontinuation due to AEs, %	Alectinib	152	14.5	0.1	-7,93: 8,14	0.98	RR: 1.0066	0.58; 1.73	0.98	Relative Risk was computed according to Altman 1991. CI on absolute difference was calculated according to Altman, 2000.	*(Mok et al. 2020)*
	Crizotinib	151	14.6								
CNS Progression, Competing Risk	Alectinib	151					HR: 0.16	(0.10; 0.28)	<0.0001	Time to cause-specific event is defined as time from randomization to the first cause-specific event. Patients with other prior competing events were no longer at risk for the cause-specific event and were censored at the time of these competing events. Patients without any events will be censored at the last assessment timepoint.	
	Crizotinib	152									

									The hazard ratio and associated p-value were obtained using a Cox proportional hazards model with randomization stratification factors (current) as covariates.	
Median PFS by BIRC assessment	Alectinib Crizotinib	151 152	25.7 (19.9; NR) 10.4 (7.7; 14.6)	15.3			HR: 0.50	0.36–0.70	<0.0001	The median PFS is based on the Kaplan–Meier estimator. The HR is based on a Cox proportional hazards model.	(Peters et al. 2017)
Rate of grade 3-5 AEs, %	Alectinib Crizotinib	151 152	52.0 56.3	4.3	-6.85; 15.30	0.45	RR: 0.9365	0.78; 1.13	0.49	Relative Risk was computed according to Altman 1991. CI on absolute difference was calculated according to Altman, 2000.	(Mok et al. 2020)
HRQoL Mean change from baseline	Alectinib Crizotinib	151 152	NR NR	NR	NR	NR	NR	NR	NR		(Medicinrådet 2018)
HRQOL Time to worsening (10 point), Months	Alectinib Crizotinib	151 152	NR NR	NR	NR	NR	0.72	0.38; 1.39	NR		(Medicinrådet 2018)

NR: Not Reported

Table A3c Results of study ALESIA

Trial name:	*ALESIA*										
NCT number:											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Hazard/Odds/ Risk ratio	95% CI	*P* value		
Median OS	Alectinib Crizotinib	125 62	Not Reached (N=8, 6%) N=12, 21%)	NE	NE	NA	HR: 0.28	0.12–0.68	NR, Data is immnature	OS is based on the Kaplan–Meier estimator. The HR is based on a Cox proportional hazards model.	*(Zhou et al. 2019)*
Discontinuation due to AEs, %	Alectinib Crizotinib	125 62	7 10	3	-4.90; 13.48	0.48	RR: 0.72	0.27; 1.93	0.51	Relative Risk was computed according to Altman 1991. CI on absolute difference was calculated according to Altman, 2000.	
CNS Progression, Competing Risk	Alectinib Crizotinib	125 62					HR: 0.14	0.06; 0.30	<0.0001	Time to cause-specific event is defined as time from randomization to the first cause-specific event. Patients with other prior competing events were no longer at risk for the cause-specific event and were censored at the time of these competing events. Patients without any events will	

									be censored at the last assessment timepoint. The hazard ratio and associated p-value were obtained using a Cox proportional hazards model with randomization stratification factors (current) as covariates.	
Median PFS by BIRC assessment, months	Alectinib Crizotinib	125 62	NR (16.7-NE) 10.7 (7.4-NE)	NE			HR: 0.37	0.22; 0.61	<0.0001	The median PFS is based on the Kaplan–Meier estimator. The HR is based on a Cox proportional hazards model.	
Rate of grade 3-4 Aes, %	Alectinib Crizotinib	125 62	29 48	19	4.34; 33.17	0.0107	RR: 0.60	0.41; 0.87	0.007	Relative Risk was calculated according to Altmann, 1991. CI on absolute difference was calculated according to Altman, 2000.	
HRQoL Mean change from baseline	Alectinib Crizotinib	125 62	Not Reported								

Results per PICO (clinical question)

Table A4 Results referring to what is the difference between brigatinib and alectinib for treatment of previously untreated ALK+ NSCLC patients.

Results per outcome	Attach forest plots and statistical results as a separate file. Results from the comparative analysis should be given in the table below, if possible.							
		Absolute difference in effect			Relative difference in effect			Methods used for quantitative synthesis
	Studies included in the analysis	Difference	CI	P value	Hazard/Odds/Risk ratio	CI	P value	
Progression Free Survival	ALTA-1L vs. ALEX & ALESIA	NA	NA	NA	HR: 1.07	0.66–1.75	Not Reported	(Elliott et al. 2020).
Overall Survival	ALTA-1L vs. ALEX & ALESIA	NA	NA	NA	HR: 1.55	0.72-3.34	Not Reported	(Elliott et al. 2020)

The above data is from a published network meta analysis (Elliott et al. 2020).
The evidence network includes chemotherapy and 4 ALK TKIS and is depicted below.

Appendix 5

This appendix describes the CNS-specific analyses available in the public domain.

Brigatinib
The following CNS-specific analyses have been reported from ALTA-1L

1. Subgroup analysis of systemic PFS in patients with or with-out baseline CNS metastasis (BIRC and Investigator assessed) (Camidge et al. 2020).
2. Subgroup analysis of intracranial PFS in patients with or with-out baseline CNS metastasis (Camidge et al. 2020).
3. *Competing Risk Analysis* of systemic vs. intracranial progression presented as *Cumulative Incidence Plots* of intracranial progression performed in the ITT populations (CHMP 2020).

Alectinib
The following CNS-specific analyses have been reported from ALEX/ALESIA

4. Subgroup analysis of systemic PFS in patients with or with-out baseline CNS metastasis from ALEX (Gadgeel et al. 2018).
5. *Competing Risk Analysis* of systemic vs. intracranial progression presented as *Cumulative Incidence Plots* of intracranial progression performed in the ITT populations (CHMP 2017; Medicinrådet 2018; Zhou et al. 2019).
6. Subgroup analysis of *Competing Risk Analysis* of systemic vs. intracranial progression presented as *Cumulative Incidence Plots* of intracranial progression performed in patients with or with-out base line CNS-metastases (Gadgeel et al. 2018).

The above analysis elucidates different clinical aspects of the treatment of ALK+ NSCLC patients as well as the efficacy of alectinib/brigatinib compared to crizotinib

- How is the systemic PFS affected by the presence/absence of CNS-metastases at baseline (analyses no. 1 & 4) ?
- How is the intracranial PFS affected by the presence/absence of CNS-metastasis at baseline (analysis no. 2)?
- What is the risk that a patient progress intracranially vs. systemic (analyses no. 3 and 5)?
- How is the risk that the patient progress intracranially vs. systemic affected by the presence/absence of CNS-metastasis at baseline (analysis no. 6)?

The clinical expert committee requested median intracranial PFS in the ITT populations.

This specific information cannot be elucidated from the available analyses describe above.

The competing risk analyses performed in the ITT populations provide a Hazard Ratio for intracranial progression in the ITT population and are thus the analysis that comes closest to providing the requested information.

Acronyms

ALK+	Anaplastic lymphoma kinase positive
BIM	Budget impact model
BIRC	Blinded independent review committee
CEAC	Cost-effectiveness plane
CNS	Central nervous system
CR	Complete response
ECG	Electro-cardiogram
EMA	European Medicines Agency
EORTC QLQ-LC13	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Lung Cancer Module
EQ-5D	EuroQol 5-dimensions
ESMO	European Society of Medical Oncology
ESS	Effective sample size
HRQoL	Health related quality of life
HTA	Health technology appraisal
IA	Interim analysis
INV	Investigator
ITC	Indirect treatment comparison
ITT	Intention to treat
MAIC	Matched adjusted indirect comparison
NA	Not available
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
NR	Not reported
NSCLC	Non-small-cell lung cancer
OS	Overall survival
PD	Progressive disease
PFS	Progression-free survival
PR	Partial response
RECIST	Response Evaluation Criteria in Solid Tumours
RPSFTM	Rank Preserving Structural Failure Time Models
SD	Stable disease
SLR	Systematic literature review
TKI	Tyrosine kinase inhibitor
TN	Treatment naïve
ToT	Time on treatment
VEGF-R	Vascular endothelial growth factor and receptor

Contents

1. Introduction

This report outlines the inputs and outputs relating to the cost-comparison model for brigatinib vs. alectinib and a budget impact model (BIM) for the treatment of patients with previously untreated anaplastic lymphoma kinase positive (ALK+) advanced non-small-cell lung cancer (NSCLC). The economic model has been developed from a Danish restricted societal perspective.

1.1. Epidemiology of ALK+ NSCLC

In Denmark, approximately 4.600 are diagnosed with lung cancer annually, which makes lung cancer is one of the most commonly occurring cancers in Denmark (1,2). At the end of 2016, almost 11,151 people lived with lung cancer, while approximately 3.700 people die annually from lung cancer (2).

The latest annual report from Danish Lung Cancer Group and Danish Lung Cancer Register shows that the 1-year survival rate for all newly diagnosed patients with lung cancer diagnosed in 2017 regardless of stage was 51.4%, while the 5-year survival for patients diagnosed in 2013 was 15.9% (3). Of the patients diagnosed with lung cancer, approx. 85-90% has non-small cell lung cancer (NSCLC)) (4). NSCLC is divided based on histology/cytology into squamous and non-squamous cell tumors. The scientific committee estimates that approx. 25% of patients have squamous cell tumors (corresponding to approx. 1,000 patients), and approx. 75% of patients have non-squamous cell tumors (equivalent to approx. 3.000 patients). The vast majority of non-squamous cell tumors are so-called adenocarcinomas (5).

Patients with incurable NSCLC receive systemic treatment in the form of chemotherapy, immunotherapy, and so-called targeted treatment with tyrosine kinase inhibitors (TKI). Choice of treatment is depending on tumor characteristics, where the presence of specific biomarkers determines the choice of treatment. If the tumor shows genetic or chromosomal changes, a targeted treatment will be the first choice. In Danish clinical practice, two biomarkers are specific for the choice of treatment; activating epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK) translocations (6). Targeted treatment is only relevant for patients with incurable NSCLC and not for patients with NSCLC in earlier stages, where treatment aimed at healing is an option (5).

ALK-positive NSCLC is characterized by ALK translocations in the tumor tissue. ALK translocations occur rearly with a frequency of less than 1% of all newly diagnosed lung cancer cases. In 2016, the frequency was 0.8% corresponding to 36 patients; in 2017, the frequency was 0.9% corresponding to 43 patients; and in 2018 the frequency was 0.6% equivalent to 30 patients (7,8).

1.2. Clinical presentation of NSCLC

Approximately 70% of patients with NSCLC have advanced disease (stage IIIB/ IV) at the time of diagnosis (9). The estimated 5-year survival rate in patients with stage IV NSCLC is ≈ 5% (10). Lung cancer may present with symptoms or be detected during chest imaging. Common symptoms include worsening cough or chest pain, hemoptysis (coughing up blood), malaise, weight loss, dyspnea (labored breathing), and hoarseness (11). Sites of distant metastasis in stage IV NSCLC frequently include the brain, bone, and liver (12,13). At diagnosis, patients may also experience symptoms including neurological defect or personality change due to brain metastases or pain due to bone metastases (11).

Patients with ALK+ NSCLC have distinct demographic and clinical features. One of the most important patient characteristics is the absence of a smoking history. Among patients with ALK+ NSCLC, > 90% are never or light smokers (≤ 10 pack-years). Other important features associated with ALK+ NSCLC include (14,15,16):

- Younger age at diagnosis than for other types of NSCLC (median age, 52 years)
- Predominantly adenocarcinoma histology
- Absence of other oncogenic drivers (eg, epidermal growth factor receptor [*EGFR*], Kirsten rat sarcoma [*KRAS*])
- Frequent brain metastases

1.3. CNS and metastasis in patients with ALK+NSCLC

The central nervous system (CNS) is a known sanctuary site in advanced ALK+ NSCLC, with CNS progression due, in part, to poor blood-brain barrier penetration of the first-generation ALK TKI (crizotinib); this poor penetration is a major limitation to durable disease control (17). Next-generation CNS-active ALK TKIs administered in the ALK TKI–naive setting has mitigated the risk of CNS progression, but agents that offer greater clinical benefit to patients with brain metastases are still needed (18,19).

Brain metastases occur frequently in patients with ALK+ NSCLC (20,21). Approximately 30% of patients have brain metastases at diagnosis, as documented in several studies from a variety of countries (22,23). A retrospective analysis of patients with ALK+ NSCLC who did not have baseline brain metastases found that 58.4% of patients still living at 3 years had developed brain metastases (24).

Brain metastases have been shown to have an impact on health-related quality of life (HRQOL); one observational study found a greater decline over time in 18 of 20 evaluated HRQOL measures in patients with brain metastases than in patients without. Patients with brain metastases showed deterioration of 28.1% within 1 year compared with an improvement of 1.8% in patients without brain metastases (25). Radiotherapy such as SRS is used for local therapy, and WBRT is often used for treating widespread intracranial disease. Radiotherapy, however, can lead to poor HRQOL and impaired cognitive function (26, 27).

1.4. Current ALK+ NSCLC first-line treatment

The ALK TKI, alectinib, is currently approved in Denmark for the first-line treatment of ALK+ NSCLC. Alectinib has shown efficacy as frontline ALK TKIs, although progression still occurs. For the ALK TKI alectinib, the pivotal data come from randomized studies comparing alectinib vs crizotinib. In the ALEX trial, by BIRC-assessment, 1L alectinib reduced the risk of disease progression or death by 50% compared with 1L crizotinib (HR, 0.50 [95% CI, 0.36-0.70]), with a median PFS of 25.7 months (95% CI, 19.9 months to NE) in the alectinib arm at the primary analysis (median follow-up, 18.6 months in the alectinib arm). By investigator assessment (primary endpoint) with a longer follow-up (median follow-up, 37.8 months in the alectinib arm) after primary analysis, alectinib reduced the risk of overall progression or death by 57% compared with crizotinib (HR, 0.43 [95% CI, 0.32-0.58]), with a final median PFS of 34.8 months (95% CI, 17.7 months to NE) (18,28). In patients with baseline brain metastases, the risk of overall progression or death was reduced by 60% (HR, 0.40 [95% CI, 0.25-0.64]) at the primary analysis and 63% (HR, 0.37 [95% CI, 0.23-0.58]) after a longer follow-up in patients receiving alectinib

compared with crizotinib(18); the median PFS was 25.4 months in patients with baseline brain metastases treated with alectinib after a longer follow-up (investigator assessed) (28).

Intracranial efficacy data with frontline alectinib were also reported for the ALEX trial. The BIRC-assessed confirmed + unconfirmed intracranial response rate was 81% (95% CI, 58%-95%) in patients with measurable lesions at baseline, and the median intracranial DOR in responders (references do not specify whether these were confirmed or confirmed + unconfirmed responders) was 17.3 months (95% CI, 14.8 months to NE) (18). However, not all patients achieved a response, including intracranial response, with alectinib, and not all patients can tolerate alectinib. Alectinib is associated with clinically relevant adverse events (AEs), such as hepatotoxicity, renal impairment, musculoskeletal pain, CPK elevation, fatigue, and bradycardia, and long-term toxicities such as edema (29). In the pivotal ALEX study, 14% of patients treated with alectinib had AEs leading to study drug discontinuation (28).

2. Product description of Brigatinib

Brigatinib is administered orally and has a convenient 1-tablet once-daily dosing schedule with or without food. The recommended starting dose is 90 mg once daily for the first 7 days, then 180 mg once daily (90 mg → 180 mg once daily) (29).

Brigatinib is available in the Danish market *in the following pack sizes*:

- 30 mg: 28 tablets (blister pack)
- 90 mg: 28 tablets (blister pack)
- 180 mg: 28 tablets (blister pack)
- Starter pack: 7 x 90 mg tablets and 21 x 180 mg tablets

2.1. Mechanism of action

Brigatinib is an orally active tyrosine kinase inhibitor (TKI) that targets ALK, c-ros oncogene 1 (ROS1), and insulin like growth factor 1 receptor (IGF-1R). Brigatinib inhibited the in vitro and in vivo viability of cells expressing echinoderm microtubule-associated protein-like 4 (EML4)–ALK and mutant forms of EML4-ALK associated with resistance to ALK TKIs (29).

3. Objectives

The objective of this report is to detail the cost-comparison model for brigatinib and alectinib for the treatment of ALK+ advanced NSCLC in patients untreated with an ALK inhibitor. The objectives of the economic model are, in accordance with the methods outlined by the Medicines Council:

- To determine the treatment cost of brigatinib compared with alectinib
- To assess the budget impact of the addition of brigatinib into this setting

4. Model structure

The model submitted is based on a global model developed for Takeda to also show cost-utility ratios and in countries where other comparators are considered relevant. It has been adapted to fit Danish Medicines Council requirements. However, traces from the CUA will still be visible in the model, like blanks where we have removed other comparators than alectinib.

In the base case, the cost-comparison model is used to compare brigatinib with alectinib. The base case assumptions are listed in the table 1 below. Double asterixs' (**) mark those base-case assumptions that only affects outcomes in case cost-effectiveness is chosen. They have been included here to secure recognition with the interface of "Model Controls" in the attached excelfile.

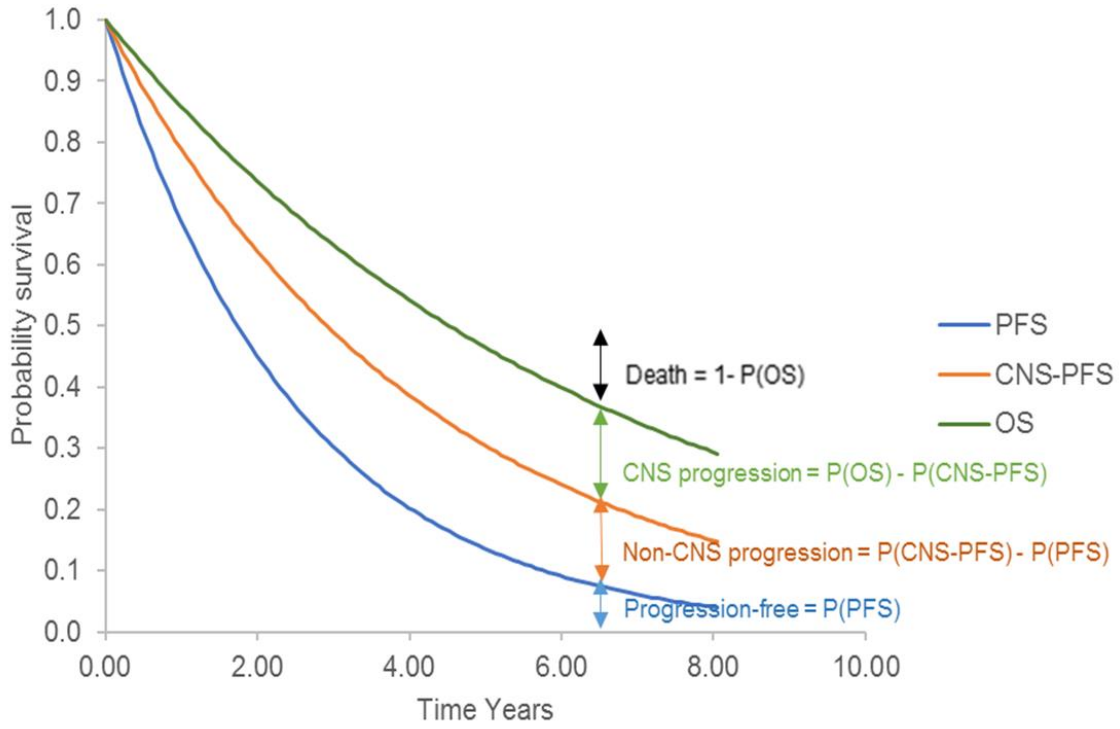
Table 1: Baseline charictaristics

Category	Variable	Base case values
Basic Settings	Time horizon (years)	30
	Cost discount rate	4.00%
	Clinical outcomes discount rate	0.00%
	Selected population	Treatment Naïve
Comparators included in the model	Comparator 1	Brigatinib
	Comparator 3	Alectinib
Patient characteristics applied in the model	Age	58.66
	Male	45%
	**Baseline EQ-5D-3L	0.71
	Body surface area	1.77
Parametric model fit for brigatinib arm	OS	Exponential
	PFS	Exponential
	CNS-PFS	Exponential
Adjustment for treatment switching in the ALTA1 trial from CRI to BRI	Treatment switching	No switching adjustment
Choice of PFS	PFS measurement	PFS BIRC
Approach to matching CNS-PFS and PFS	Approach to adjust inconsistencies between CNS-PFS and PFS	CNS-PFS adjusted to PFS
Effect-data	Cost-comparison is chosen as the base case	ALTA-1

3.1 Cost model

The cost model was developed in Microsoft Excel 2010 as an area-under-the-curve partitioned survival model with four health states: pre-progression, central nervous system (CNS) progression, non-CNS progression and death – Figure 1.

Figure 1: Model structure



Abbreviations: CNS, central nervous system; OS, overall survival; PFS, progression-free survival

This model structure considers alectinib in the frontline ALK+ advanced NSCLC setting. In line with alectinib, it was considered important to separate CNS and non-CNS progression due to the considerable cost burden associated with CNS progression.

The AUC model extrapolates three endpoints from the ALTA-1L trial for the comparison of brigatinib and crizotinib (progression-free survival; PFS, CNS-PFS and OS) – the state membership is determined by these independently modelled and non-mutually exclusive survival curves, as reflected in Figure 1 it is the area under and between the curves that define this membership. ITCs inform the relative efficacy estimates for brigatinib vs. alectinib. Other model structures were considered (for example: a state transition model). However, the availability of comparator data limited these options.

The model considers a lifetime horizon (30-years) and a 28-day cycle length, which reflects the cycle length for brigatinib and alectinib in the untreated ALK+ advanced NSCLC setting. In the base case, costs are discounted using a 4% annual discount rate after year 1. The impact of applying no discount rate is possible to explore in the model and is described in section 7.4.

