Medicinrådet

Baggrund for Medicinrådets anbefaling vedrørende brigatinib som mulig standard-behandling til ALK-positiv ikke-småcellet lungekræft

Versionsnr.: 1.0

Medicinrådet

Om Medicinrådet

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

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

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

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

Om anbefalingen

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

Lægemidlet vurderes efter Metodehåndbog for Medicinrådets arbejde med at udarbejde fælles regionale vurderinger af nye lægemidlers og nye indikationers kliniske merværdi – version 1. Se Medicinrådets metodehåndbog for yderligere information.

Dokumentoplysninger	
Godkendelsesdato	25. september 2019
Ikrafttrædelsesdato	25. september 2019
Dokumentnummer	55618
Versionsnummer	1.0

Medicinrådet, Dampfærgevej 27-29, 3. th., 2100 København Ø
www.medicinraadet.dk
Sprog: dansk
Format: pdf
Udgivet af Medicinrådet, 25. september 2019

Indhold

1 Lægemiddelinformationer

Lægemidlets oplysninger	
Handelsnavn	Alunbrig
Generisk navn	Brigatinib
Firma	Takeda Pharma
ATC-kode	L01XE43
Virkningsmekanisme	Anaplastisk Lymfom Kinase (ALK)-hæmmer
Administration/dosis	Tablet 90 mg én gang dagligt i de første syv dage og derefter 180 mg én gang dagligt.
EMA-indikation	*Alunbrig is indicated for the treatment of adult patients with anaplastic lymphoma kinase (ALK) positive advanced non-small cell lung cancer (NSCLC) previously treated with crizotinib.*

2 Medicinrådets anbefaling

Medicinrådet **anbefaler** brigatinib som mulig standardbehandling til patienter med ALK-positiv ikke-småcellet lungekræft, som tidligere er behandlet med crizotinib.

Medicinrådet vurderer, at der er et rimeligt forhold mellem den kliniske effekt og de omkostninger, brigatinib forventes at have.

Medicinrådet anbefaler, at der ikke behandles med ALK-TKI'er i flere på hinanden følgende behandlingslinjer, medmindre der foreligger klinisk dokumentation.

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

Hvad er den kliniske merværdi af brigatinib til patienter med uhelbredelig ALK-positiv ikke-småcellet lungekræft, som tidligere har fået behandling med crizotinib?

3 Formål

Formålet med Baggrund for Medicinrådets anbefaling vedrørende brigatinib som mulig standardbehandling til uhelbredelig ALK-positiv ikke-småcellet lungekræft er at skabe gennemsigtighed om det materiale, der ligger til grund for Medicinrådets anbefaling.

4 Baggrund

I 2017 blev 4.856 danskere diagnosticeret med lungekræft. Under 1 % af disse har uhelbredelig ikke-småcellet lungekræft (NSCLC) med ALK-translokation. I alt svarer det til omkring 40 patienter årligt. Fagudvalget skønner at 0-5 af disse årligt er kandidater til behandling med brigatinib.

Yderligere baggrundsinformation findes i "Medicinrådets vurdering af klinisk merværdi for brigatinib til behandling af ALK-positiv ikke-småcellet lungekræft" (Bilag 4).

4.1 Sagsbehandlingstid og proces for Medicinrådets vurdering

Medicinrådet modtog den foreløbige ansøgning fra Takeda Pharma den 15. oktober 2018. Protokollen for vurdering af brigatinib til ALK-positiv ikke-småcellet lungekræft blev godkendt af Medicinrådet den 4. februar 2019, og sekretariatet modtog den endelige ansøgning den 27. marts 2019.

Vurdering af klinisk merværdi blev godkendt af Rådet den 19. juni 2019. Der har været clockstop mellem den 18. august 2019 og den 15. september 2019 grundet prisforhandlingen.

Den samlede sagsbehandlingstid var 22 uger og 0 dage fra modtagelse af den kliniske del af ansøgningen.

5 Medicinrådets vurdering af samlet klinisk merværdi

Medicinrådet vurderer, at brigatinib til patienter med ALK-positiv ikke-småcellet lungekræft, som tidligere er behandlet med crizotinib, giver en **ikkedokumenterbar klinisk merværdi** sammenlignet med alectinib. Evidensens kvalitet kan ikke defineres.

På trods af den ikkedokumenterbare kliniske merværdi af brigatinib, anser Medicinrådet det som et relevant behandlingstilbud til en meget lille gruppe patienter.

6 Høring

Ansøger fremsendte et høringssvar den 26. juni 2019 (Bilag 3), som ikke opponerede mod kategoriseringen, men udtrykte et ønske om, at det økonomiske beslutningsgrundlag blev baseret på en antagelse om ens behandlingslængde for brigatinib og komparator (alectinib). Høringssvaret indeholder fortrolige oplysninger, som ikke offentliggøres med baggrunden for anbefaling.

7 Resumé af økonomisk beslutningsgrundlag

Amgros har udarbejdet en sundhedsøkonomisk analyse, som vurderer de gennemsnitlige meromkostninger pr. patient og budgetkonsekvenser ved brug af brigatinib til patienter med ALK-positiv ikke-småcellet lungekræft. Amgros' hovedanalyse bygger på ansøgers hovedanalyse. Amgros' hovedanalyse viser, at behandling med brigatinib er forbundet med betydelige meromkostninger pr. patient sammenlignet med alectinib. I hovedanalysen antager ansøger, at behandlingsvarigheden er længere for brigatinib end for alectinib.

Amgros har foretaget en følsomhedsanalyse, hvori det antages, at behandlingsvarigheden for brigatinib og alectinib er ens. Under denne forudsætning er der ikke meromkostninger forbundet med anvendelse af brigatinib sammenlignet med alectinib.

Der er ikke dokumenteret længere progressionsfri overlevelse (som afspejler behandlingsvarigheden) for behandling med brigatinib i vurderingen af klinisk merværdi. Derfor vurderer Medicinrådet, at følsomhedsanalysen bedst afspejler de forventede meromkostninger.

Medicinrådet vurderer, at der er et rimeligt forhold mellem den kliniske merværdi og de omkostninger, brigatinib forventes at have.

Medicinrådet anbefaler derfor brigatinib som mulig standardbehandling til de få patienter, som tidligere har fået behandling med crizotinib.

Amgros' beslutningsgrundlag og Amgros' sundhedsøkonomiske analyse (baseret på SAIP-priser) er vedlagt som bilag 1 og 2.

8 Overvejelser omkring alvorlighed/forsigtighed

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

9 Sammensætning af fagudvalg og kontaktinformation til Medicinrådet

Medicinrådets fagudvalg vedrørende lungekræft

Formand	**Indstillet af**
Christa Haugaard Nyhus Overlæge	Lægevidenskabelige Selskaber
Medlemmer	**Udpeget af**
Kan ikke udpege	Region Nordjylland
Halla Skuladottir Overlæge, dr.med.	Region Midtjylland
Stefan Starup Jeppesen Overlæge, ph.d.	Region Syddanmark
Jeanette Haar Ehlers Overlæge	Region Sjælland
Lotte Engell-Nørregård Afdelingslæge, ph.d.	Region Hovedstaden
Henrik Hager Overlæge	Inviteret af formanden
Nille Behrendt Overlæge	Dansk Patologiselskab
Peder Fabricius Overlæge	Dansk Selskab for Lungemedicin
Nina Hannover Bjarnason Overlæge, dr.med.	Dansk Selskab for Klinisk Farmakologi
Annie Lorenzen Farmaceut	Dansk Selskab for Sygehusapoteksledelse
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
Sekretariatets arbejdsgruppe: Jane Skov (projekt- og metodeansvarlig) Vibe Charlotte Nylander (projektdeltager) Hjalte Holm Andersen (projektdeltager) Charlotte Wulff Johansen (fagudvalgskoordinator) Tenna Bekker (teamleder)

10 Versionslog

Version	Dato	Ændring
1.0	25. september 2019	Godkendt af Medicinrådet.