4 Clinical parameters

4.1 Clinical data

A clinical SLR was conducted to identify the evidence informing outcomes associated with brigatinib and alectinib in the untreated with an ALK inhibitor ALK+ advanced NSCLC setting.

The patient level data from the ALTA-1L clinical trial provides evidence for brigatinib vs. crizotinib (34,35). Two publications were identified describing the outcomes of alectinib vs. crizotinib from the ALEX clinical trial (18,28). Within this document we consider the key differences between the identified clinical trials (ALTA-1L and ALEX) in terms of trial designs (Section 4.1.1) and the baseline characteristics (Section 4.1.2). These differences hinder our ability to obtain robust relative efficacy estimates through statistical methods, such as ITCs. Some of the differences are unable to be adjusted for – for example: imbalances in subsequent therapies, definition of progression endpoints and follow-up times. Whilst other differences have been explored through statistical methods, for example: treatment crossover, proportion of patients with baseline CNS metastases and proportion of patients receiving prior chemotherapy before a frontline ALK inhibitor. However, these statistical methods add uncertainty and it is unlikely that they adjust for the full effect of bias caused by the imbalances. Therefore, the results of the statistical analyses should be interpreted with caution.

4.1.1 Differences in trial designs

Table 2 resents the differences in trial designs between the identified clinical trials. Key differences included: whether crossover was permitted, the definition of the progression endpoints, and the follow-up times reported in the publications.

Table 2: Differences in trial designs

Design	ALTA-1L[6, 7]	ALEX[2-4]
Prior chemotherapy for advanced disease	Allowed	Not allowed
Stratification	Prior chemotherapy (Y/N) Presence of brain metastases (Y/N)	Performance status 0-1 vs. 2 Race (Asian vs non-Asian) Presence of brain metastases (Y/N)
Primary endpoint	BIRC assessed PFS	Investigator assessed PFS
Definition of progression events	Progressive disease, death, radiotherapy to the brain	Progressive disease, death
Median follow-up time	11.0 months (IA1, brigatinib) 24.9 months (IA2, brigatinib)	18.6 months (primary, alectinib) 27.8 months (follow-up, alectinib) 37.8 months (final, alectinib)
ALK testing	Use local test to enrol	Only enrol central lab test positive patients

Abbreviations: ALK, anaplastic lymphoma kinase; BIRC, blinded independent review committee; IA, interim analysis; PFS, progression-free survival

Crossover and subsequent therapies

In the ALTA-1L clinical trial, at the discretion of the investigator and with the sponsor's medical monitor approval, patients who experience progression as assessed by the blinded independent review committee (BIRC) or received radiotherapy to the brain while on crizotinib therapy could cross over to treatment with brigatinib. This protocol-defined crossover summed to 44.20% (n=61) of patients from the crizotinib arm – further subsequent brigatinib use was identified in the crizotinib arm through the concomitant medications (this use may have been later line or after the window had closed for being termed an "official switcher"). Therefore, the total amount of crossover summed to 52.90% (n=73). This is compared with the ALEX trial where protocol-defined crossover was not permitted – a small proportion (6.6%; n=10) received alectinib after crizotinib reflecting specific country practices. Table 3 presents the reported subsequent therapy use from the key clinical trials.

Table 3: Differences in subsequent therapies received after frontline treatment

Subsequent Anti-Cancer Treatment	Brigatinib ALTA-1L (N=137) no. (%)	Crizotinib ALTA-1L (N=138) no. (%)	Alectinib ALEX (N=152) no. (%)
Surgery	0	2 (1.5)	NA
Radiotherapy	1 (0.7)	10 (7.3)	NA
Systemic Therapy	35 (5.7)	97 (70.8)	40 (26.3)
ALK TKI	31 (22.8)	93 (67.9)	18 (11.8)
ALECTINIB	10 (7.4)	24 (17.5)	0 (0.0)
BRIGATINIB	1 (0.7)	73 (53.3)	NA
CERITINIB	4 (2.9)	5 (3.6)	4 (2.6)
CRIZOTINIB	11 (8.1)	5 (3.6)	9 (5.9)
LORLATINIB	14 (10.3)	12 (8.8)	NA
Other (lorlatinib, brigatinib, gefitinib, entrectinib, erolotinib)	NR	NR	6 (3.9)
Chemotherapy	15 (11.0)	16 (11.7)	39 (25.7)
Immunotherapy	3 (2.2)	4 (2.9)	2 (1.3)
VEGF-R	3 (2.2)	4 (2.9)	2 (1.3)
Other	2 (1.5)	1 (0.7)	4 (2.6)

Abbreviations: ALK, anaplastic lymphoma kinase; NA, not available; NR, not reported; TKI, tyrosine kinase inhibitor; VEGF-R, vascular endothelial growth factor and receptor

A point to note from comparing the subsequent therapies is that more ALK inhibitors are being used after brigatinib in the ALTA-1L trial than after alectinib in the ALEX trial. This likely reflects the evolving paradigm of treatment for ALK+ advanced NSCLC – the ALTA-1L trial shows the latest data and as the

data matures will provide important information with regards to the sequencing on multiple ALK inhibitors. Due to lack of patient level data for alectinib, this imbalance in subsequent therapies cannot be addressed. Therefore, it should be noted as a limitation when comparing the OS analyses.

The model holds the possibility to adjust for the crossover which is explained in further detail in section 4.2.5 and explored in SA.

Definition of progression events

The definition of the progression events used in the clinical trials differs between ALTA-1L and ALEX – impacting PFS BIRC-assessed, PFS investigator assessed (INV) and CNS-PFS outcomes. The ALTA-1L clinical trial defines a progression event as a RECIST progression, radiotherapy for brain metastases or death – whichever occurred first. Whereas the ALEX trial defined a PFS event as a RECIST progression or death – whichever occurred first. The number of events defined by radiotherapy to the brain was small in the ALTA-1L trial; n=2 in the brigatinib arm and n=8 in the crizotinib arm for PFS BIRC-assessed. Therefore, it was not considered to be a driver of results. Nevertheless, it should be considered when making indirect comparisons with ALEX. This is reflected in the model, which is explained in further detail in section 4.2.

Follow-up time

The follow-up times for the data relevant to each comparator are different – these further differ by endpoint. Table 4 details the data cut and length of follow-up for each outcome considered within the model. CNS-PFS outcomes are not available from the ALEX trial.

Table 4: Clinical data used for each endpoint

	OS	PFS BIRC	PFS INV	CNS-PFS
Brigatinib ALTA-1L	Individual patient level data 28th June 2018 IA2 24.9 months follow-up in the brigatinib arm			
Crizotinib ALTA-1L	Individual patient level data 28th June 2018 IA2 24.9 months follow-up in the brigatinib arm			
Alectinib ALEX	Mok et al. (2019) 30th November 2018 37.8 months follow-up in the alectinib arm. Note: only hazard ratios and confidence intervals available. KMs are available for both earlier data cuts in Peters et al. (2017) (18.6 months follow-up in the alectinib arm) and Camidge et al. (2018) (27.8	Peters et al. (2017) 9th February 2017 18.6 months follow-up	Mok et al. (2019) 30th November 2018 37.8 months follow-up	NA

	OS	PFS BIRC	PFS INV	CNS-PFS
	months follow-up in the alectinib arm)			

Abbreviations: BIRC, blinded independent review committee; CNS, central nervous system; INV, investigator assessed; KM, Kaplan Meier Curves; NA, not available; OS, overall survival; PFS, progression-free survival

4.1.2 Differences in baseline characteristics

Table 5 presents the key differences in baseline characteristics between the identified clinical trials. These include: the proportion of patients with baseline CNS metastases and the proportion of patients who have had prior chemotherapy.

Table 5: Differences in baseline characteristics

	ALTA-1L		ALEX	
	Brigatinib	**Crizotinib**	**Alectinib**	**Crizotinib**
N	137	138	152	151
CNS metastases	40 (29%)	41 (30%)	64 (42%)	58 (38%)
Prior chemo to advanced disease	36 (26%)	37 (27%)	0 (0%)	0 (0%)

Abbreviations: CNS, central nervous system

Proportion of patients with CNS metastases at baseline

The imbalance of the proportion of patients with baseline CNS metastases is reflected by a higher proportion of patients in the ALEX trial with CNS involvement in both the alectinib and the crizotinib arms (42% and 38%, respectively) compared with those seen in the ALTA-1L (brigatinib: 29%, crizotinib 30%) trial. The presence of baseline CNS metastases is less prognostic for patients treated with brigatinib or alectinib i.e. treatments that are efficacious in passing the blood-brain barrier – this is also reflected in the ALTA-1L data where brigatinib is similarly effective in patients with or without baseline CNS metastases. Therefore, the imbalance is particularly important where the crizotinib data are considered in indirect comparisons – the ALTA-1L and ALEX crizotinib arms are looking at different

populations and so we would expect different outcomes. This impacts the crizotinib outcomes and the treatment effects of brigatinib vs. crizotinib and alectinib vs. crizotinib. Furthermore, a standard network meta-analysis (NMA) linking brigatinib through the crizotinib arms to alectinib will be biased by this imbalance. Therefore, methods that attempt to account for this imbalance may be preferable e.g. matched adjusted indirect comparisons (MAICs). These methods are summarised in Section 4.3 and further elaborated in section 10.1.1 of the appendices to secure readability. Further, appendix 10.1.4 and 10.1.5 illustrates the weights used for the MIAC analysis.

The true proportion of patients with baseline CNS metastases in a real-world setting is difficult to determine as many centres do not routinely scan for brain involvement at baseline – often due to capacity restrictions. An EORTC survey found that brain metastases screening was approximately 63% for patients with stage III disease and 43% for patients with stage IV disease (38). The real-world evidence reporting baseline CNS metastases range from 19.9%-28.9% for patients with untreated ALK+ advanced NSCLC – these more closely align with the ALTA-1L trial (39-42).

Proportion of patients having received prior chemotherapy

The final key difference in baseline characteristics is the proportion of patients who have received prior chemotherapy – the ALTA-1L trial considered 26% and 27% in the brigatinib and crizotinib arms, respectively, whilst the ALEX trial did not allow for prior chemotherapy. This variable was not found to be a significant driver of outcomes.

4.2 Extrapolated outcomes

To inform the inputs for brigatinib in the economic model, the data from the IA2 analysis from the ALTA-1L trial (median follow-up 24.9 months) were used and extrapolated for the following outcomes: OS, PFS BIRC, PFS INV and CNS-PFS. The definition of each endpoint is presented in Table 6. The model base case applies the PFS BIRC data in line with the primary endpoint from the ALTA-1L trial. The analysis of IA2 data has been heavily influenced by medical input at Takeda and clinical input from international clinical advisors – methods and results were presented from IA1 analysis, discussed and validated at a UK-specific advisory board in February 2019.

Assessment of proportional hazards determined whether to use stratified or independent parametric models for the treatment arms. Following this, seven parametric distributions (exponential, Weibull, Gompertz, gamma, log-normal, log-logistic and generalised gamma) were fit to the patient level data for each outcome. The fit of each parametric model to the survival data was assessed through AIC/BIC statistics, comparison with the Kaplan-Meier curves and experts' judgements on long-term clinical plausibility. All curves were fitted using the *'flexsurv'* package in the statistical software R.

Table 6: Definitions of endpoints from ALTA-1L informing the economic model

	Review	Event	Censor
PFS BIRC	Central independent review committee	• Death • BIRC determined RECIST progression • Radiotherapy for CNS metastases	• Patients who did not experience an event • Missing or incomplete baseline scans or no evaluable on-treatment scans

	Review	Event	Censor
			• Commencement of any other anti-cancer therapy prior to a PFS event • Two consecutive missed disease assessments
PFS INV	Investigator	• Death • Investigator determined RECIST progression • Radiotherapy for CNS metastases	• Patients who did not experience an event • Missing or incomplete baseline scans or no evaluable on-treatment scans • Commencement of any other anti-cancer therapy prior to a PFS event • Two consecutive missed disease assessments
CNS-PFS	Intracranial CNS disease burden was assessed using a different central independent review committee	• Death • Radiological progression of brain lesions as assessed by modified RECIST criteria • Radiotherapy for CNS metastases	• Patients who did not experience an event • Missing or incomplete baseline scans or no evaluable on-treatment scans • Commencement of any other anti-cancer therapy prior to a PFS event • Two consecutive missed disease assessments
OS	NA	• Death of any cause	• Censored for patients still alive at end of follow-up

Abbreviations: BIRC, blinded independent review committee; CNS, central nervous system; INV, investigator; NA, not applicable; OS, overall survival; PFS, progression-free survival

It is important to note that the CNS-PFS outcome is assessed by a different central independent review committee to PFS BIRC and considered a modified CNS-RECIST.

The modified CNS-RECIST considers three groups of patients categorized on baseline CNS status: (1) no intracranial CNS disease – these patients are followed up for new lesions in the brain, (2) intracranial CNS disease present but not measurable – readers were instructed to enter as many non-target lesions as possible and (3) measurable intracranial CNS disease – patients in this category must have at least one target lesion (i.e. ≥10 mm in the longest diameter). The standard RECIST criteria allows up to five target lesions but specifies that no more than two target lesions can be in the same organ system. Whereas, the modified CNS-RECIST assessment allows up to five target lesions in the brain. It is important to note: if a patient progresses due to lesions outside the CNS, this patient is continued to be evaluated as stable disease (SD), partial response (PR) or complete response (CR) in this analysis until progression in the intracranial CNS or discontinuation from the study treatment. Therefore, events in the CNS-PFS variable may reflect progressions during frontline treatment or later line treatment.

Due to these differences, there are a small number of inconsistencies between the endpoints i.e. where a progression event has been recorded under CNS-PFS but not under PFS BIRC (n=12). This inconsistency is to be expected as the modified CNS-RECIST measurement tool is more sensitive and will highlight progressions that would not be identified under the standard RECIST criteria. Three approaches have been explored:

- Unadjusted data for PFS BIRC and PFS CNS. Please note, this will include the inconsistencies between endpoints
- Where there is an inconsistency define CNS progression as per the modified RECIST i.e. add the event to the PFS BIRC data
- Where there is an inconsistency define CNS progression as per the standard RECIST i.e. remove the event from the CNS-PFS data

Each of these analyses are included within the model and can be selected on the *'Model Controls'* sheet. In the base case the third option is considered. Despite the challenges in capturing CNS efficacy, we consider these are outweighed by the importance of including intracranial outcomes within the model.

4.2.2 BIRC progression-free survival

PFS in the ALTA1 trial was based on BIRC, whereas INV PFS was used as endpoint in ALEX. As per the discussion in Section 4.1, this Section presents the unadjusted analyses for PFS BIRC (based on the standard RECIST criteria) and the adjusted analyses for PFS BIRC (based on the modified CNS-RECIST criteria). The unadjusted analyses are applied in the base case.

Unadjusted

The Kaplan-Meier plot for PFS BIRC outcomes for brigatinib vs. crizotinib from the ALTA-1L trial is presented in Figure 2.

[redacted]

Table 7 presents the AIC and BIC values for each parametric survival distribution. There are limited differences in terms of how well each of the parametric curves fit the observed data; less than three points between the AIC and less than eight points between the BIC for brigatinib and less than six points between the AIC and less than seven points between the BIC for crizotinib. The exponential appears the best fit to the observed data for brigatinib. The log-logistic, log-normal, generalised gamma and the exponential provide reasonable fits to the crizotinib data.

[redacted]

mittee; PFS, progression-free survival

A comparison of the Kaplan-Meier plots with the extrapolated curves is presented in Figure 3 and Figure 4 for brigatinib and crizotinib, respectively. As would be expected given the maturity of the

data, the choice of parametric curve has a larger impact for brigatinib outcomes compared to crizotinib outcomes.

Based on the AIC/BIC statistics and the comparison with the Kaplan-Meier curves, the exponential curve is selected in the base case for brigatinib. Alternative parametric curves are can be explored in the model.

Adjusted

The adjusted PFS BIRC outcomes are considered in a the model, however, the scenario must be selected. In this scenario, where there is an inconsistency between PFS BIRC and CNS-PFS the event observed in the CNS-PFS is added to the PFS BIRC i.e. PFS BIRC includes both standard RECIST and the modified CNS-RECIST. Figure 5 presents a comparison of the unadjusted PFS BIRC Kaplan-Meier curves with the adjusted PFS BIRC Kaplan-Meier curves – it should be noted that the change is minimal.

Table 8 presents the AIC and BIC values for each parametric survival distribution. The rank of the goodness of fit statistics are in line with those for the unadjusted PFS BIRC.

A comparison of the Kaplan-Meier plots with the extrapolated curves is presented in Figure 6 and Figure 7 for brigatinib and crizotinib, respectively. As would be expected given the maturity of the data, the choice of parametric curve has a larger impact for brigatinib outcomes compared to crizotinib outcomes.

4.2.3 INV progression-free survival

PFS INV can be explored in a scenario analysis. Figure 8 presents a comparison between the Kaplan-Meier data for PFS BIRC and PFS INV. This comparison indicates the high level of congruency between the two endpoints.

As per the discussion in Section 4.1, this Section presents the unadjusted analyses for PFS INV (based on the standard RECIST criteria) and the adjusted analyses for PFS INV (based on the modified CNS-RECIST criteria). Both of which can be considered as scenarios.

[redacted]

Unadjusted

Table 9 presents the AIC and BIC values for each parametric survival distribution. A comparison of the Kaplan-Meier plots with the extrapolated curves is presented in Figure 9 for brigatinib and Figure 10 for crizotinib.

[redacted]

Adjusted

In this scenario, where there is an inconsistency between PFS INV and CNS-PFS the event observed in the CNS-PFS is added to the PFS INV i.e. PFS INV includes both standard RECIST and the modified CNS-RECIST. Figure 5 presents a comparison of the unadjusted PFS INV Kaplan-Meier curves with the adjusted PFS INV Kaplan-Meier curves – it should be noted that the change is minimal.

[redacted]

Table 10 presents the AIC and BIC values for each parametric survival distribution. A comparison of the Kaplan-Meier plots with the extrapolated curves is presented in Figure 12 for brigatinib and Figure 13 for crizotinib.

[redacted]

[redacted]

[redacted]

4.2.4 CNS-PFS

As per the discussion in Section 4.1, this Section presents the unadjusted analyses for CNS-PFS (based on the modified CNS-RECIST criteria) and the adjusted analyses for CNS-PFS (based on the standard RECIST criteria) – there are two sets of adjusted analyses: (1) for PFS BIRC outcomes (used in the base case) and (2) for PFS INV outcomes (used in a scenarios analysis).

Figure 14 presents the Kaplan-Meier plots for each of the analyses. There is limited difference between the unadjusted CNS-PFS outcomes and the adjusted outcomes.

[redacted]

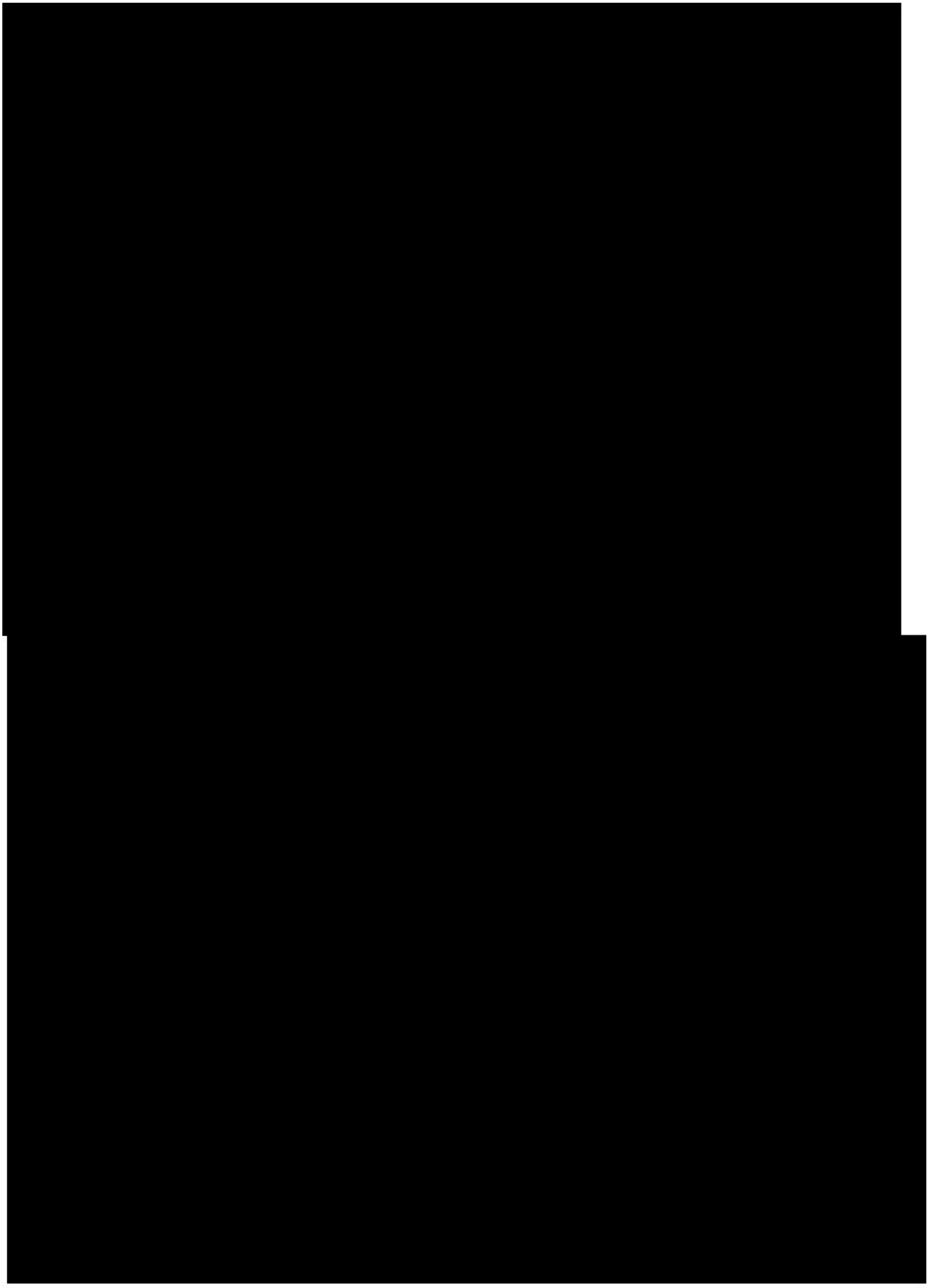
Adjusted based on PFS BIRC

The adjusted CNS-PFS based on PFS BIRC makes an adjustment to align the CNS-PFS outcomes with the PFS BIRC outcomes i.e. to remove any events defined by the modified CNS-RECIST which were not identified by the standard RECIST. Therefore, this scenario considers the standard RECIST and is more reflective of real-word practice.

In line with PFS BIRC outcomes, independent parametric curves were fit to the data. Table 11 presents the AIC and BIC values for each parametric survival distribution. The exponential appears the best fit to the observed data for brigatinib. The log-normal, Gompertz and generalised gamma provide the best fits to the crizotinib data.

[redacted]

A comparison of the Kaplan-Meier plots with the extrapolated curves is presented in Figure 15 and Figure 16 for brigatinib and crizotinib, respectively.



Abbreviations: BIRC, blinded independent review committee; PFS, progression-free survival

Based on the AIC/BIC statistics and the comparison with the Kaplan-Meier curves, the exponential curve is selected in the base case for both brigatinib and crizotinib. Alternative parametric curves can be explored in scenario analysis.

Adjusted based on PFS INV

The adjusted CNS-PFS based on PFS INV outcomes makes an adjustment to align the CNS-PFS outcomes with the PFS INV outcomes i.e. to remove any events defined by the modified CNS-RECIST which were not identified by the standard RECIST.

In line with PFS BIRC outcomes, independent parametric curves were fit to the data. Table 11 presents the AIC and BIC values for each parametric survival distribution. The exponential appears the best fit to the observed data for brigatinib. The log-normal, Gompertz and generalised gamma provide the best fits to the crizotinib data.

A comparison of the Kaplan-Meier plots with the extrapolated curves is presented in Figure 15 and Figure 16 for brigatinib and crizotinib, respectively.

Unadjusted

Table 13 presents the AIC and BIC values for each parametric survival distribution. The rank of the goodness of fit statistics are in line with those for the adjusted CNS-PFS.

[redacted]

A comparison of the Kaplan-Meier plots with the extrapolated curves is presented in Figure 19 and Figure 20 for brigatinib and crizotinib, respectively.

[redacted]

4.2.5 Overall survival

As discussed in Section 4.1, the OS data observed in the ALTA-1L trial is confounded by crossover (52.90% from the crizotinib to the brigatinib arm) and subsequent ALK inhibitors which may not be reflective of current clinical practice.

The model includes the option to use the unadjusted data from the ALTA-1L trial or to use the cross-over-adjusted data for the crizotinib arm which attempts to remove the effect of subsequent brigatinib in this arm. This analysis only considers subsequent brigatinib in the crizotinib arm and does not account for other subsequent ALK inhibitors received in the brigatinib nor the crizotinib arm. In this report, the unadjusted data are used in the base case and scenario analyses can explore the impact of the crossover-adjusted data.

Unadjusted

The Kaplan-Meier plot for OS outcomes for brigatinib vs. crizotinib from the ALTA-1L trial is presented in Figure 21. Due to the different mechanisms of action, it is not expected proportional hazards to hold between brigatinib and crizotinib. However, it is expected proportional hazards to hold between brigatinib and alectinib – based on similar mechanisms of action across the second/third generation ALK inhibitors. Therefore, independent parametric models were fit to the brigatinib and crizotinib data.

Table 14 presents the AIC and BIC values for each parametric survival distribution. There are limited differences in terms of how well each of the parametric curves fit the observed data; less than three points between the AIC and less than nine points between the BIC for brigatinib and crizotinib. The most reasonable fits to the observed data include: exponential, Gompertz, log-logistic and log-normal.

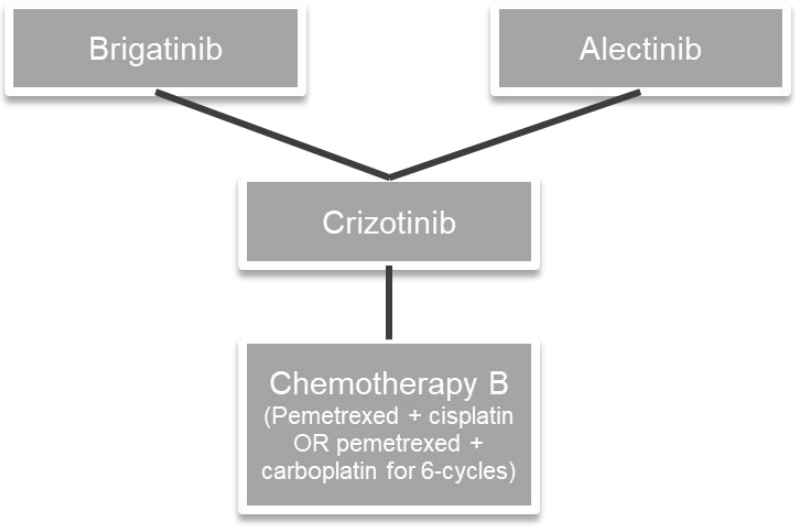
A comparison of the Kaplan-Meier plots with the extrapolated curves is presented in Figure 3 and Figure 4 for brigatinib and crizotinib, respectively. As would be expected given the maturity of the data, the choice of parametric curve has a larger impact for brigatinib outcomes compared to crizotinib outcomes.

4.3 Indirect treatment comparisons

In the absence of head-to-head data between brigatinib and alectinib, indirect synthesis methods were required.

Figure 24 presents the network formed by studies identified from the clinical SLR. The solid lines represent links through head-to-head trials; the ALTA-1L trial provides the evidence for brigatinib vs. crizotinib, the ALEX trial provides the evidence for alectinib vs. crizotinib

Figure 24: Network plot for indirect treatment comparisons[2-6]



In the base case, a simple cost-comparison is recommended for brigatinib vs. alectinib. Therefore, the indirect comparisons presented in Section 4.3.1 should be used to support the statement: *"brigatinib is at least as efficacious as alectinib"*.

4.3.1 Brigatinib vs. alectinib

Three methods were explored in the indirect comparison with alectinib:

1. Unadjusted Bucher
2. Anchored MAIC
3. Unanchored MAIC

Firstly, the unadjusted Bucher analysis which applies the Bucher's indirect technique (thus preserving intra-trial randomisation) with no adjustments applied for differences in prognostic factors or treatment effect modifiers. The common crizotinib arms from ALTA-1L and ALEX provide the necessary inter-trial link required for this analysis.

As discussed in Section 4.1.1, there are a number of differences between the ALTA-1L trial and the ALEX trial – these limit the interpretation of indirect comparisons. Anchored MAIC methods can explore the impact of accounting for differences in any treatment effect modifying variables, whilst

preserving the intra-trial randomisation (as in the unadjusted Bucher). The proportion of baseline CNS metastases was identified as the only treatment effect modifier based on the ALTA-1L patient level data. Therefore, an anchored MAIC approach was also considered with an adjustment for the imbalance in baseline CNS metastases between the trials. The anchored MAIC involved two separate matchings on baseline CNS metastases proportions: (1) brigatinib ALTA-1L patient level data were matched to the alectinib arm in ALEX and (2) crizotinib ALTA-1L patient level data were matched to the crizotinib arm in ALEX.

Receipt of prior chemotherapy was not identified as a treatment effect modifier using the ALTA-1L data. However, subgroup analyses using treatment naïve data only from the ALTA-1L trial (i.e. no prior chemotherapy) were explored to allow for a more like-with-like comparison between the ALTA-1L and ALEX clinical trials. The ALEX trial only considered patients who were treatment naïve. Therefore, the alectinib data are the same for both the ITT (ALK inhibitor naïve) and the treatment naïve analyses. However, the ALTA-1L trial was not set-up to assess outcomes for this subgroup. Therefore, the ITT analyses (i.e. patients who are ALK inhibitor naïve) should be considered in the base case.

As the unadjusted Bucher method and the anchored MAIC method use the crizotinib link to estimate a relative efficacy estimate, the OS estimates are biased by the treatment switching which occurred in the ALTA-1L crizotinib arm and not in the ALEX crizotinib arm.

Finally, an unanchored MAIC was also explored between brigatinib vs. alectinib. The rationale for this analysis was that the key differences impacting outcomes between the ALTA-1L and ALEX clinical trials are specific to the crizotinib arm – i.e. baseline CNS metastases is shown to be prognostic for patients treated with crizotinib, but not brigatinib and treatment switching impacted OS estimates in the crizotinib arm only. The unanchored MAIC considers the brigatinib arm from the ALTA-1L trial and the alectinib arm from the ALEX trial as if they were from single arm studies and ignores the data from the crizotinib arms. Therefore, this analysis avoids the bias that would be introduced relating to the crizotinib arms. The unanchored MAIC balances the data based on: age, smoking status, race, baseline CNS metastases, ECOG score and receipt of prior chemotherapy – the same list of variables was used in the unanchored MAICs for brigatinib in the post-crizotinib setting.

PFS BIRC

Figure 25 presents a naive comparison of the Kaplan-Meier data from the ALTA-1L trial and the ALEX trial for PFS BIRC outcomes. The data for PFS BIRC from the ALEX trial was obtained from Peters et al. (2017); the PFS BIRC outcome was only reported in the primary analysis with a median follow-up of 18.6 months (30). Whilst in the ALTA-1L trial there appears to be an earlier separation of curves, the trend is similar between the two trials. This supports the rationale for a cost-comparison analysis.

Table 15 presents the results for the unadjusted Bucher, the anchored MAIC analysis, and the unanchored MAIC analysis for PFS BIRC outcomes for the ITT and treatment naïve populations. The confidence intervals are wide for each of the comparisons and span one – indicating non-significant outcomes. The hazard ratios for the ITT population vary between 0.969 and 1.04 indicating that brigatinib provides similar outcomes to alectinib in terms of PFS BIRC – advocating the use of the cost-comparison analysis in the base case. The cost-comparison analysis assumes a hazard ratio of one for all outcomes i.e. brigatinib and alectinib are assumed identical in terms of PFS BIRC outcomes.

PFS INV

Figure 26 presents a naive comparison of the Kaplan-Meier data from the ALTA-1L trial and the ALEX trial for PFS INV outcomes. The data for PFS INV from the ALEX trial was obtained from Mok et al.

(2019) – this is the latest publication with a median follow-up of 37.8 months.[4] Whilst in the ALTA-1L trial there appears to be an earlier separation of curves, the trend is similar between the two trials. This supports the rationale for a cost-comparison analysis.

Table 16 presents the results for the unadjusted Bucher, the anchored MAIC analysis and the unanchored MAIC analysis for PFS INV outcomes for the ITT and treatment naïve populations. The confidence intervals are wide for each of the comparisons and span one – indicating non-significant outcomes. The hazard ratios for the ITT population vary between 0.965 and 1.046 indicating that brigatinib provides similar outcomes to alectinib in terms of PFS INV – these outcomes closely align with those seen for PFS BIRC above.

CNS-PFS

The CNS-PFS variable is not publicly available from the ALEX trial. However, the Kaplan-Meier curves have been redacted. Therefore, the hazard ratio for CNS-PFS for brigatinib vs. alectinib is assumed to be the same as the hazard ratio for PFS. Given that the cost-comparison is likely to be used in the base case, where all outcomes are assumed the same, this is not considered to be a key driver of results.

OS

Figure 27 presents the Kaplan-Meier plot for brigatinib from the ALTA-1L data alongside the digitised OS data from Camidge et al. (2018) – the latest publication showing a Kaplan-Meier plot for alectinib (31). Based on this naïve comparison, there is no clear difference between brigatinib and alectinib. This supports the rationale for a cost-comparison analysis.

Table 17 presents the results for the unadjusted Bucher, the anchored MAIC analysis and the unanchored MAIC analysis for OS outcomes for the ITT and treatment naïve populations.

Like the PFS outcomes, the confidence intervals are wide for each of the comparisons and span one – indicating non-significant outcomes. However, there is a much bigger difference between the unadjusted Bucher and anchored MAIC when compared with the unanchored MAIC – based on the ITT population these analyses are associated with hazard ratios of 1.359, 1.21 and 0.832 for brigatinib vs. alectinib, respectively. Two potential drivers of differences were explored: (1) different follow-ups from the ALEX trial contributing to the data and (2) differences in subsequent therapies in the crizotinib arms between the ALTA-1L and ALEX clinical trials.

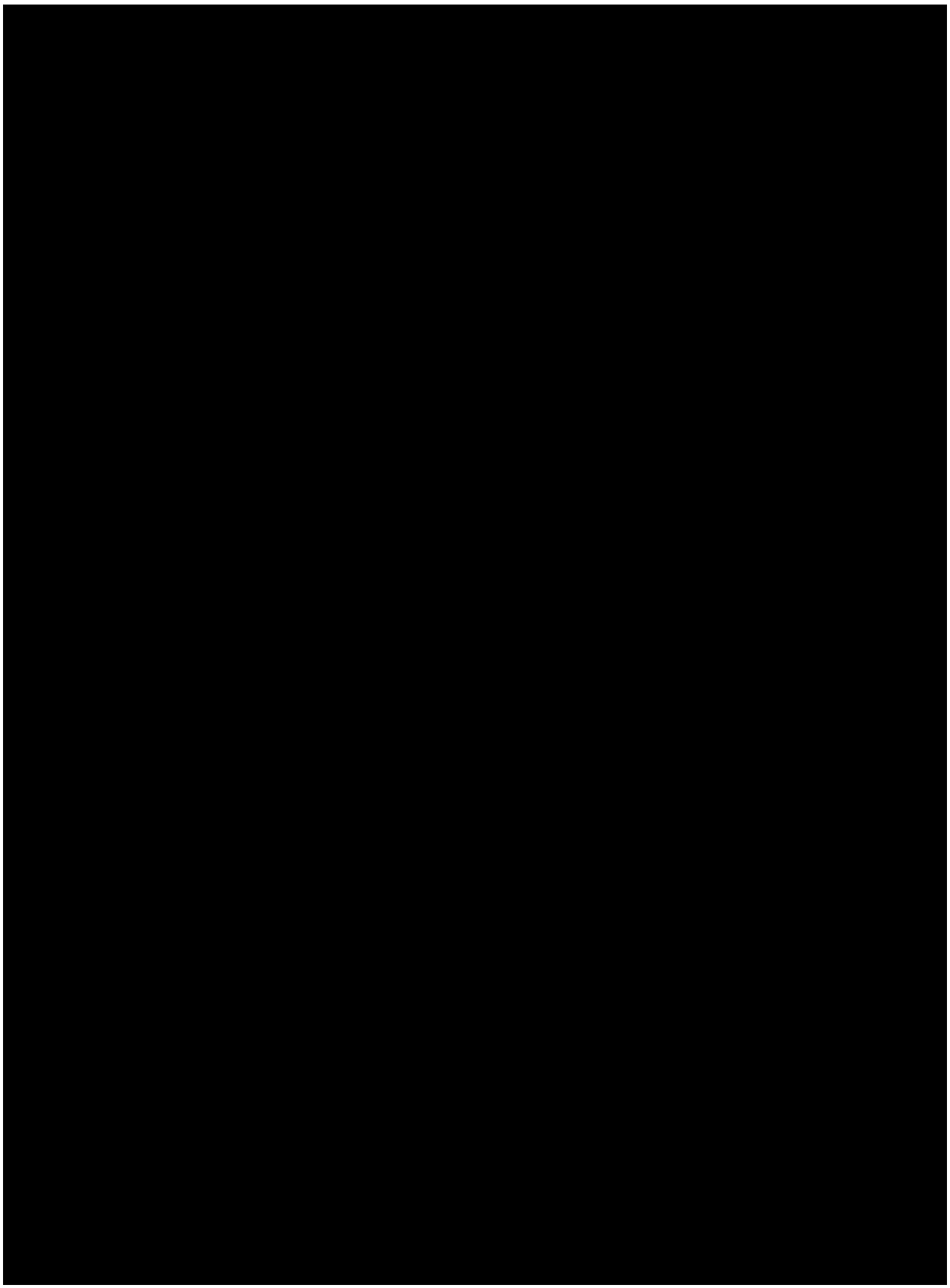
The unadjusted Bucher and anchored MAIC use data from the latest publication for ALEX – Mok et al. (2019) – 37.8 months of follow-up in the alectinib arm (32). However, this publication only reports the hazard ratio and confidence interval. Whereas, the unanchored MAIC makes use of an earlier publication (Camidge et al. (2018) – 27.8 months of follow-up in the alectinib arm) where a Kaplan-Meier plot is presented for OS outcomes (31). To explore the impact of this mismatch in data, Table 17 presents the results of the unadjusted Bucher and anchored MAIC when the earlier data cut is used i.e. consistent with the unanchored MAIC. Whilst the point estimates for these analyses move closer to the unanchored MAIC, the data source does not fully explain the differences.

As discussed in Section 4.1.1, crossover was permitted in the ALTA-1L trial. Whereas, this was not permitted in ALEX. As a result, most patients progressing in the crizotinib arm in the ALTA-1L trial went on to receive brigatinib as a subsequent therapy (73 of the 74 patients who progressed). In comparison only ten patients went onto receive alectinib as a subsequent therapy in the ALEX trial. Furthermore, at this second interim data cut, there are 93 instances in the crizotinib arm where patients are receiving or have received subsequent therapy with an ALK inhibitor in the ALTA-1L.

The unadjusted Bucher and anchored MAIC do not account for this. Therefore, the results will be biased against brigatinib – the relative treatment effect of brigatinib vs. crizotinib will be biased by the efficacious subsequent therapies in the crizotinib arm. The statistical analyses explored methods of adjusting for treatment switching within the unadjusted Bucher and anchored MAIC approaches – these are presented in Table 18 based on both the latest Mok et al. (2019) publication and the earlier Camidge et al. (2018) publication. These adjustments move the point estimates closer to the unanchored MAIC. However, the difference between methods is still noteworthy.

Section 4.1.1 describes the extensive differences between the ALTA-1L and ALEX clinical trial – statistical methods are unable to account for all these differences. Therefore, there may be something else driving the difference between the analyses. In addition, the treatment switching adjustments embedded within the unadjusted Bucher and anchored MAIC analyses may not be fully accounting for the bias from subsequent brigatinib use in the crizotinib arm.

The range of point estimates and the associated uncertainty indicate that no conclusion can be made based on the indirect analyses for OS. It should be noted that the model only includes indirect analyses based on the most recent data available (i.e. uses Mok et al. (2019) for all unadjusted Bucher and anchored MAIC analyses) – the analyses based on the earlier data cut are presented here as illustrative only. All other analyses are on the "Efficacy" sheet of the economic model.



4.4 Time on treatment

Patients in the ALTA-1L clinical trial continued treatment with brigatinib or crizotinib until they experienced BIRC assessed progressive disease, intolerable toxicity, or were discontinued for other reasons. It was permitted that patients in the brigatinib arm who experienced BIRC-assessed progressive disease could continue to be treated with brigatinib if, in the opinion of the treating investigator, they continued to experience clinical benefit. Patients in the crizotinib arm were not permitted to continue treatment with crizotinib on study after BIRC-assessed progressive disease. However, these patients were permitted to crossover to the brigatinib arm.

Figure 28 presents the Kaplan-Meier data for time on treatment (ToT) compared with PFS BIRC for brigatinib and crizotinib. The median exposure time in the ALTA-1L trial for brigatinib was 24.3 months vs. 8.4 months for crizotinib; compared with the median PFS BIRC of 24 vs.11 months respectively. The difference in median estimates reflects what is shown in Figure 28; on average patients treated with brigatinib seem to discontinue at progression and patients treated with crizotinib seem to discontinue shortly before progression.

In the real-world setting, patients with ALK+ advanced NSCLC are often treated beyond progression. This is reflected in the clinical trials to date in the ALK+ advanced NSCLC setting; a recent review of clinical trials in this setting explored the relationship between time to treatment discontinuation and PFS and found that a proportion of patients with ALK+ advanced NSCLC continued treatment beyond progression – 22.9% received ≥3 months of treatment beyond progression (47). This review included trials for brigatinib post-crizotinib, alectinib and crizotinib.

It should be noted that whilst the exact relationship between progression and discontinuation is uncertain, there are no treatment-specific reasons to discontinue or prolong treatment beyond progression.

Based on this information, the following options are included in the model: assume discontinuation at progression, continued treatment for one cycle post-progression, continued treatment for two cycles post-progression, continued treatment for three cycles post-progression and to use the clinical trial data directly for brigatinib and crizotinib. Clinical trial data for ToT are unavailable for alectinib. Therefore, this option is not included for this comparator and the model will default to treat until progression for alectinib. If a cost-comparison model is selected for brigatinib vs. alectinib, then the ToT is assumed identical between the treatments. In the base case it is assumed all patients receive three cycles post-progression. Other methods can be explored in scenario analyses.

4.5 Clinical parameter summary

Figure 29, Figure 30 and Figure 31 present the base case extrapolated outcomes for PFS BIRC, CNS-PFS and OS for brigatinib, crizotinib, and alectinib. As a cost-comparison is applied in the base case for brigatinib vs. alectinib, the extrapolated curves for brigatinib and alectinib are identical. Certinib is not in the scope of the Danish application, but can't be excluded from the global model.

Figure 32 and Figure 33 show the base case extrapolated curves for the four key efficacy outcomes (PFS BIRC, CNS-PFS, ToT and OS) for brigatinib, crizotinib, and alectinib.

4.6 Adverse events

Treatment with TKIs result in a variety of adverse events. Any-cause grade 3/4 adverse events occurring in ≥3% of patients in the relevant clinical trials (ALTA-1L and ALEX) were included in the economic analysis.

The latest publication of the ALEX trial does not provide a breakdown of adverse events. However, the total number of grade 3/4 adverse events is reported as 74 (32). The second publication for the ALEX trial only reports all grade adverse events that differed by ≥5% in frequency between treatment arms (31). Therefore, the primary publication for the ALEX trial has been used to source grade 3/4 adverse events occurring in ≥3% of patients – this describes 63 grade 3/4 adverse events (30). Therefore, some adverse events are missing from the alectinib arm due to lack of reporting.

Adverse events were modelled only for patients on treatment; it was assumed that adverse events for all therapies cease once treatment is discontinued. It was further assumed that adverse events lasted one model cycle (i.e. 28 days). Table 19 presents the number of events associated with each adverse event included in the model.

The number of events and the median exposure time was used to calculate a per cycle event rate (Table 20). Where adverse events were not reported in specific publications, the model assumes an event rate of zero.

Table 19: Number of adverse events for each treatment

Adverse Events	Occurrence		
	Brigatinib (35)	Crizotinib (35)	Alectinib (30)
Blood creatinine phosphokinase increased	32	1	4
Amylase increased	8	1	NR
Nausea	2	3	1
Hypertension	10	0	NR
Increased AST	3	7	8
Increased ALT	2	11	7
Increased lipase level†	17	5	NR
Neutropenia	0	4	0
Anaemia	2	0	7
Diarrhoea	1	4	0
Vomiting	0	1	0
Gamma-glutamyl transferase increased	1	2	1
Myalgia	0	0	0
Fatigue	0	0	1
Pneumonia	1	0	4
Urinary tract infection	NR	NR	4
Acute kidney injury	0	1	4
Weight decreased	0	0	NR
Dizziness	0	0	0

Adverse Events	Occurrence		
	Brigatinib (35)	Crizotinib (35)	Alectinib (30)
Dysgeusia	0	0	0
Asthenia	0	1	NR

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; NR, not reported

Table 20: Rate of adverse events per model cycle

Adverse events	**Rate per cycle**		
	Brigatinib	**Crizotinib**	**Alectinib**
Blood creatinine phosphokinase increased	0.0089	0.0008	0.0008
Amylase increased	0.0022	0.0008	0.0000
Nausea	0.0006	0.0024	0.0002
Hypertension	0.0028	0.0000	0.0000
Increased AST	0.0008	0.0056	0.0017
Increased ALT	0.0006	0.0088	0.0015
Increased lipase level†	0.0047	0.0040	0.0000
Neutropenia	0.0000	0.0032	0.0000
Anaemia	0.0006	0.0000	0.0015
Diarrhoea	0.0003	0.0032	0.0000
Vomiting	0.0000	0.0008	0.0000
Gamma-glutamyl transferase increased	0.0003	0.0016	0.0002
Myalgia	0.0000	0.0000	0.0000
Fatigue	0.0000	0.0000	0.0000
Pneumonia	0.0003	0.0000	0.0008
Urinary tract infection	0.0000	0.0000	0.0000
Acute kidney injury	0.0000	0.0008	0.0000
Weight decreased	0.0000	0.0000	0.0000
Dizziness	0.0000	0.0000	0.0000
Dysgeusia	0.0000	0.0000	0.0000
Asthenia	0.0000	0.0008	0.0000
Total	0.0220	0.0329	0.0067

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase

5 Resource use and costs

Resource use and cost inputs are in line with the Danish restricted societal perspective of the model. All costs represent the 2020/2021 cost year and have been obtained from the Danish DRG-code and Medicinpriser.dk (61,62).

5.1 Intervention and comparator resource use and costs

5.1.1 Treatment costs

Frontline therapies

The unit costs associated with treatment acquisition are shown in Table 21 at list price. The model includes the option to apply a simple discount to each of the list prices and a complex scheme whereby the cost of treatment is refunded past a specific cycle – these selections can be made on the 'Costs' sheet. All results in this document are presented based on list price.

The dose schedule of brigatinib is aligned with the ALTA-1L clinical trial and aligns with the proposed Marketing Authorisation (34). The dose schedule of alectinib aligns with the ALEX clinical trial and the SmPC for alectinib (18,63).

The model includes the option to account for patients who may not take the full course of doses due to dose interruption or reduction associated with adverse events or non-compliance. The mean relative dose intensities are 85.51% (SD: 19.44) for brigatinib and 95.6% for alectinib (35-37). The base case applies these dose intensities, a scenario analysis explores the impact of 100% dose intensity for all treatments. The reason for including the treatments relative dose intensities in the base case, even though the ALTA-1L and ALEX protocols show difference in study structure, is because studies has shown correlation between relative dose intensities and outcomes (69). The actual relative dose intensity of the studies is therefore used as the base case. The base case assumes that all costs relating to dose reductions or missed doses can be saved by the healthcare system. Whereas, the scenario analysis assumes that none of the costs can be saved.

Table 21: Unit costs associated with the technology in the economic model

	Brigatinib	Alectinib
Unit dose	180mg once daily with a 7-day lead-in at 90mg	600mg twice daily
Pack size	28 tablets	224 tablets
Unit cost at list price	[redacted]	
Cost per 28-days – dose intensity applied		
Cost per 28-days – dose intensity not applied		
Treatment duration	Three cycles post progression	Three cycles post progression

Subsequent therapies

The model provides two options for modelling subsequent therapies: (1) as per the clinical trial data and (2) based on treatments inputs from Danish clinical expert [redacted] The model base case assumes option (2) to reflect the Danish practice. A scenario analysis explored option (1).

Table 3 in Section 4.1.1 presents the subsequent therapies received following frontline treatment in each of the relevant clinical trials. The subsequent therapy inputs in the economic model simplify this distribution through the following assumptions:

1. Remove subsequent radiotherapy as this is captured in CNS management
2. Assume other ALK inhibitors reported for the ALEX trial to be lorlatinib
3. Assume other therapies to be chemotherapy

Table 22 presents the subsequent therapy distribution applied when Option (1) is selected within the model i.e. when subsequent therapies are modelled as per the clinical trial data. At the end of the second data cut from the ALTA-1L trial, 54 patients in the brigatinib arm and 74 patients in the crizotinib arm had had a progression event (as defined by PFS BIRC). Based on the ALEX trial, 41 patients in the alectinib arm had had an event. The subsequent therapy data for alectinib was obtained from the NICE submission and it is unclear which data cut this was from.

Table 22: Subsequent therapy distribution as per clinical trials (applied in scenario analysis)

Subsequent Anti-Cancer Treatment	Brigatinib	Alectinib
ALK TKI	55.56%	43.90%
ALECTINIB	18.52%	0.00%
BRIGATINIB	1.85%	0.00%
CERITINIB	7.41%	9.76%
CRIZOTINIB	20.37%	21.95%
LORLATINIB	24.07%	14.63%
Chemotherapy	24.07%	95.12%
Immunotherapy	9.26%	14.63%
VEGF-R	5.56%	4.88%

Abbreviations: ALK, anaplastic lymphoma kinase; TKI, tyrosine kinase inhibitor; VEGF-R, Vascular Endothelial Growth Factor

Table 23 presents the subsequent therapy distribution applied in the scenario where option (2) is considered i.e. subsequent therapies are costed based on input from a Danish clinical expert [redacted] The selection of chemotherapy and immunotherapy as second-line treatment is in line with guidelines from Dansk Lunge Cancer Gruppe (70). Its has not been possible to obtain distributions for the regimes based on Danish guidelines, and clinical input from a Danish expert has, therefore, been valued as the best choice. However, the Medicines Council did in 2018 choose to narrow the indication of most immunotherapies (pembrolizumab/nivolumab/atezolizumab) to apply only to patients with PD-L1 expression > 1%. Patients who are assessed as unfit for second-line immunotherapy are assessed for second-line treatment chemotherapy. This can contribute to the explanation of the

distributions seen between the subsequent treatments. Lastly, the model assumes that all patients receive best supportive care (BSC) after exhaustion of active therapies. The distribution has been chosen as a precautionary measure to ensure that the costs are not underestimated.

Table 23: Subsequent therapy distribution applied in base case

Subsequent Anti-Cancer Treatment	Brigatinib	Alectinib
ALK TKI	0%	0%
ALECTINIB	0%	0%
BRIGATINIB	0%	0%
CERITINIB	0%	0%
CRIZOTINIB	0%	0%
LORLATINIB	0%	0%
Chemotherapy	90%	90%
Immunotherapy	5%	5%
VEGF-R	0%	0%
BSC	100%	100%

Abbreviations: ALK, anaplastic lymphoma kinase; TKI, tyrosine kinase inhibitor; VEGF-R, Vascular Endothelial Growth Factor

Cleare differences in distributions are seen between the two options. The reason for the differences is attributed to the differences in clinical practice between countries. In the ALTA-1 trial 18 countries, including Denmark, are listed as location countries, and in the ALEX trial 30 countries excluding Denmark are listed as location countries. The differences in clinical practice regarding second-line treatment between countries is assumend to affect the distributions and therefore showing a difference between the two options in this model.Since equal assumptions are applied to 2L treatment for both alectinib and brigatinib it will not bias cost-estimations in the model in any direction.

Table 24 presents the dose and cost information associated with each of the subsequent ALK inhibitors, immunotherapy (assumed atezolizumab) and VEGF-R (assumed nintedanib). Atezolizomab has been chosen based on price and placement in treatment guidelines. In the guideline from Dansk Lunge Cancer Grupper, Pembrolizumab, nivolumab, and atezolizumab are all equally placed in regards to the recommended use. Based on Takeda estimates, atezolizumab has been assessed to be the most costly out of the three possible regimes and is therefore selected in the model to ensure the most conservative budget impact, rather than underestimating this. Dosing schedules are based on the pivotal trials informing the efficacy in patients with previously treated ALK+ advanced NSCLC in the table below. All costs are applied based on list prices, and as it can be assumed that Amgros had secured a certain level of discount on the products, the prices will represent an upper limit. The option is available within the model to add a simple discount to subsequent therapies on the 'Costs' sheet.

Table 24: Cost and dosing information for subsequent ALK inhibitors, immunotherapies and VEGF-Rs

Intervention	Dose	Cycle length (days)	Duration of therapy (weeks)	Pack size	mg	Cost per pack	Cost per cycle	Source
Alectinib	600mg twice daily	28	60.20	224	150	[redacted]	[redacted]	ALUR clinical trial (4)
Brigatinib	180 mg once daily	28	83.49	28	180	[redacted]	[redacted]	ALTA clinical trial (56)
Crizotinib	250mg twice daily	28	48.14	60	250	[redacted]	[redacted]	PROFILE-1005 clinical trial (57)
Lorlatinib	100mg once daily	28	45.66	30	100	[redacted]	[redacted]	Study 1001 and NICE Committee papers (63)
Atezolizumab	1,200mg every 3-weeks	21	33.83	20	60	[redacted]	[redacted]	OAK trial and NICE Committee papers (64)
Nintedanib	200mg twice daily	21	14.78	60	100	[redacted]	[redacted]	LUME Lung-1 clinical trial and NICE Committee papers (58, 65)

Abbreviations: ALK, anaplastic lymphoma kinase; mg, milligram; VEGF-R, Vascular Endothelial Growth Factor

Table 25 below shows the cost and dose for BSC. The information has been obtained from Medicinpriser.dk and Pro.Medicin.dk.

Table 25: cost and dosing information for BSC

Category	Dose	Unit cost (kr)	Per cycle cost
Radiotherapy	-	747.00 kr.	186.75 kr.
Steroids (dexamethasone)	0.5mg daily	619.00 kr.	21.67 kr.
NSAIDs (ibuprofen)	75mg daily	38.00 kr.	0.80 kr.
Morphine	40-60mg daily (average 50mg)	84.06 kr.	117.68 kr.
Bisphosphonate (alendronic acid)	10mg daily	7.50 kr.	2.50 kr.
Denosumab	120mg every 4 weeks	2,101.88 kr.	2,101.88 kr.

The model includes five different chemotherapy regimens to increase flexibility, including: pemetrexed + cisplatin, pemetrexed + carboplatin, pemetrexed monotherapy, pemetrexed maintenance and docetaxel. The cost breakdown for each of these regimens is presented in Table 47 in the appendix.

In the model base case, patients are assumed to receive pemetrexed 500mg/m2 + carboplatin 75mg/m2 every 3-weeks for a maximum of four cycles followed by pemetrexed maintenance 500mg/m2 every 3-weeks. The assumption has been validated by Danish clinical expert [redacted] The type of chemotherapy costed within the model can be edited on the 'Costs' sheet within the economic model.

5.1.2 Administration costs

Frontline therapies

Brigatinib and alectinib are oral therapies. Therefore, there is no expected administration cost associated with each treatment.

Subsequent therapies

Subsequent ALK inhibitors (i.e. brigatinib, crizotinib, alectinib, and lorlatinib) and subsequent VEGF-R (i.e. nintedanib) are oral therapies. Therefore, these are costed as per the frontline therapies.

5.1.3 Concomitant medications

Concomitant medications were obtained from the ALTA-1L clinical trial and were included if they were received by ≥10% of patients. A total of 21 concomitant medications were included in the model – see Table 26.

Costs were obtained from the Medicinpriser.dk when available. 5 out of 21 CMs were unavailable, and and no substitute could be found, the costs were therefore excluded. Three medications required weight-based dosing – the average of the mean weight in the brigatinib arm (68.37kg) was applied here (35).

Table 26: Concomitant medications

Concomitant medication	Description	Dose	Brigatinib	Crizotinib	Recommended units (e.g. tablets) per day	Number of units per pack	Costs for Brigatinib	Costs for Crizotinib
PARACETAMOL	Paracetamol 500mg tablets / Pack size 100	6 * 500mg / day	55.15%	35.77%	6	300	8.51 kr.	5.52 kr.
METOCLOPRAMIDE	Metoclopramide 10mg tablets / Pack size 28	1 * 10mg / day	9.56%	16.79%	1	100	1.34 kr.	2.35 kr.
DEXAMETHASONE	Dexamethasone 4mg tablets / Pack size 100	2 * 4mg / day	18.38%	15.33%	4	100	127.44 kr.	106.27 kr.
METOCLOPRAMIDE HYDROCHLORIDE	Metoclopramide 10mg	1 mg/kg	11.76%	18.25%	6.85	100	11.28 kr.	17.49 kr.
LOPERAMIDE HYDROCHLORIDE	Loperamide hydrochloride 200 microgram per 1 ml	500 micrograms daily	12.50%	13.87%	0.5	20	- kr.	- kr.
AMOXI-CLAVULANICO	Amoxicillin	500mg daily	14.71%	10.22%	1	20	4.30 kr.	2.99 kr.
ENOXAPARIN SODIUM	Enoxaparin sodium 100 mg per 1 ml	1mg/kg	10.29%	12.41%	68.4735	1000	171.71 kr.	206.98 kr.
ACETYLSALICYLIC ACID	Aspirin	300mg daily	11.03%	10.22%	3	100	4.37 kr.	4.05 kr.

Concomitant medication	Description	Dose	Brigatinib	Crizotinib	Recommended units (e.g. tablets) per day	Number of units per pack	Costs for Brigatinib	Costs for Crizotinib
LOPERAMIDE	Loperamide 2mg capsules (standard pack) / Pack size 30	4 * 2 mg / day	11.03%	8.76%	4		- kr.	- kr.
ACETYLCYSTEINE	2g/10ml solution	100mg/kg	8.82%	10.22%	6847.35	20000	90.29 kr.	104.57 kr.
SENNOSIDE A+B	Senna	7.5mg daily	7.35%	10.22%	1	100	- kr.	- kr.
OMEPRAZOLE	Omeprazole 40mg gastro-resistant capsules / Pack size 28	1 * 40mg / day	17.65%	15.33%	1	112	7.86 kr.	6.82 kr.
HYDROCORTISONE	Hydrocortisone 20mg tablets / Pack size 30	1 * 20mg / day	11.76%	8.03%	2	50	475.78 kr.	324.71 kr.
LORAZEPAM	Lorazepam 1mg tablets (scored) / Pack size 28	2 * 1mg / day	8.82%	12.41%	2	100	1.38 kr.	1.95 kr.
MAGNESIUM OXIDE	Magnesium hydrox-ide 79 mg per 1 ml	1 * 30mL	5.88%	11.68%	30	200	- kr.	- kr.
FUROSEMIDE	Furosemide 40mg tablets / Pack size 28	1 * 40mg / day	12.50%	18.25%	1	500	0.69 kr.	1.00 kr.

Concomitant medication	Description	Dose	Brigatinib	Crizotinib	Recommended units (e.g. tablets) per day	Number of units per pack	Costs for Brigatinib	Costs for Crizotinib
IBUPROFEN	Ibuprofen 200mg tablets / Pack size 100	3 * 200mg / day	7.35%	12.41%	3	100	1.23 kr.	2.08 kr.
LEVOFLOXACIN	Levofloxacin 500mg tablets / Pack size 10	1 * 500mg / day	7.35%	13.87%	1	10	- kr.	- kr.
PANTOPRAZOLE	Pantoprazole 40mg gastro-resistant tablets / Pack size 28	2 * 40mg / day	7.35%	16.79%	2	100	0.78 kr.	1.77 kr.
LACTULOSE	Lactulose 10g/15ml oral solution 15ml sachets sugar free / Pack size 10	3 * 15ml sachet / day	5.15%	13.14%	3	10	- kr.	- kr.
PREDNISOLONE	Prednisolone 25mg tablets / Pack size 30	1 * 25mg / day	19.12%	5.84%	1	100	14.93 kr.	4.56 kr.

Due to lack of comparator evidence the model assumes that the type and proportion of patients receiving concomitant medications whilst on treatment are the same for brigatinib and alectinib. In the model, the cost of CMs is only considered for patients on treatment. Further, it is assumed that the concomitant medications are attributed as the patient's own payment.

5.2 Health state resource use and costs

Health state resource use was defined by whether a patient was receiving frontline treatment (i.e. on-treatment), whether a patient had discontinued frontline treatment (i.e. off-treatment) and whether a patient had progressed in their CNS.

5.2.1 On-treatment resource use and costs

Table 34 presents the resource use assumed for patients receiving frontline treatment. These estimates are applied irrespective of treatment arm and based on Takeda base case estimates. Table 27 presents the unit costs associated with each resource item.

Table 27: Unit costs associated with health state resource use

Resource	Unit cost	Source
Biochemistry/Full blood test	2,998.00 kr.	04SP01
CT scan	2,032.00 kr.	30PR06
X-ray	747.00 kr.	30PR17
MRI	2,768.00 kr.	30PR02
ECG	2,737.00 kr.	05PR04

Abbreviations: CT, computerised tomography; ECG, electro-cardiogram; GP, general practitioner; MRI, magnetic resonance imaging; NHS, National Health Service

Table 28: Resource use associated with on-treatment

Category	Item	Frequency per month	% of patient requiring resource	Cost per month
(1) Adjustment opening cycle				
Tests and procedures				
	Biochemistry/Full blood test	1.00	100%	2,998.00 kr.
			Total cost per cycle:	2,757.91 kr.
(2) On-going cycles				
Tests and procedures				
	Biochemistry/Full blood test	1.00	100%	2,998.00 kr.
	CT scan	0.50	100%	1,016.00 kr.

Category	Item	Frequency per month	% of patient requiring resource	Cost per month
	MRI	0.20	50%	276.80 kr.
	X-ray	0.30	50%	112.05 kr.
	ECG	1.00	100%	2,737.00 kr.

Abbreviations: CT, computerised tomography; ECG, electro-cardiogram; GP, general practitioner; MRI, magnetic resonance imaging

5.2.2 Off-treatment resource use and costs

Table 29 presents the resource use assumed for patients who have discontinued frontline therapy. These estimates are applied irrespective of treatment arm and irrespective of site of progression and based on Takeda base case estimates. Unit costs are as per the on-treatment phase.

Table 29: Resource use associated with off-treatment

Category	Item	Frequency per month	% of patient requiring resource	Cost per month
Tests and procedures				
	Biochemistry/Full blood test	1.50	100%	2,998.00 kr.
	CT scan	0.75	100%	1,016.00 kr.
	MRI	0.50	80%	276.80 kr.
	X-ray	0.50	60%	112.05 kr.

Abbreviations: CT, computerised tomography; ECG, electro-cardiogram; GP, general practitioner; MRI, magnetic resonance imaging

5.2.3 CNS progression resource use and costs

Additional resource use is applied for patients in the CNS progression health state to reflect the resource intensive nature of this site of progression. The management of CNS metastases is based on Takeda base case assumptions – the final distribution of therapy includes steroids (10%), stereotactic radiotherapy (SRS) (50%), and whole brain radiotherapy (WBRT) (5%).

Table 30 presents the additional resource use and associated unit costs for CNS management. It is assumed that there is a lifetime exposure limit for SRS and WBRT of six doses. The total cost of six doses of SRS, and WBRT are applied as a one-off cost for patients entering the CNS-progression health state. The cost of steroids is applied per cycle.

Table 30: Additional resource use for CNS management

Category	Proportion of patients	Lifetime exposure limit (dose)	Unit cost	Source
SRS	50%	6.00	747 kr.	30PR17
WBRT	5%	6.00	747 kr.	30PR17
Steroids (dexamethasone)	10%	NA	693.28 kr	Medicinpriser.dk

Abbreviations: CNS, central nervous system; SRS, stereotactic radiotherapy; WBRT, whole brain radiotherapy

5.3 Adverse event resource use and costs

Section 4.6 describes how adverse events were included in the economic model. Table 31 presents the costs applied to each adverse event - these were costed using the DRG2020 index.

Table 31: Adverse event costs

Adverse Events	Unit cost of adverse events	*Sources*
Blood creatinine phosphokinase increased	1,847.00 kr.	05MA08
Amylase increased	25,825.00 kr.	07MA14
Nausea	5,211.00 kr.	03MA02
Hypertension	14,514.00 kr.	05MA11
Increased AST	25,825.00 kr.	07MA14
Increased ALT	25,825.00 kr.	07MA14
Increased lipase level†	25,825.00 kr.	07MA14
Neutropenia	27,036.00 kr.	01MA04
Anaemia	4,732.00 kr.	16PR02
Diarrhoea	5,297.00 kr.	06MA11
Vomiting	5,211.00 kr.	06MA11
Gamma-glutamyl transferase increased	25,825.00 kr.	07MA14
Myalgia	1,796.00 kr.	08MA17
Fatigue	2,412.00 kr.	01PR02

Adverse Events	Unit cost of adverse events	*Sources*
Pneumonia	37,050.00 kr.	04MA13
Urinary tract infection	24,726.00 kr.	11MA07
Acute kidney injury	43,160.00 kr.	11MA01
Weight decreased	2,739.00 kr.	10MA07
Dizziness	5,211.00 kr.	03MA02
Dysgeusia	8,349.00 kr.	03SP07
Asthenia	2,412.00 kr.	01PR02

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase

5.4 Patient costs

The average time a patient spends at hospital per cycle, both pre-progression and post-progression are shown in the table below. Each visit is attributed transportation time to and from hospital and time at the clinic. The total time consumption is multiplied with the unit costs defined by the Medicine Council (66).

Transportation time is assumed to be 1 hour in total. According to the Medicine Council, patient transportation cost is estimated to be 100 kr. per hospital visit (includes the hospital visit itself) (66). The table below lists the indirect costs used within the model.

Table 32:: Patient costs both pre- and post-progression

Category	Item	Frequency per month	% of patient requiring resource	Cost per month
Physician visits	Oncology outpatient (s)	1.00	100%	179.00 kr.
	Transportaion time (hour)	1.00	100%	179.00 kr.
	Travel reimbursement	1.00	100%	100.00 kr.

6 Budget impact model

The BIM takes the perspective of the Danish regions, using a time horizon of 5-years. The BIM uses the calculations and costs from the cost-comparison model to estimate the incremental and cumulative budget impact. Therefore, changing key assumptions in the cost-comparison model, e.g. relative efficacy estimates, will impact the BIM results. The BIM provides two options: (1) include only price of frontline treatment regimess and (2) include all relevant hospital costs. In the base case, option (2) i.e. all relevant hospital costs are considered.

6.1 Population

Population input assumptions are based on data from the Danish Lung Cancer Group and Danish Lung Cancer Register. As described in the epidemiology section of this report, ALK-positive NSCLC is characterized by ALK translocations in the tumor tissue. ALK translocations occur rearly with a frequency of less than 1% of all newly diagnosed lung cancer cases. In 2016, the frequency was 0.8% corresponding to 36 patients; in 2017, the frequency was 0.9% corresponding to 43 patients; and in 2018 the frequency was 0.6% equivalent to 30 patients. For this report, it is estimated that 35 patients are eligible for first-line treatment with an ALK inhibitor across Denmark (7,8). A population growth factor (0.0218%) is applied each year in the BIM based on estimates from the Office of National Statistics (67).

6.2 Market share

Table 33 presents the market share inputs for the setting without brigatinib, while

Table 34 presents the market share inputs for the setting where brigatinib is introduced to the market. It is assumed that in the scenario where brigatinib is introduced to the market, the usage of brigatinib will increase with 10 percentage points per year until the market is split 50-50% between alectinib and brigatinib.

Table 33: Market share inputs in setting without brigatinib

	Year 1	Year 2	Year 3	Year 4	Year 5
Brigatinib	0%	0%	0%	0%	0%
Alectinib	100%	100%	100%	100%	100%

Table 34: Market share inputs in setting with brigatinib

	Year 1	Year 2	Year 3	Year 4	Year 5
Brigatinib	15%	35%	45%	50%	50%
Alectinib	85%	65%	55%	50%	50%

7 Results

7.1 Cost analysis base case results

The base case results for brigatinib compared alectinib are shown in Table 35. These results are based on Danish list prices for all treatments, a lifetime horizon (i.e. 30-year time horizon) and 4% annual discount rate applied to costs.

The results for brigatinib vs. alectinib are based on a cost-comparison framework in the base case. Therefore, the incremental life years are zero i.e. there is no difference between the efficacy outcomes accrued through these frontline options. In the base case, alectinib is shown to cost [redacted] more than brigatinib based on list prices. Section 7.1.3 presents the disaggregated costs driving this result.

Table 35: Base case results

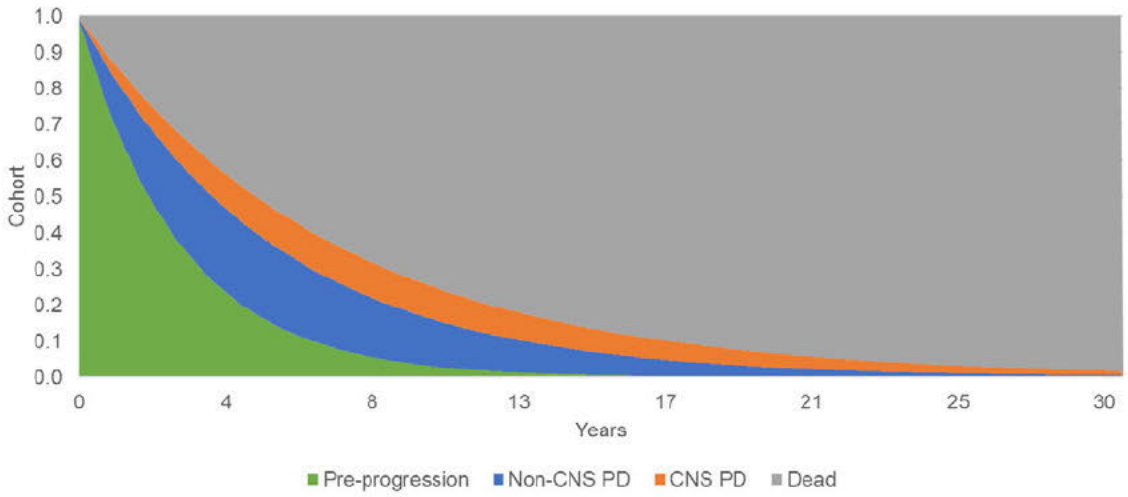
Intervention	Total Costs	Total Life Years	Inc Costs
Brigatinib	[redacted]		
Alectinib			

Abbreviations: Inc, incremental

7.1.1 Clinical outcomes

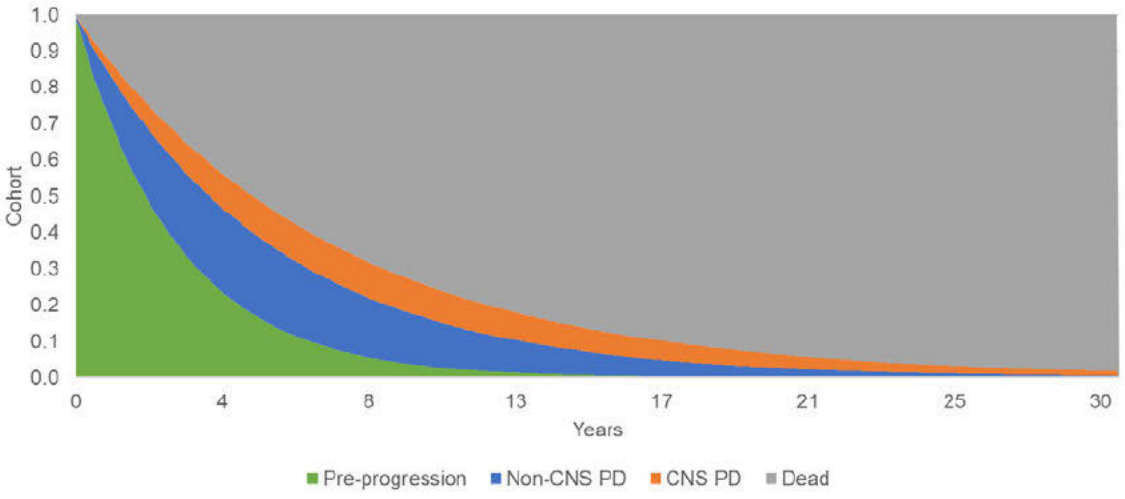
Figure 34 and Figure 35, show the Markov traces for brigatinib and alectinib, respectively.

Figure 34: Markov trace for brigatinib



Abbreviations: CNS, central nervous system; PD, progressive disease

Figure 35: Markov trace for alectinib



Abbreviations: CNS, central nervous system; PD, progressive disease

7.1.2 Disaggregated life years

Table 36 presents the disaggregated discounted life years. For the comparison of brigatinib vs. alectinib, it is shown that all the life years are equivalent across all health states – as would be expected under the base case cost-comparison.

Table 36: Disaggregated life years

Intervention	Pre-progression	Non-CNS Post-progression	CNS Post-progression
Brigatinib	[redacted]		
Alectinib			

Abbreviations: CNS, central nervous system

7.1.3 Disaggregated costs

Table 37 presents the disaggregated discounted costs for pre-progression and progressed disease. Table 38 presents a further breakdown based on treatment, concomitant medications, resource use including patient cost, subsequent therapy, and adverse events.

In the comparison of brigatinib vs. alectinib, brigatinib is shown to accrue fewer costs in the pre-progression health state (driven by the lower cycle cost of brigatinib based on list prices). All other costs are equal between brigatinib and alectinib, which is reflective of the cost-comparison structure and assumptions of similarity between the two treatments. Importantly in a cost-comparison framework, the comparison can be refined down to the cost per treatment cycle.

Table 37: Disaggregated discounted health state costs

Intervention	Pre-Progression	Progressed disease (includes non-CNS and CNS progression)
Brigatinib	[redacted]	

Alectinib	[redacted]

Table 38: Disaggregated discounted costs

Intervention	Brigatinib	Alectinib
Direct hospital cost (frontline medication costs)	[redacted]	
Patient costs (Concomitant medications)		
Resource use on treatment (hospital)		
Patient time on treatment (patient)		
Transportaion time on treatment (patient)		
Resource use off treatment (hospital)		
Patient time off treatment (patient)		
Transportaion time off treatment (patient)		
Ressource use CNS (hospital)		
Subsequent therapy (hospital)		
Adverse events (hospital)		
Total		

7.2 Cost analysis - sensitivity analyses

7.2.1 One-way sensitivity analysis

One-way sensitivity analyses were performed to evaluate the sensitivity of the model results to individual inputs, holding all else constant. Distributional information associated with each parameter is presented in the 'Parameters' sheet of the model. Model results were recorded after changing each input to its upper and lower bound value in turn. Tornado diagrams are generated for the cost analysis. Due to the correlation between coefficients associated with parametric curve choices, these were not varied within the one-way sensitivity analysis.

Table 39 presents a tornado diagram with the six most influential parameters driving results for the brigatinib vs. alectinib comparison, shown in descending order of cost sensitivity. All six parameters have been varied by 30% of the mean to best illustrate how they each impact the result. The imperative for selecting the specific parameters was to define the uncertainty in the model prediction and to show how much of the output variance is controlled by each parameter. Limited information about second-line treatment and concomitant treatment has been possible to obtain and it is therefore

valued important to illustrate how these inputs might impact the model. Costs of adverse events have been selected on the basis that AEs often are viewed as a driver for hospital costs. However, this analysis shows a relatively small impact even by varying the input by 30%,

Table 40 displays this information in a tabular format. The cost of subsequent therapies in both the brigatinib and alectinib treatment arms is the key driver of differences in costs. Based on current clinical practice, there is no rationale as to why the receipt of subsequent therapies would differ based on frontline treatment with brigatinib or alectinib.

Abbreviations: CNS, central nervous system; EQ-5D-3L, EuroQol 5-dimensions 3-levels; PD, progressive disease

Table 40: Numerical results of one-way sensitivity analysis - brigatinib vs. crizotinib

Parameter	Lower Bound	Upper Bound	Difference
Subsequent therapy - Alectinib			
Subsequent therapy - Brigatinib			
Concomitant medications_Base cost - Brigatinib			
Concomitant medications_Relative costs - Alectinib			
Costs of adverse events_Brigatinib cycle cost			
Costs of adverse events_Alectinib cycle cost			

7.3 Budget impact base case results

7.3.1 Population

Table 41 presents the total number of patients receiving each of the relevant frontline treatments in the setting without brigatinib based on the population and market share assumptions outlines in Section 6.1 and Section 6.2, respectively. Table 42 then presents these patient numbers for the setting with brigatinib. Based on the market share assumptions, brigatinib is shown to displace alectinib use until the patients are evenly distributed between the treatments.

Table 41: Patient distribution in the frontline setting without brigatinib

	Year 1	Year 2	Year 3	Year 4	Year 5
Brigatinib	0	0	0	0	0
Alectinib	35	35	35	35	35
Total patients	35	35	35	35	35

Table 42: Patient distribution in the frontline setting with brigatinib

	Year 1	Year 2	Year 3	Year 4	Year 5
Brigatinib	5	12	16	18	18
Alectinib	30	23	19	18	18
Total patients	35	35	35	35	35

7.3.2 Budget impact

Table 43 presents the incremental budget impact comparing the frontline setting without brigatinib vs. the frontline setting with brigatinib. The introduction of brigatinib is shown to accrue savings after the first year based on Danish list prices – this is because the list price of brigatinib is lower relatively to alectinib. changing the market share assumptions to reflect brigatinib taking over alectinib market share will also result in a budget saving. Table 44 shows the cumulative budget impact.

Table 43: Incremental budget impact results

	Year 1	Year 2	Year 3	Year 4	Year 5
Total cost of pathway with brigatinib	[redacted]				
Total cost of pathway without brigatinib					
Difference					

Table 44: Cumulative budget impact results

	Year 1	Year 2	Year 3	Year 4	Year 5
Total cost of pathway with brigatinib	[redacted]				
Total cost of pathway without brigatinib					
Difference					

As all evidence used for the budget impact calculation is derived from the cost-model, limitations associated with the economic model remain apparent in the budget impact estimates. However, as the budget impact time horizon is limited to 5-years there is less uncertainty associated with long-term extrapolation encompassed within these results. Finally, the eligible patient numbers used in the budget impact analysis are subject to uncertainty due to the changing treatment environment for patients with ALK+ advanced NSCLC.

7.4 Scenario analysis

Table 45 below illustrates all the different possibilities for changing parameters and where it can be changed in the model sheets. The parameters are influential for both the cost analysis and the BIM.

Table 45: Options for the scenario analysis

Parameter	Options	Location in the model
Population	ITT Treatment naïve 1 prior chemotherapy	Model controls sheet
Parametric model fits for OS	Weibull Gompertz Log-logistic Log-normal Gamma Gen. Gamma Exponential	Model controls sheet
Parametric model fits for PFS BIRC	Weibull Gompertz Log-logistic Log-normal Gamma Gen. Gamma Exponential	Model controls sheet
Parametric model fits for PFS INV	Weibull Gompertz Log-logistic	Model controls sheet

	Log-normal Gamma Gen. Gamma Exponential	
Parametric model fits for CNS-PFS	Weibull Gompertz Log-logistic Log-normal Gamma Gen. Gamma Exponential	Model controls sheet
Treatment switching adjustments	No switching adjustment Adjusted for official switchers, no re-censoring Adjusted for official switchers, re-censoring	Model controls sheet
Approach to match CNS-PFS and PFS data	PFS adjusted to CNS-PFS Unadjusted CNS-PFS adjusted to PFS	Model controls sheet
Time on treatment	Treat until progression Treat one cycle post-progression Treat two cycles post-progression Treat three cycles post-progression	Model controls sheet
Relative dose intensity	Apply relative dose intensity (RDI) Not apply relative dose intensity (RDI)	Cost sheet
Source of subsequent therapy	Source from ALTA-1L and relevant clinical trials User defined	Model controls sheet
Discount rate used in the model	Selection by typing	Model controls sheet
Time horizon	Selection by typing	Model controls sheet

Table 46 below shows two different scenarios created by changing the parameters in the table above. The first scenario aims to create as little difference between the costs of the treatment arms as possible.

In the scenario, time on treatment has been changed from “threat three cycles pros-progression” to “treat until progression”. Further, instead of not including relative dose intensity, the scenario includes relative dose intensity.

The second scenario aims to widen the gap in costs between the two treatment arms the most. The parameter from the table above that increases the incremental cost between the treatment arms the most, is the source of subsequent therapy. By selecting the clinical trial data instead of the user-defined, the incremental cost increases.

The outcome is presented both from the perspective of the cost analysis and the BIM.

Table 46: scenario analysis

	Changed parameters	Result of the incremental cost analysis	Result of the cumulative BIM
Base case	[redacted]		
Scenario 1			
Scenario 2			

8 Conclusion

This report outlines the cost-comparison (brigatinib vs. alectinib) and BIM of implementing brigatinib to the market. the cost analysis and BIM highlights the potential for brigatinib to be cost-saving when compared the alectinib, whilst delivering similar efficacy. The BIM indicates that the addition of brigatinib into the market will offset costs in the mid to long term – market share assumptions indicate brigatinib will shift market share away from alectinib.

The base case cost analysis shows the life time cost per patient treated with brigatinib to be [redacted] kr., while the life time cost per patient treated with alectinib is [redacted] kr. The incremental difference between the two treatments accumulates to [redacted]

The cumulative budget impact analysis shows a total sum of [redacted] kr. for the scenario where brigatinib treatment is approved as first line treatment, while in the scenario where brigatinib is not approved, treatment accumulates to [redacted] kr. The total difference between the treatments are shown to be [redacted] kr. over a 5-year period.

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10 Appendices

Table 47: Chemotherapy costs breakdown

Regimen	Dosing	Drug	Days in cycle	Number of cycles	mg/capsule/vial	Units	Cost/pack	Cost/chemo cycle	Cost/model cycle	Source
IV pemetrexed + cisplatin	Pemetrexed 500mg/m2 + cisplatin 75mg/m2 every 3-weeks for a maximum of six cycles (PROFILE-1014) or four cycles (ASCEND-4)	Pemetrexed 100mg powder for soln for inf in vial	21	4 or 6	100	1	2,168.47 kr.	19,516.23 kr.	14,637.17 kr.	*https://medicinpriser.dk/Default.aspx?id=15&vnr=120062*
		Pemetrexed 500mg powder for soln for inf in vial	21		500	1	9,035.31 kr.	18,070.62 kr.	13,552.97 kr.	*https://medicinpriser.dk/Default.aspx?id=15&vnr=019797*
		Cisplatin 1mg/ml conc for soln for inf in vial, 50ml	21		50	1	100.00 kr.	300.00 kr.	225.00 kr.	*https://medicinpriser.dk/Default.aspx?id=15&vnr=598049*
IV pemetrexed + carboplatin	Pemetrexed 500mg/m2 + carboplatin (area under the concentration-time curve of 5 to 6 mg	Pemetrexed 100mg powder for soln for inf in vial	21	4 or 6	100	1	2,168.47 kr.	19,516.23 kr.	14,637.17 kr.	*https://medicinpriser.dk/Default.aspx?id=15&vnr=120062*
		Pemetrexed 500mg powder	21		500	1	9,035.31 kr.	18,070.62 kr.	13,552.97 kr.	*https://medicinpriser.dk/Default.aspx?id=15&vnr=019797*

Regimen	Dosing	Drug	Days in cycle	Number of cycles	mg/capsule/vial	Units	Cost/pack	Cost/chemo cycle	Cost/model cycle	Source
	mL/min) every 3-weeks for a maximum of six cycles (PROFILE-1014) or four cycles (ASCEND-4)	for soln for inf in								
		Carboplatin 600mg/60ml solution for infusion vials	21		50	1	203.00 kr.	203.00 kr.	152.25 kr.	*https://medicinpriser.dk/Default.aspx?id=15&vnr=439635*
Pemetrexed monotherapy	Pemetrexed 500mg/m2 every 3-weeks until disease progression	Pemetrexed 100mg powder for soln for inf in vial	21	9	100	1	2,168.47 kr.	19,516.23 kr.	14,637.17 kr.	*https://medicinpriser.dk/Default.aspx?id=15&vnr=120062*
		Pemetrexed 500mg powder for soln for inf in	21		500	1	9,035.31 kr.	18,070.62 kr.	13,552.97 kr.	*https://medicinpriser.dk/Default.aspx?id=15&vnr=019797*
Pemetrexed maintenance	Pemetrexed 500mg/m2 every 3-weeks	Pemetrexed 100mg powder for soln for inf in vial	21	9	100	1	2,168.47 kr.	19,516.23 kr.	14,637.17 kr.	*https://medicinpriser.dk/Default.aspx?id=15&vnr=120062*

Regimen	Dosing	Drug	Days in cycle	Number of cycles	mg/capsule/vial	Units	Cost/pack	Cost/chemo cycle	Cost/model cycle	Source
	until disease progression	Pemetrexed 500mg powder for soln for inf in	21		500	1	9,035.31 kr.	18,070.62 kr.	13,552.97 kr.	*https://medicinpriser.dk/Default.aspx?id=15&vnr=019797*
Docetaxel	Docetaxel 75mg/m2 every 3-weeks until disease progression	Docetaxel 160mg/8ml solution for infusion vials (20mg/ml)	21	2	20	1	309.00 kr.	309.00 kr.	231.75 kr.	*https://medicinpriser.dk/Default.aspx?id=15&vnr=571704*

10.1.1 Treatment switching adjustments to overall survival

For ethical reasons, treatment switching was permitted in ALTA-1L. The RCT study statistical analysis plan made provision for the "official" crossover from crizotinib to brigatinib following disease progression – 61 such patients being identified in the SAS ADaM files with additional/ new overall survival estimates variables based on time from crossover. Additional or "extra" patients not included in this "official" crossover were identified on inspection of the concomitant medicines taken during the trial and subsequent therapy. This identified an additional 12 patients switching from crizotinib to brigatinib and 11 patients randomised to brigatinib who switched to crizotinib.

The impact of subsequent brigatinib in the crizotinib arm also impacts the indirect comparisons with alectinib, when an anchored approach is used i.e. a network meta-analysis (NMA) or anchored matched adjusted indirect comparison (MAIC). These approaches link brigatinib to alectinib through the crizotinib arms in the ALTA-1L and ALEX trials, respectively. The ALEX clinical trial did not allow treatment switching. Therefore, their crizotinib arm has fewer ALK inhibitiors received as a subsequent therapy than the crizotinib arm in the ALTA-1L trial. This results in a worse OS profile from the crizotinib arm in the ALEX study compared with the crizotinib arm in the ALTA-1L study – which is evident when you Naïvely compare the Kaplan-Meiers. Therefore, where anchored indirect methods are used to obtain a relative efficacy estimate between brigatinib and alectinib, it is of interest to explore removing the bias associated with subsequent brigatinib in the crizotinib arm of the ALTA-1L trial. Furthermore, unanchored MAICs have also been explored, which remove the 'noise' associated with treatment switching adjustments and compares brigatinib and alectinib using the data from ALTA-1L and ALEX as if these treatment arms were single arm trials i.e. ignores the problematic crizotinib link.

Naïve ways of attempting to adjust for treatment switching such as omitting such patients altogether or attributing a censoring at the time of switching will lead to biases. Omitting such patients leads to bias because the fact that they switched indicates their future survival probability trajectory, at the moment before switching, is almost certainly going to be different (worse) than the remaining patients on the same initial treatment. This follows from the recognition that the likely cause of switch is progression. Censoring is similarly inappropriate – its implementation in a survival algorithm switches how that patient is analysed (survival probability replacing the density function in the log likelihood) in such a way that it was as if the censoring never occurred – again failing to recognise a fundamental change. Fundamentally, these simple methods do not address the differences in patient and disease characteristics relevant to the switchers which are often prognostic or treatment effect modifying. Therefore, differences in outcomes would be expected had these switchers not switched.

The following methods were candidates for the treatment switching analysis: Inverse Probability of Censoring Weights (IPCW), Rank Preserving Structural Failure Time Models (RPSFTM), Two Stage Method (following progression), and Iterative Parameter Estimation (IPE) approach.

Two of these four methods, IPCW and IPE, were not pursued from the outset for the purposes of economic modelling. The IPCW method censors switchers at the point of switch and remaining observations are weighted with the aim of removing any censoring-related selection bias. It requires the "no unmeasured confounders" assumption – that is, data must be available on baseline and time-dependent variables that predict both treatment-switching and prognosis. This assumption will never hold exactly but realistic estimates can result if the main influencing variables are modelled correctly. The method often results with very high weights attached to a few patients unless sample sizes are in the many thousand, making results unstable (these few patients dominate the results) and often it is difficult or impossible to access pertinent time varying prognostic data necessary for the algorithm. The IPE approach is very similar to RPSFTM in theoretical terms and the two approaches most often produce very similar adjusted results. The IPE approach requires a parametric survival model unlike RPSFTM. Hence, RPSFTM is preferred to it – very difficult to establish whether the parametric model form used in IPE is appropriate.

The two-stage method was examined carefully against ALTA-1L data to ensure it could be implemented. The method is appropriate when switching only occurs (and very soon after) progression (or some other factor which is clearly identifiable and can be matched). It utilises an acceleration factor, ACF parametric regression model comparing within a randomisation arm those that switch to those that do not. The calculated ACF coefficient is used to adjust survival times post progression (ACF is explained in more detail below as regards to RPSFTM). Further, the ACF schemes can be found in appendix 10.1.6. Pertinent explanatory variables need to be adjusted for, which is often possible as other readings are often taken when progression is diagnosed. Assuming progression is the only reason for treatment switching, the three assumptions underlying the technique are no unmeasured confounders at progression, no time dependent confounding between the time of disease progression and the time of treatment, and finally the parametric model chosen is appropriate.

RPSFTM was implemented to perform treatment switch adjustments. This method assumes that the only difference between randomised groups is the treatment received and there is a 'common treatment effect'. The first assumption should be satisfied by trial randomisation. The common treatment effect assumption states that the (relative) treatment effect is the same for all participants (with respect to time spent on treatment) regardless of when treatment is received. The RPSFTM estimates a parameter ψ (Greek symbol psi) where $\exp(-\psi)$ is the ACF. Multiplying the survival time under

crizotinib by the ACF gives the expected survival time under brigatinib (i.e. ACF > 1 implies brigatinib superior to crizotinib). The method uses this ACF value to adjust the raw survival times to show what would have happened (assuming model is correct) if the patients had remained on their randomised treatment. Updated Cox regressions can then be run on this "adjusted data" to produce new hazard ratios. Appropriate covariates mimicking the official ALTA-1L SAP were used in both the RPSFTM and Coz regressions – binary variables of prior chemotherapy and baseline presence of CNS-metastases were included in the ALKi naïve modelling (treatment naïve omitting prior chemotherapy).

One complication with RPSFTM (also relevant to two stage method) relates to censoring problems – the readings are taken before everyone's death time is known. With a common censoring time-point, this affects the treatments unequally (unless equally efficacious) distorting comparisons. Re-censoring mechanisms have been proposed to account for these distortions but they themselves can cause biases. A recommendation is to run such models twice, once incorporating these mechanisms and once without – this advice has been followed.

An additional complication relates to how to account for the uncertainty related with the RPSFTM method itself – simply inserting the RPSFTM updated survival times and running analysis on them as if they were the true values takes no account of the fact that extra uncertainty has been introduced. A way to handle this extra uncertainty is to estimate it within a non-parametric bootstrapping procedure: in each bootstrap sample, the full procedure is replicated – conducting the RPSFTM to calculate psi, adjusting the patient survival data accordingly and then running a cox model on the new data and storing the (log) hazard ratio and psi values. This bootstrapped method was pursued. Two separate methods of generating confidence intervals were calculated from it to check for consistency/agreement. These two methods are known as "norm" and "basic" within R function "boot.ci" and both apply bias correction with the "norm" producing symmetric intervals around the unbiased estimate whilst the basic allows for non-symmetrical.

For the purpose to create a comparison of brigatinib versus alectinib the adjustment should seek to produce an outcome with characteristics similar to the ALEX trial. The following scheme is therefore thought most appropriate in this instance where in ALEX no official switching was approved/sanctioned but obviously did occur via concomitant medications/subsequent therapy records:

> Attempt to adjust for only the "officially" recognised ALTA-1L treatment switches. In the treatment switching algorithm that calculates the necessary adjustment to survival estimates for this sub-group, the data made available to perform such calculations should exclude all other additionally identified switched patients. This ensures such "extra" switched patients do not

form part of the “unswitched” group inputted into the RPSFTM algorithm. Once the survival adjustments are made according to RPSFTM principles, the excluded extra switched data is merged unaltered back with it to restore the full sample size.

The scheme just outlined leaves unaltered all “extra” switched data, as occurred in ALEX modelling, whilst adjusting appropriately for the official switches that were not sanctioned under the ALEX protocol.

Such a scheme was appropriately incorporated into the bootstrapping algorithm – stratified bootstrapping was implemented which recognised this “extra” switch group and could mimic the behaviour above within each bootstrapped sample. The same scheme was adopted in the “standard” non-bootstrapped approach for this scenario.

The standard, non-bootstrapped confidence intervals are important to compare against the bootstrapped: In theory, to account for all uncertainty in brigatinib *vs.* alectinib the bootstrapping algorithm should have been extended to incorporate the anchored MAIC algorithm within it. However, it was computationally too demanding to do this (many hours needed to run existing algorithms which excluded it). Therefore, the results from the anchored MAIC algorithm were based on the deterministic individual patient treatment switch survival estimate adjustments provided by the RPSFTM algorithm, when in fact they should incorporate the uncertainty in these deterministic estimates. Hence the confidence intervals around anchored MAIC hazard ratio estimates are likely to be too narrow in brigatinib *vs.* alectinib OS contrasts. Visually comparing the difference in width of the confidence intervals between “standard” and bootstrapped versions of hazard ratios in brigatinib *vs.* crizotinib contrasts provides some guide as to the extent of this under-representation.

10.1.2 Anchored Matching-Adjusted Indirect Treatment Comparison brigatinib against alectinib

An anchored MAIC was conducted between ALEX and ALTA-1L with bCNS-m as the only (treatment effect) variable required to be controlled for. To adjust for the imbalance in baseline CNS metastases, which was identified as a treatment effect modifier, an anchored MAIC was conducted.

A simulated treatment comparison (STC) approach offered no benefits over the MAIC approach and was not deemed suitable, unlike the MAIC approach, for the unanchored indirect comparisons. This is pertinent since anchored methods (MAIC or STC) could not be expected to provide unbiased estimates for OS because of treatment switching inter-trial discrepancies whilst unanchored methods are in

theory not affected by it. Thus, it is desirable to run unanchored methods in addition to anchored for which MAIC methods are thus much preferred over STC.

The underlying causal modelling process underpinning MAICs aims to produce balance between treatment arms/comparisons in terms of factors that could affect the outcome studied. With such imbalances removed, comparisons can be made by contrast comparisons.

A MAIC approach involves utilising individual patient data (IPD) from the index study (ALTA-1L) and the reported aggregate level data on baseline characteristics from the comparator study (ALEX) that need to be controlled for. The index study IPD is then reweighted in order to counter imbalances arising from varying study populations that need to be matched/controlled for (bCNS-m only in this anchored instance). The weights are estimated using a method of moments approach that is reported in the NICE Decision Support Unit (DSU) Technical Support Document (TSD) 18,[17] which is equivalent to minimising the objective function:

$$\sum_{i,t} \exp(\boldsymbol{\alpha}_1^T \mathbf{X}_{it}^{EM}) \quad \text{when } \bar{\mathbf{X}}_{(AC)}^{EM} = 0.$$

After applying the weights, the (reweighted) means of the index study matched that (very close to) the unweighted means recorded in the compactor study for the variables matched on. The weights from the MAIC analysis may also be used in the estimation of the MAIC-OR using logistic regression for objective/overall response rates.

The actual MAIC scheme implemented involved two separate matchings on bCNS-m proportions: brigatinib ALTA-1L was matched to ALEX alectinib, and ALTA-1L crizotinib was matched to ALEX crizotinib. This was done so as not to be accused of favouring brigatinib over alectinib. The ALEX trial, although randomised, resulted in a small imbalance between arms on bCNS-m which was in crizotinib's favour (smaller at 38% compared to 42%).

For the survival endpoints, a Cox regression was run between the MAIC weighted crizotinib and brigatinib ALTA-1L arms. The log hazard ratio together with a "robust/sandwich" variance estimate was extracted, and Bucher technique applied to produce the brigatinib versus alectinib contrast. For the non-survival (binary) ORR endpoint a similar procedure was followed replacing Cox regressions and log hazard ratios with Logistic regression and log odds ratios, respectively.

One uncertainty with the approach adopted was whether the two separately calculated MAIC weights for brigatinib and crizotinib should both be reweighted to equal their respective original sample sizes

(thus preserving the relative weights of the two arms) – no published advice could be found. Sensitivity analysis showed it made no practical difference (same estimates to four decimals). All results presented therefore do not implement such reweighting.

Effective sample size (ESS) was calculated following reweighting, and validity checks performed: confirming the MAIC had resulted in parity on bCNS-m at ALEX levels on the weighted ALTA-1L data.

"Unweighted Bucher" analysis is where no adjustment for imbalances on bCNS-m between the two trials was implemented. This was achieved by replacing the weights calculated by the MAIC algorithm by the value 1 in every instance, then proceeding in the same manner. This simplifies to the Bucher technique hence the label.

10.1.3 Unanchored Matching-Adjusted Indirect Treatment Comparisons

Relative efficacy estimates for brigatinib vs. alectinib were estimated through unanchored MAICs. These methods were explored for brigatinib *vs.* alectinib despite the link between the ALTA-1L and ALEX clinical trials with the crizotinib arm, to explore an analysis which avoided the complications associated with the crizotinib arm i.e. imbalances in bCNS-m (which was identified as a treatment effect modifier) and treatment switching.

The unanchored MAIC approach used age, ever-smoked, Asian, bCNS-m, ECOG score 2, and whether patients had one previous chemotherapy (latter in AN population only) as the prognostic variables to be matched. This agreed with the list used in the brigatinib 2L NICE HTA submission and validated at the January 2020 advisory board.

In order to generate a MAIC adjusted proportional hazard ratio for survival endpoints, it was necessary to create artificial/pseudo IPD survival data for the non brigatinib arms for which Takeda do not have access to IPD. This was done by digitising (Engauge Digitizer 10.2 software) published KM curves for OS, BIRC PFS and INV PFS from relevant alectinib and crizotinib publications which were then utilised in an algorithm developed by Guyot *et al.* (2012)(68). KM curves created from these artificial data were plotted against curves plotting the raw digitised survival probability-time points, as well as visual comparisons against the published KM curves. Both together acting as validation of the technique.

For survival endpoints, a weighted Cox regression was applied to a dataset combining this artificial alectinib IPD to the brigatinib arm of ALTA-1L which included the unanchored MAIC weights (for alectinib, weights of constant 1 were assigned). Robust variance estimates being calculated for the resultant log HR. For ORR, a similar process to the above was followed with "Logistic" and "Log OR" replacing

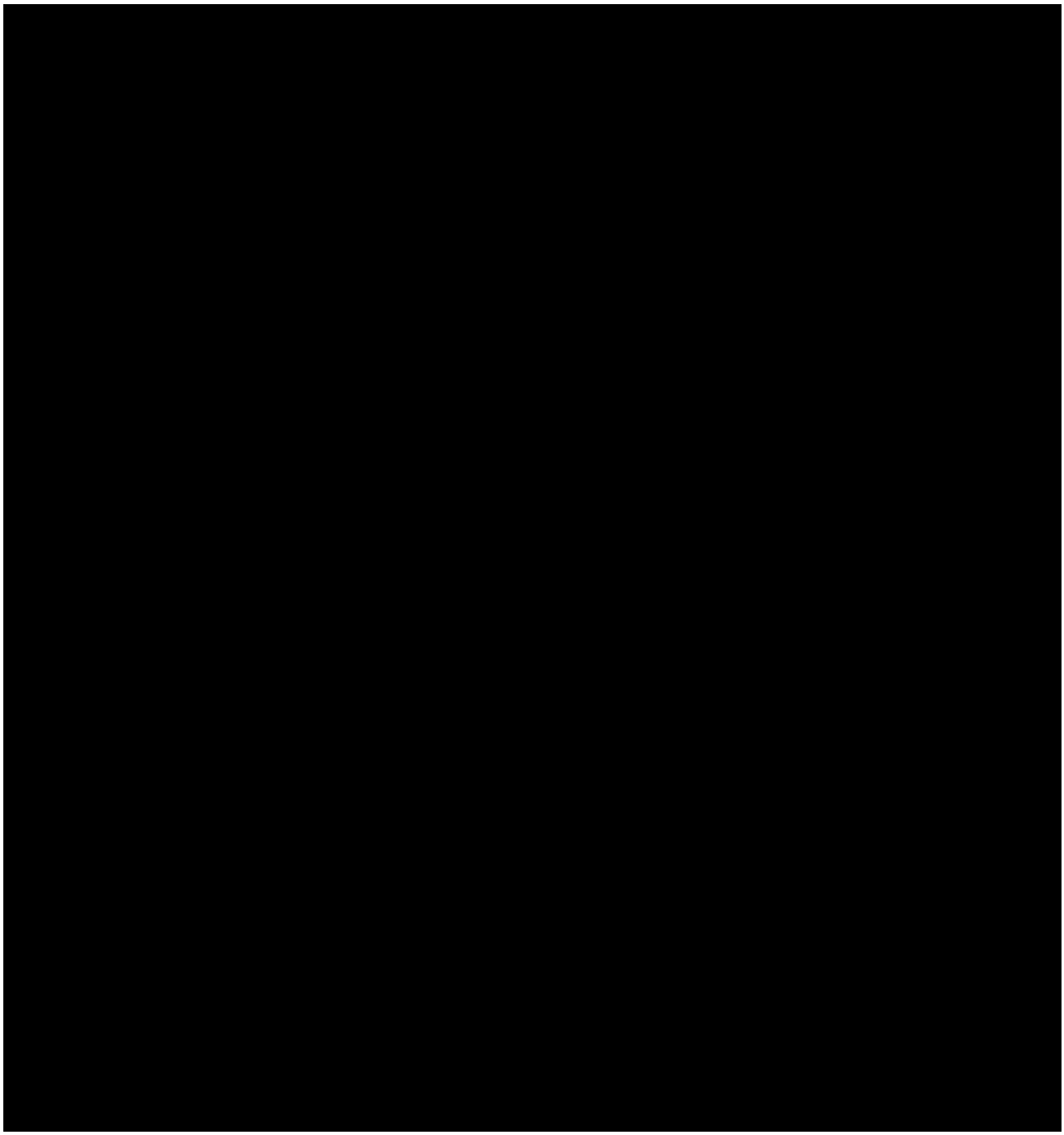
"Cox" and "Log HR", respectively.

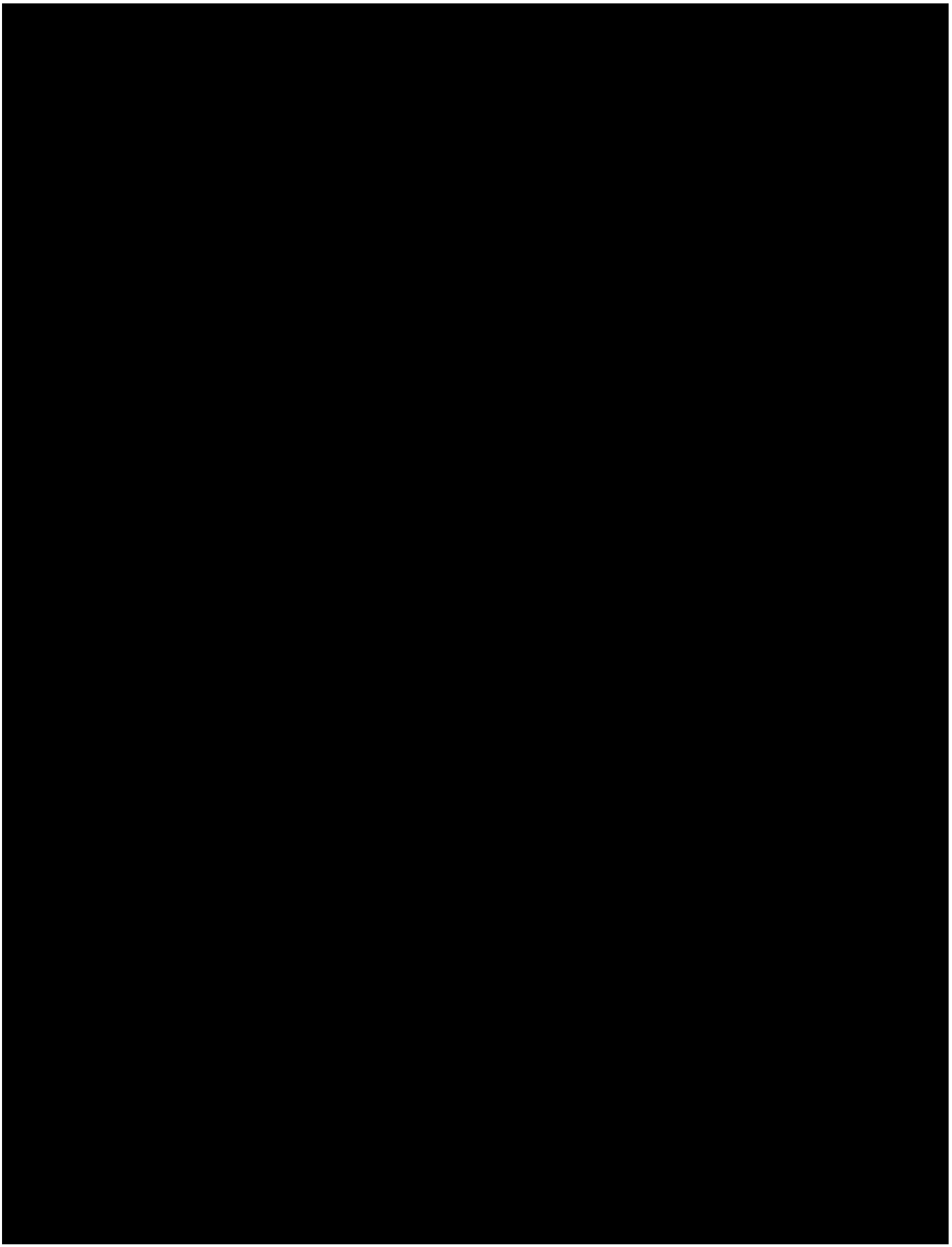
Similar MAIC validity checks and "unadjusted" analyses as detailed in the anchored comparison to alectinib were also implemented.

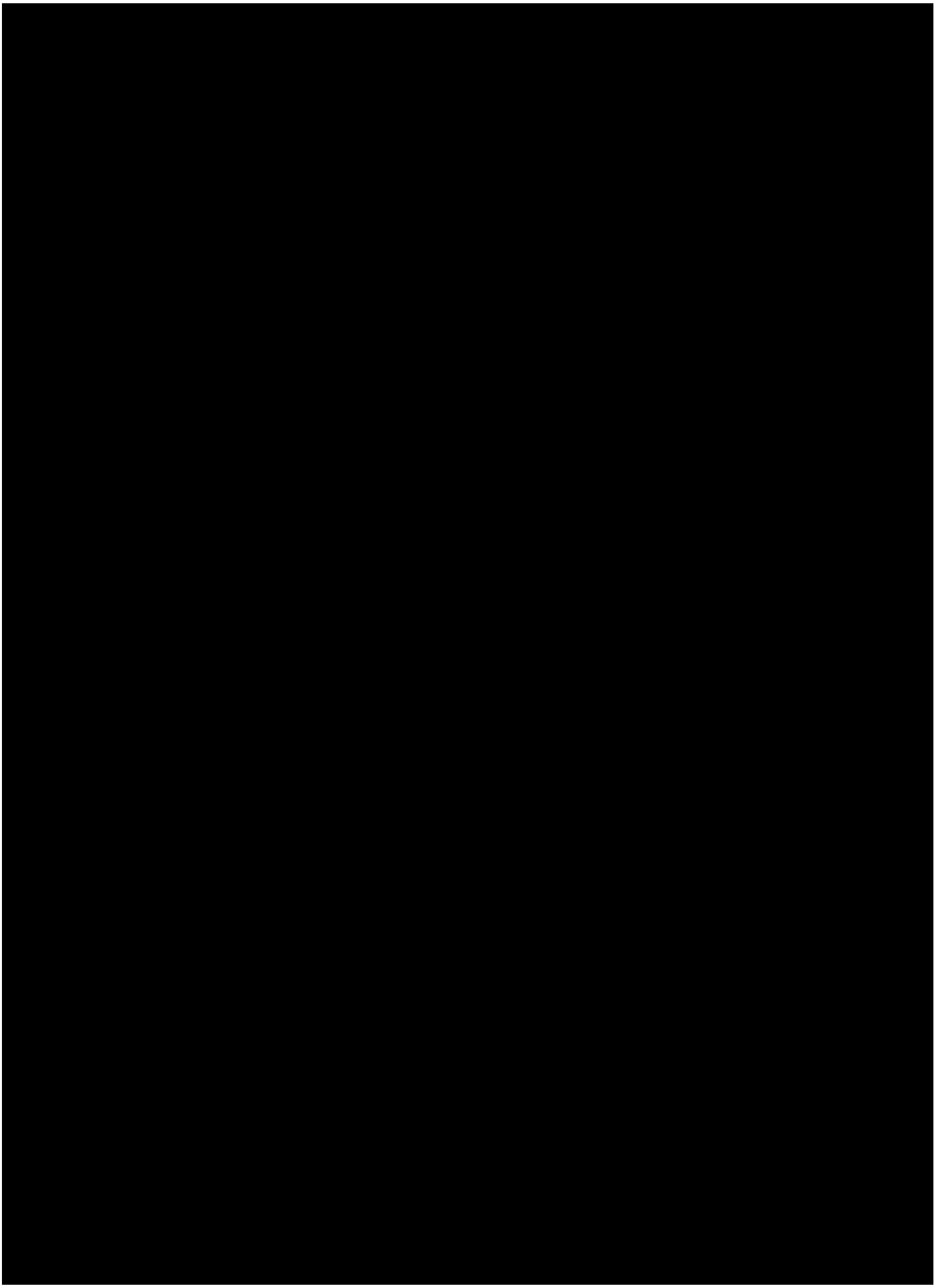
STC was not a viable alternative to an unanchored MAIC. In survival analysis it is the number of events not the number of patients that determines the effective sample size/degrees of freedom in any type of parametric or semi parametric regression type analysis. The lower this figure the lower the number of predictors that can be included in the model. There are not enough events to be able to pursue STC where all prognostic in addition to treatment modifying variables must be accounted for (particularly for OS). The underlying causal modelling process underpinning MAICs to provide an unbiased comparison between two treatments is completely different to that of STCs. To provide an unbiased comparison, it is not necessary to model the actual outcome endpoint equation itself. As previously stated, the aim is to balance the arms so that they match each other on all, measurable and collected, factors that could impact on the relevant endpoint. To achieve this balance, unanchored MAICs follow a process which is akin to running a logistic regression where the endpoint modelled is treatment. Crucially though, now that endpoint is not of the survival type, the degrees of freedom is much closer to number of patients when the analysis commences. This is a huge advantage over STC.

10.1.4 Covariate Balance and Weight Checks in Brigatinib Anchored MAIC to Alectinib

As there was only one binary variable to be matched in the two MAICs, histograms are not needed (only two unique weight values possible in each MAIC) – comparing ESS to N is enough. All ESS values very close to N. With the exception of investigator unconfirmed duration of response, the balance results for the remaining endpoints with no missing values are identical for each endpoint within a stated population. Not shown, to save unnecessary repetition, are the balance tables for all the treatment switch adjusted OS MAICs – these are identical to the OS tables (for the pertinent stated population) given below.





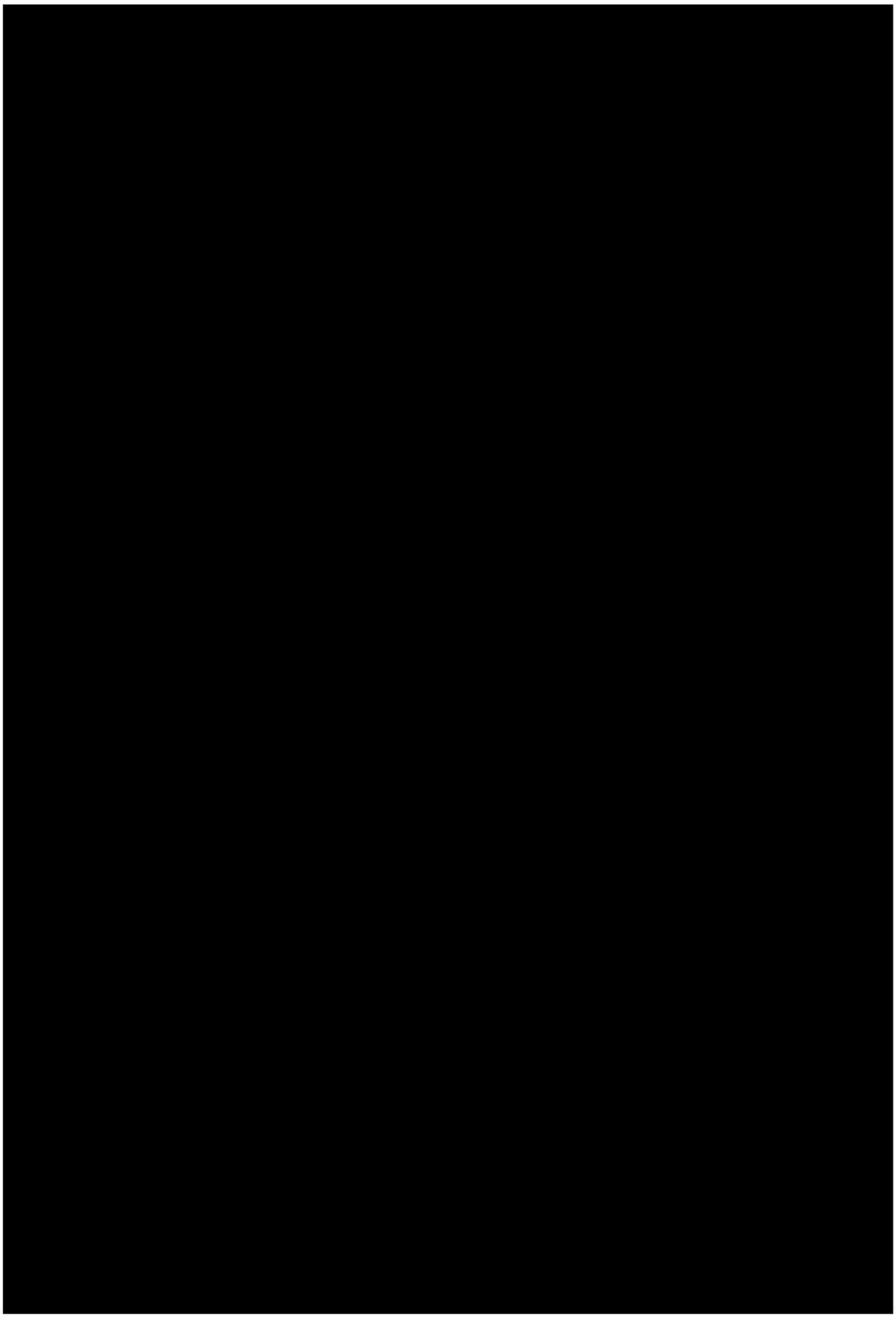


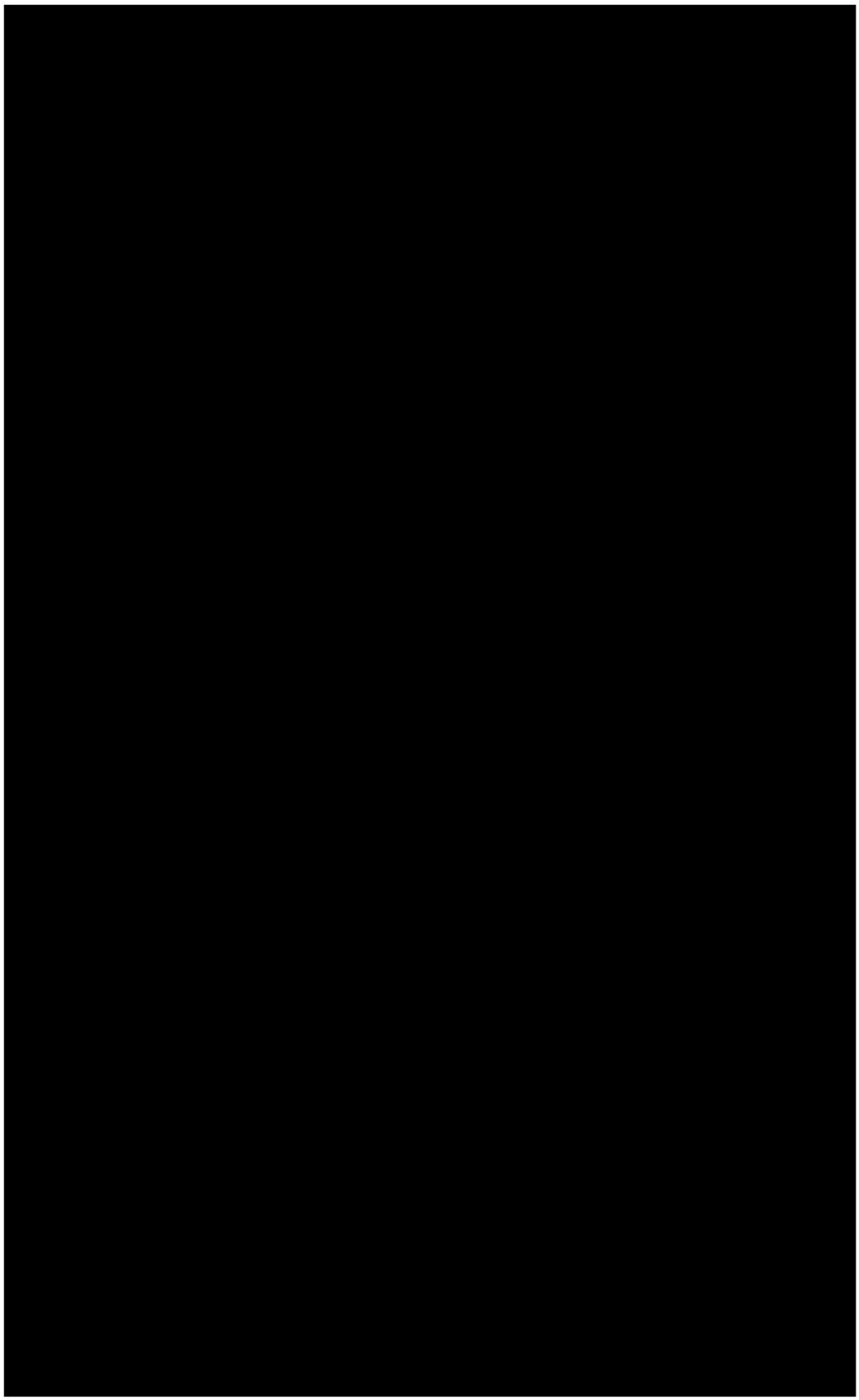
[redacted]

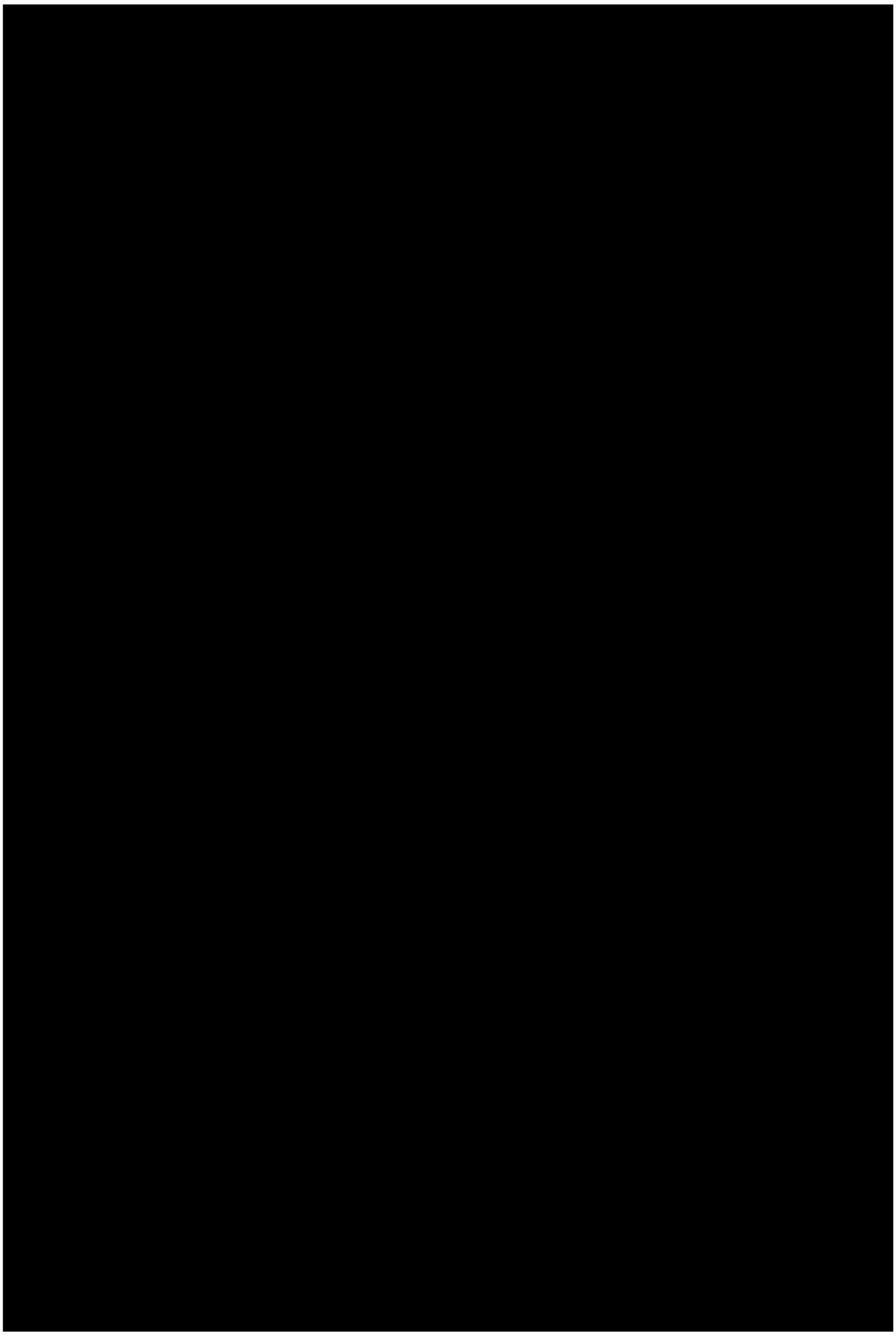
10.1.5 Covariate Balance and Weight Checks in Brigatinib Unanchored MAIC to Alectinib

All balance statistics shown in this Section are re-assuring. With the exception of investigator unconfirmed duration of response, the balance results for the remaining endpoints, with no missing values, are identical for each endpoint within a stated population.

[redacted]







Appendix attached separately.

Medicinrådet

BESTIL PDF/UA

Medicinrådets protokol for vurdering af brigatinib til førstelinjebehandling af uhelbredelig ALK-positiv ikke-småcellet lungekræft

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 16. juli 2020
Dokumentnummer 79502
Versionsnummer 1.0

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

Indhold

1 Begreber og forkortelser

ALK	*Anaplastic Lymphoma Kinase*
CNS	Centralnervesystemet
EGFR	*Epidermal Growth Factor Receptor*
EMA	Det Europæiske Lægemiddelagentur (*European Medicines Agency)*
EORTC	*European Organisation for Research and Treatment of Cancer*
EPAR	*European Public Assessment Report*
GRADE	System til at vurdere evidens (*Grading of Recommendations, Assessment, Development and Evaluation*)
ITT	*Intention to treat*
MKRF	Mindste klinisk relevante forskel
NSCLC	*Non-small cell lung cancer* (ikke-småcellet lungekræft)
OS	Samlet overlevelse (*overall survival)*
PFS	Progressionsfri overlevelse (*progression free survival)*
PICO	Population, intervention, komparator og effektmål (*Population, Intervention, Comparator and Outcome)*
QLQ-C30	*Quality-of-life Questionnaire-Core 30*
ROS1	*ROS proto-oncogene 1 receptor tyrosine kinase*
SMD	*Standardized Mean Difference*
TKI	Tyrosinkinaseinhibitor
TNM	System til at klassificere tumorer (*Tumor, Node, Metastasis)*

2 Introduktion

Protokollen er udarbejdet, fordi Medicinrådet har modtaget en foreløbig ansøgning fra Takeda, som ønsker, at Medicinrådet vurderer brigatinib til behandling af uhelbredelig anaplastisk lymfom kinase (ALK)-positiv ikke-småcellet lungekræft, som ikke er tidligere blevet behandlet med en ALK-TKI (førstelinjebehandling). Medicinrådet modtog den foreløbige ansøgning den 28. april 2020.

Brigatinib blev anbefalet af Medicinrådet i september 2019 til patienter med uhelbredelig ALK-positiv ikke-småcellet lungekræft, der tidligere har modtaget crizotinib (andenlinjebehandling).

2.1 Ikke-småcellet lungekræft

Omtrent 4.600 danskere diagnosticeres årligt med lungekræft, og dermed er lungekræft en af de hyppigst forekommende kræftsygdomme i Danmark [1,2]. I slutningen af 2016 levede knap 11.151 personer med lungekræft, mens cirka 3.700 personer årligt dør af lungekræft [2]. Den seneste årsrapport fra Dansk Lunge Cancer Gruppe & Dansk Lunge Cancer Register viser, at 1-årsoverlevelsesraten for samtlige nydiagnosticerede patienter med lungekræft udredt i 2017 uanset stadie var 51,4 %, mens 5-årsoverlevelsen for patienter udredt i 2013 var 15,9 % [3]. Der er altså tale om en sygdom med en dårlig prognose og kort overlevelse efter diagnosetidspunkt for størstedelen af patienterne.

Af de diagnosticerede patienter med lungekræft har ca. 85-90 % ikke-småcellet lungekræft (*non-small-cell lung cancer* (NSCLC)) [4]. NSCLC inddeles på baggrund af histologi/cytologi i planocellulære og ikke-planocellulær tumorer. Fagudvalget estimerer, at ca. 25 % af patienterne har planocellulære tumorer (svarende til ca. 1.000 patienter), og ca. 75 % af patienterne har ikke-planocellulære tumorer (svarende til ca. 3.000 patienter). Langt de fleste ikke-planocellulære tumorer er såkaldte adenokarcinomer.

Symptomer på lungekræft kan være hoste, åndenød og smerter i brystkassen. Hvis kræften spreder sig til andre organer (f.eks. andre strukturer i brystkassen, knogler eller hjerne), kan patienterne få symptomer fra disse i form af kvalme, opkast, smerter, forvirring og kognitive problemer.

Lungekræft er inddelt i stadier afhængigt af udbredelsesgrad, jævnfør International Association for the Study of Lung Cancer (IASCL) Tumor, Node, Metastasis (TNM)-klassifikation for lungekræft. Langt de fleste kliniske studier benytter TNM version 7 [5], mens man i dansk klinisk praksis i dag anvender version 8 [6]. I henhold til version 7 har patienter med spredning til lymfeknuder svarende til N3-sygdom i stadium IIIB, mens stadium IV betegner metastatisk sygdom. Disse stadier betragtes som udgangspunkt som uhelbredelig NSCLC.

Behandlingsmålet for patienter med uhelbredelig NSCLC er symptomlindring og levetidsforlængelse. Patienter med uhelbredelig NSCLC får systemisk behandling i form af kemoterapi, immunterapi og såkaldt targeteret behandling med tyrosinkinasehæmmere (*tyrosin kinase inhibitor* (TKI)). Valg af behandling er afhængig af tumorkarakteristika, hvor tilstedeværelsen af bestemte biomarkører afgør valg af patientens behandling. Hvis en undersøgelse af tumoren viser genetiske eller kromosomale ændringer, som en behandling kan målrettes mod, vil en targeteret behandling være første valg. I dansk klinisk praksis drejer det sig på nuværende tidspunkt om to biomarkører; aktiverende epidermal growth factor receptor (EGFR)-mutationer samt anaplastisk lymfomkinase (ALK)-translokationer [7]. Dertil kommer ROS proto-oncogene 1 receptor tyrosinekinase (ROS1) som en mulig tredje biomarkør, hvortil Medicinrådet er ved at vurdere et targeteret lægemiddel. Targeteret behandling er kun relevant for patienter med uhelbredelig NSCLC og ikke for patienter med NSCLC i tidligere stadier, hvor en behandling med sigte på helbredelse er en mulighed.

ALK-positiv NSCLC kendetegnes ved ALK-translokationer i tumorvævet, som aktiverer adskillige signaleringskaskader involveret i tumordannelse. ALK-translokationer forekommer sjældent med en frekvens på under 1 % ud af alle nydiagnosticerede lungekræfttilfælde. I 2018 lå frekvensen på 0,6 %

svarende til 30 patienter [3]. Overlevelsen for patienter med ALK-positiv NSCLC er betydeligt bedre end for den samlede gruppe af patienter med lungekræft, når de behandles med en ALK-TKI. I et klinisk forsøg med ALK-TKI'en alectinib til førstelinjebehandling af uhelbredelig ALK-positiv NSCLC (ALEX-studiet) var der en median progressionsfri overlevelse på mindst 34,8 måneder [8].

Omkring halvdelen af patienter med uhelbredelig ALK-positiv NSCLC vil i deres sygdomsforløb få metastaser til centralnervesystemet (CNS), herefter omtalt som hjernemetastaser. Patienter med hjernemetastaser oplever betydelig morbiditet og reduceret livskvalitet, ofte med neurologiske dysfunktioner og kognitive ændringer [9–11].

2.2 Brigatinib

Brigatinib er en tyrosinkinasehæmmer (TKI) med specifik aktivitet mod ALK, IGF-1R, ROS1 og EGFR. ALK er et af de molekyler, som spiller en afgørende rolle for cellevækst og differentiering. Ved at hæmme ALK reduceres aktiviteten af de signaleringskaskader, der har betydning for cellernes overlevelse og proliferation, og som er særligt aktive i ALK-positiv NSCLC [12]. På den måde mindsker brigatinib tumors vækst samt spredning.

Brigatinib har fået en indikationsudvidelse fra Det Europæiske Lægemiddelagentur (*European Medicines Agency* (EMA)). Den nye indikation er:

Brigatinib er indiceret som monoterapi til behandling af voksne patienter med ALK-positiv, fremskreden ikke-små cellet lungekræft (NSCLC) som ikke tidligere er behandlet med en ALK-TKI.

Brigatinib har også følgende EMA-indikation, hvortil det også blev anbefalet i Medicinrådet i september 2019:

Brigatinib er indiceret som monoterapi til behandling af voksne patienter med fremskreden ALK-positiv, ikke-småcellet lungecancer (NSCLC), som tidligere har fået behandling med crizotinib.

Brigatinib administreres oralt som én tablet dagligt. Efter en syvdages indkøringsperiode med 90 mg én gang dagligt, øges dosis til 180 mg én gang dagligt. Lægemidlet gives indtil sygdomsprogression eller intolerable bivirkninger.

Ifølge fagudvalget vil omkring 43 patienter med uhelbredelig ALK-positiv NSCLC årligt være kandidater til førstelinjebehandling med brigatinib i Danmark.

2.3 Nuværende behandling

Målet med behandling af uhelbredelig NSCLC er livsforlængelse og symptomlindring. For patienter med uhelbredelig NSCLC med en genetisk ændring, hvortil der er en targeteret behandling, vil den targeterede behandling være førstevalg for hovedparten af patienterne. Medicinrådets behandlingsvejledning for førstelinjebehandling af uhelbredelig NSCLC beskriver behandlingen af patienter med ALK-translokation og aktiverende EGFR-mutation [7]. Her er alectinib førstevalg til førstelinjebehandling af patienter med uhelbredelig ALK-positiv NSCLC. Fagudvalget forventer, at langt størstedelen af de danske patienter med ALK-translokation bliver behandlet med alectinib i førstelinje.

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.

3.1 Klinisk spørgsmål 1

Hvilken værdi har brigatinib sammenlignet med alectinib i førstelinjebehandling af patienter med uhelbredelig ALK-positiv ikke-småcellet lungekræft?

Population
Patienter med uhelbredelig ALK-positiv NSCLC, som ikke tidligere har modtaget en ALK-TKI.

Intervention
Brigatinib; syvdages indkøringsperiode med 90 mg oralt én gang dagligt, derefter 180 mg én gang dagligt.

Komparator
Alectinib; 600 mg oralt to gange dagligt.

Effektmål
De valgte effektmål står i tabel 1.

3.2 Effektmål

Medicinrådet mener, at vurderingen af lægemidlets værdi bliver bedst understøttet af de effektmål, vi har nævnt i tabel 1. For hvert 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. Af hensyn til intern konsistens har fagudvalget valgt at benytte tilsvarende effektmål og MKRF, som blev benyttet for targeterede behandlinger i behandlingsvejledningen for førstelinjebehandling af uhelbredelig NSCLC.

Fagudvalget har valgt ikke at vurdere rater for overlevelse, PFS og CNS-progression, da det er uvist, på hvilket tidspunkt (12 måneder, 18 måneder eller flere år) en rate vil være mest informativ.

Tabel 1. Effektmål.

Effektmål	Vigtighed	Effektmålsgruppe	Måleenhed	Mindste klinisk relevante forskel
OS (overall survival)	Kritisk	Dødeligehed	Median, mdr.	3 måneder
Behandlingsophør grundet uønskede hændelser	Kritisk	Livskvalitet, alvorlige symptomer og bivirkninger	Forskel i andel patienter som ophører behandling	5 %-point
CNS-progression	Vigtig	Livskvalitet, alvorlige symptomer og bivirkninger	Median, mdr.	3 måneder
PFS (progressionsfri overlevelse)	Vigtig	Livskvalitet, alvorlige symptomer og bivirkninger	Median, mdr.	3 måneder
Uønskede hændelser	Vigtig	Livskvalitet, alvorlige symptomer og bivirkninger	Andel patienter der oplever mindst en grad 3-4 uønsket hændelse	5 %-point
			Gennemgang af bivirkningsprofil	Kvalitativ vurdering

Livskvalitet	Vigtig	Livskvalitet, alvorlige symptomer og bivirkninger	Gennemsnitlig ændring over tid i EORTC-QLQ-C30	10 point

For alle effektmål ønsker vi data med længst mulig opfølgningstid, med mindre andet er angivet.

3.2.1 Kritiske effektmål

Overlevelse (OS)
Da der er tale om uhelbredelig sygdom, vurderes forbedret samlet overlevelse (OS) med mindst mulig toksicitet som afgørende. Derfor vurderer fagudvalget, at OS er et kritisk effektmål. Der findes mange relevante effektmål for overlevelse, og i denne sammenhæng har fagudvalget vurderet median OS som det mest relevante effektmål, da den sammen med den relative effektforskel (vurderet som en HR) afspejler overlevelsen for den samlede studiepopulation.

Patienter med targeterbare biomarkører overlever generelt længere end lungekræftpatienter uden. Den gennemsnitlige overlevelse for patienter med ALK-positiv NSCLC ligger på omkring 6-7 år [13].

Fagudvalget vurderer, at 3 måneder er den mindste klinisk relevante forskel. Dette svarer til den mindste klinisk relevante forskel defineret i tidligere vurderinger af targeteret behandling til uhelbredelig NSCLC.

Behandlingsophør grundet uønskede hændelser
Fagudvalget finder, at ophør med en potentielt effektiv behandling er kritisk for patienterne. For targeterede behandlinger vil der ikke være effekt efter ophør med behandlingen (som der evt. kan være for *check point inhibitor* immunterapi), og patienterne kan risikere hurtig udvikling af sygdommen, hvis behandlingen stoppes (*flare up*). Derfor sætter fagudvalget behandlingsophør grundet bivirkninger som et kritisk effektmål.

Fagudvalget vurderer, at hvis der er en forskel mellem brigatinib og alectinib på mere end 5 % af andelen af patienter, som stopper med behandlingen grundet uønskede hændelser, er der en klinisk relevant forskel mellem lægemidlerne. Dette svarer til den mindste klinisk relevante forskel defineret i tidligere vurderinger af targeteret behandling til uhelbredelig NSCLC.

3.2.2 Vigtige effektmål

CNS-progression
Patienter med ALK-positiv NSCLC har ofte spredning til hjernen, hvilket medfører betydelig morbiditet. Derfor anser fagudvalget udvikling af sygdom i centralnervesystemet (CNS)-progression som et vigtigt effektmål.

Effektmålet omfatter både CNS-progression hos patienter med hjernemetastaser på inklusionstidspunktet samt patienter, der får hjernemetastaser under behandlingen. Fagudvalget vurderer, at 3 måneder er den mindste klinisk relevante forskel, når CNS-progression opgøres som et *time-to-event* effektmål, hvilket foretrækkes. Dette svarer til den mindste klinisk relevante forskel defineret i tidligere vurderinger af targeteret behandling til uhelbredelig NSCLC.

Progressionsfri overlevelse (PFS)
Progressionsfri overlevelse (PFS) bliver anvendt til at vurdere, hvor lang tid der går, inden sygdommen udvikler sig. PFS er defineret som tiden fra randomisering til første dokumentation af progression i henhold til *Response Evaluation Criteria in Solid Tumors* (RECIST) v1.1 [14] eller dødsfald.

Patienter tåler generelt behandling med en TKI godt i sammenligning med andre typer behandling såsom kemoterapi. Fagudvalget vurderer derfor, at det har stor betydning for patienterne at forblive i behandling med en TKI længst muligt pga. den favorable bivirkningsprofil. I senere behandlingslinjer vil patienterne blive tilbudt platinbaseret kemoterapi, der betragtes som mere bivirkningstungt. Derfor vurderer fagudvalget, at PFS er et vigtigt effektmål, som i dette tilfælde ikke er et surrogat for overlevelse, men derimod afspejler patienternes symptombyrde og varighed af respons.

Fagudvalget vurderer, at 3 måneder er den mindste klinisk relevante forskel. Dette svarer til den mindste klinisk relevante forskel defineret i tidligere vurderinger af targeteret behandling til uhelbredelig NSCLC.

Uønskede hændelser
Forekomst af uønskede hændelser grad 3-4 er et udtryk for alvorlig toksicitet af lægemidlet [15]. På den baggrund vurderer fagudvalget, at uønskede hændelser er et vigtigt effektmål. Fagudvalget ønsker data på nedenstående måleenheder.

Uønskede hændelser grad 3-4
Fagudvalget finder, at forskellen i andelen af patienter, som i løbet af opfølgningstiden oplever én eller flere hændelser af grad 3 eller 4, er relevant for vurderingen. Hændelser af grad 3-4 er defineret i henhold til National Cancer Institute CTCAE version 4.03 [15].

Fagudvalget vurderer, at en forskel på 5 %-point i andelen af patienter, der får hændelser af grad 3-4, er klinisk relevant. Dette svarer til den mindste klinisk relevante forskel defineret i tidligere vurderinger af targeteret behandling til uhelbredelig NSCLC.

Kvalitativ gennemgang af uønskede hændelser
Fagudvalget ønsker at foretage en gennemgang af alle uønskede hændelser, der opstår ved behandling med brigatinib og alectinib med henblik på at vurdere hændelsernes type, håndterbarhed og reversibilitet. Der ønskes desuden en liste med alle uønskede hændelser, som fører til behandlingsophør, og deres frekvens i både komparator- og interventionsgruppen. Fagudvalget vil specielt fokusere på de hændelser, som adskiller sig mellem de to grupper.

Livskvalitet
Livskvalitet kan for NSCLC-patienter måles med flere forskellige instrumenter. I dette tilfælde vil vurdering af livskvalitet blive baseret på følgende: European Organisation for Research and Treatment of Cancer Quality-of-life Questionnaire-Core 30 (EORTC QLQ-C30) [16,17].

EORTC QLQ-C30 består af 30 spørgsmål omhandlende funktionsniveau, symptomer samt selvevalueret globalt helbred og livskvalitet. Data fra hvert domæne konverteres til en scoringsskala fra 0-100 [16]. Fagudvalget vil i deres vurdering tage udgangspunkt i resultater for global livskvalitet. Den mindste klinisk relevante forskel baserer sig på en lille ændring, defineret som 5-10 point på den globale skala [18]. En moderat ændring er 10-20 point, og en stor ændring er > 20 point. Fagudvalget har defineret den mindste klinisk relevante forskel som ≥ 10 point, da dette vil overstige mindstegrænsen for en lille ændring. Dette svarer til den mindste klinisk relevante forskel defineret i tidligere vurderinger af targeteret behandling til uhelbredelig NSCLC.

I den foreløbige ansøgning har ansøger ønsket, at livskvalitet skulle opgøres på sepcifikke EORTC QLQ-C30 og QLQ-LC13 subdomæner, som blandt andet fokuserer på dyspnø. Af hensyn til intern konsistens med tidligere vurderinger har fagudvalget valgt at tage udgangspunkt i resultater for global livskvalitet ved kategorisering af effektmålet. Data på subdomæner kan bidrage til en kvalitativ gennemgang af livskvalitet, der evt. kan perspektivere effektmålet.

4 Litteratursøgning

Medicinrådet har på baggrund af den foreløbige ansøgning undersøgt, om der findes en eller flere fuldtekstartikler publiceret i videnskabelige, fagfællebedømte tidsskrifter, hvor brigatinib er sammenlignet direkte med alectinib.

Medicinrådet har ikke fundet fuldtekstartikler, der indeholder en direkte sammenligning mellem brigatinib og alectinib. Derfor skal ansøger søge efter artikler, der beskriver kliniske studier, til en indirekte sammenligning. Søgestrengen fremgår nedenfor. Derudover skal ansøger konsultere EMAs European public assessment reports (EPAR) for både det aktuelle lægemiddel og dets komparator.

Søgestreng til PubMed:

#	Query PubMed	Hits	Kommentar
1	brigatinib[nm] OR brigatinib[tiab] OR Alunbrig*[tiab] OR AP26113[tiab]	170	Søgetermer for lægemidler
2	alectinib[nm] OR alectinib[tiab] OR Alecensa*[tiab] OR CH5424802[tiab] OR RO5424802[tiab]	503	
3	NSCLC[tiab]	42279	Søgetermer for ALK-positiv NSCLC
4	Carcinoma, Non-Small-Cell Lung[mh]	52312	
5	Adenocarcinoma of Lung[mh]	8227	
6	(nonsmall cell[tiab] or non-small cell[tiab] or squamous cell[tiab] or large cell[tiab]) AND lung[tiab] AND (cancer[tiab] or carcinoma[tiab] or carcinomas[tiab] OR adenocarcinoma*[tiab])	75742	
7	Anaplastic Lymphoma Kinase[mh]	3163	
8	(anaplastic lymphoma kinase[tiab] or ALK[tiab]) AND (mutat*[tiab] OR mutant*[tiab] OR translocat*[tiab] OR rearrange*[tiab] OR positiv*[tiab] OR fused[tiab])	6326	
9	"ALK+"[tiab] OR ALK-R[tiab]	8943	
10	(#1 OR #2) AND (#3 OR #4 OR #5 OR #6) AND (#7 OR #8 OR #9)	448	Kombination af lægemidler og indikation
11	case report[ti] OR review of the literature[tiab] OR retrospective[ti] OR observational[ti]	424792	Eksklusion af specifikke publikationstyper
12	Case Reports[pt] OR Comment[pt] OR Editorial[pt] OR Guideline[pt] OR Letter[pt] OR (Review[pt] NOT (Systematic Review[pt] OR Meta-Analysis[pt]))	6121165	
13	Animals[mh] NOT Humans[mh]	4698496	
14	#10 NOT (#11 OR #12 OR #13)	206	Endeligt resultat

Søgestreng til CENTRAL:

#	Query CENTRAL	Hits	Kommentar
1	(brigatinib or Alunbrig* or AP26113):ti,ab,kw	73	Søgetermer for lægemidler
2	(alectinib or Alecensa* or CH5424802 or RO5424802):ti,ab,kw	107	
3	NSCLC:ti,ab	8742	Søgetermer for ALK-positiv NSCLC
4	("Carcinoma, Non-Small-Cell Lung" or "non small cell lung cancer" or "Adenocarcinoma of Lung" or "large cell lung carcinoma" or "lung adenocarcinoma" or "squamous cell lung carcinoma"):kw	4415	

5	(("nonsmall cell" or "non small cell" or "squamous cell" or "large cell") NEAR/2 lung NEAR/2 (cancer or carcinoma* or adenocarcinoma*)):ti,ab	10909	
6	(lung NEAR/2 adenocarcinoma):ti,ab	324	
7	("anaplastic lymphoma kinase"):kw	92	
8	(("anaplastic lymphoma kinase" or ALK*) and (mutat* or mutant* or translocat* or rearrange* or positiv*)):ti,ab	1424	
9	ALK-R:ti,ab	0	
10	(#1 or #2) and (#3 or #4 or #5 or #6) and (#7 or #8 or #9)	113	Kombination af lægemidler og indikation
11	(clinicaltrials.gov or trialsearch):so	326336	Eksklusion af specifikke publikationstyper
12	review:pt or erratum:ti	19556	
13	#10 not (#11 or #12)	79	
14	embase:an not pubmed:an	337060	Eksklusion af resultater, der kommer fra PubMed
15	#13 and #14 in Trials	54	Endeligt resultat

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.
- Brug som udgangspunkt ansøgningsskemaet til ekstraktion af al relevant data.
- Krydstjek de ekstraherede data med de resultater, der fremgår af de relevante EPARs.
- Angiv årsager, hvis der er uoverensstemmelser mellem resultaterne fra artikler og EPARs.
- Angiv årsager, hvis der er uoverensstemmelser i forhold til PICO mellem protokollen og studierne.
- Vurdér, hvordan uoverensstemmelserne påvirker estimaterne.

Statistiske analyser

- Begrund valget af syntesemetode (metaanalyse eller narrativ beskrivelse), og lad specifikke analysevalg fremgå tydeligt.
- Udfør en komparativ analyse for hvert enkelt effektmål på baggrund af de ekstraherede data.
- Hvis data for et effektmål ikke er baseret på alle deltagere i et studie, skal ansøger ikke gøre forsøg på at erstatte manglende data med en meningsfuld værdi.
- Angiv for hvert effektmål og studie, hvilken analysepopulation (f.eks. intention to treat (ITT), per-protocol) der er anvendt.
- Angiv en sensitivitetsanalyse baseret på ITT-populationen, hvis den komparative analyse ikke er baseret herpå.
- Angiv for hvert effektmål og studie, hvilken statistisk analysemetode der er anvendt.
- Basér de statistiske analyser for dikotome effektmål på den relative forskel.
- Beregn den absolutte forskel med udgangspunkt i den estimerede relative forskel for et antaget niveau på hændelsesraten i komparatorgruppen (jævnfør Appendiks 5 i Håndbog for Medicinrådets proces og metode vedr. nye lægemidler og indikationsudvidelser).
- Foretag eventuelt en indirekte analyse, hvis der ikke foreligger direkte sammenlignende studier, og hvis intervention og komparator er sammenlignet med samme alternative komparator i separate studier. Anvend eventuelt Buchers metode for indirekte justeret sammenligning.

Metaanalyser

- Foretag en metaanalyse for de effektmål, hvor det er metodemæssigt forsvarligt, hvis der er mere end ét sammenlignende studie.
- Basér metaanalyser vedr. effektmål, hvor forskellige måleinstrumenter er brugt på tværs af de inkluderede studier, på standardized mean difference (SMD). Omregn den estimerede SMD til den foretrukne skala for effektmålet (jævnfør Appendiks 7 i Håndbog for Medicinrådets proces og metode vedr. nye lægemidler og indikationsudvidelser).
- Udfør alene netværksmetaanalyse i de undtagelsesvise situationer, hvor Medicinrådet specifikt beder om det i protokollen. Redegør i disse tilfælde for, i hvilken grad antagelserne om transitivitet og konsistens er opfyldt (gerne ved hjælp af passende statistiske metoder).
- Begrund for alle statistiske analyser valget mellem ’fixed effects’- og ’random effects’-modeller.
- Beskriv den anvendte metode detaljeret.

Narrative analyser

- Begrund valget af syntesemetode (metaanalyse eller narrativ beskrivelse), og lad specifikke analysevalg fremgå tydeligt.
- Syntetisér data narrativt, hvis det ikke er en mulighed at udarbejde komparative analyser baseret på statistiske metoder.
- Beskriv studie- og patientkarakteristika samt resultater fra de inkluderede studier narrativt og i tabelform med angivelse af resultater pr. effektmål for både intervention og komparator(er).
- Beskriv forskelle mellem studier og vurdér, hvorvidt resultaterne er sammenlignelige. .

Vær opmærksom på, at Medicinrådets sekretariat forbeholder sig retten til at foretage sensitivitets- og subgruppeanalyser på baggrund af studiernes validitet og relevans, uanset valg af analysemetode.

6 Evidensens kvalitet

Medicinrådet anvender GRADE (Grading of Recommendations, Assessments, Development and Evaluation) til at foretage en systematisk og transparent vurdering af kvaliteten af evidensen. Evidensens kvalitet fortæller, i hvor høj grad vi kan have tiltro til den evidens, vi baserer vurderingen af lægemidlets værdi på.

7 Andre overvejelser

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.

Tilsvarende ønsker Medicinrådets sekretariat, at den sundhedsøkonomiske ansøgning skal afspejle eventuelle forskelle i efterfølgende behandlinger.

8 Relation til behandlingsvejledning

I vurderingsrapporten vil fagudvalget tage stilling til brigatinibs foreløbige placering i forhold til de andre lægemidler, der er beskrevet i Medicinrådets behandlingsvejledning for første linjebehandling af uhelbredelig NSCLC.

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10 Sammensætning af fagudvalg og kontaktinformation til Medicinrådet

Medicinrådets fagudvalg vedrørende lungekræft

Formand	**Indstillet af**
Halla Skuladottir Overlæge, dr.med.	Lægevidenskabelige Selskaber
Medlemmer	**Udpeget af**
Kan ikke opfylde Medicinrådets habilitetskrav	Region Nordjylland
Udpegning i gang	Region Midtjylland
Stefan Starup Jeppesen Overlæge, ph.d.	Region Syddanmark
Jeanette Haar Ehlers Overlæge	Region Sjælland
Lotte Engell-Nørregård Overlæge, ph.d.	Region Hovedstaden
Nille Behrendt Overlæge	Dansk Patologiselskab
Peder Fabricius Ledende overlæge	Dansk Selskab for Lungemedicin
Nina Hannover Bjarnason Overlæge, dr.med.	Dansk Selskab for Klinisk Farmakologi
Annie Lorenzen Klinisk farmaceut	Dansk Selskab for Sygehusapoteksledelse
Morten Hiul Suppli Afdelingslæge, ph.d.	Dansk Selskab for Klinisk Onkologi
Ønsker ikke at udpege yderligere medlemmer	Dansk Onkologisk Lungecancer Gruppe
Ønsker ikke at udpege yderligere medlemmer	Dansk Lunge Cancer Gruppe
Finn Klausen Patient/patientrepræsentant	Danske Patienter
Lisbeth Søbæk Hansen Patient/patientrepræsentant	Danske Patienter

Medicinrådets sekretariat

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

11 Versionslog

Version	Dato	Ændring
1.0	16. juli 2020	Godkendt af Medicinrådet.