Bilag

1. Amgros' beslutningsgrundlag
2. Amgros' sundhedsøkonomiske analyse
3. Høringssvar fra Takeda Pharma ang. vurdering af klinisk merværdi - indeholder fortrolige oplysninger
4. Medicinrådets vurdering af klinisk merværdi for brigatinib til behandling af ALK-positiv ikke-småcellet lungekræft – version 1.0
5. Endelig ansøgning fra Takeda Pharma vedr. brigatinib
6. Medicinrådets protokol for vurdering af klinisk merværdi for brigatinib til behandling af ALK-positiv ikke-småcellet lungekræft – version 1.0.

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Beslutningsgrundlag til Medicinrådet

Dette dokument er Amgros' vurdering af brigatinib (Alunbrig) er indiceret som monoterapi til voksne patienter med fremskreden ALK-positiv, ikke-småcellet lungecancer (NSCLC), som tidligere har fået behandling med crizotinib. Vurderingen er baseret på lægemidlets gennemsnitlige inkrementelle omkostninger, baseret på SAIP (sygehusapotekets indkøbspris) sammenholdt med Medicinrådets vurdering af den kliniske merværdi.

Dato for Medicinrådsbeslutning	25-09-2019
Firma	Takeda (ansøger)
Lægemiddel	Brigatinib (Alunbrig)
Indikation	Monoterapi til behandling af voksne patienter med fremskreden anaplastisk lymfom-kinase(ALK)-positiv, ikke-småcellet lungecancer (NSCLC), som tidligere har fået behandling med crizotinib.

Amgros' vurdering

- Amgros vurderer, at der **ikke** er et rimeligt forholdet mellem meromkostningerne og den kliniske merværdi for brigatinib (Alunbrig) som mulig standardbehandling til voksne patienter med fremskreden anaplastisk lymfom-kinase(ALK)-positiv, ikke-småcellet lungecancer (NSCLC), som tidligere har fået behandling med crizotinib sammenlignet med behandling med alectinib (Alecensa)

Overordnet konklusion

Medicinrådet har vurderet, at brigatinib (Alunbrig) sammenlignet med alectinib (Alecensa) giver:

- Ikkedokumenterbar klinisk merværdi.

Behandling med brigatinib (Alunbrig) er forbundet med høje meromkostninger sammenlignet med alectinib (Alecensa). Meromkostninger drives af lægemiddelprisen og behandlingslængden.

Andre overvejelser

Amgros' vurdering er baseret på ansøgers indsendte analyse, der er i overensstemmelse med Amgros' Metodevejledning. På baggrund af dette, er analysen baseret på gennemsnitlige behandlingslængder, beregnet ud fra ekstrapolerede data af progressionsfri overlevelse (PFS). De ekstrapolerede data giver anledning til forskellige gennemsnitlige behandlingslængder af henholdsvis behandling med brigatinib (Alunbrig) og alectinib (Alecensa). Da forskellen i behandlingslængden driver de inkrementelle omkostninger, har dette stor betydning for analysens resultat. En følsomhedsanalyse med ens behandlingslængder er derfor præsenteret, se tabel 4.

Amgros har indgået en aftale med Takeda om indkøb af brigatinib (Alunbrig) til en aftalepris, som er lavere end AIP. Amgros vurdering af brigatinib (Alunbrig) resulterer i høje meromkostninger.

Konklusion for populationen

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

Population	Komparator	Merværdi	Usikkerhed for klinisk merværdi	Amgros' konklusion om forholdet mellem meromkostninger og merværdi
Voksne patienter med fremskreden ALK-positiv, NSCLC, som tidligere har fået behandling med crizotinib.	Alectinib (Alecensa)	Ikkedokumenterbar klinisk merværdi	Lav evidenskvalitet	Ikke rimeligt

Supplerende informationer (resumé af resultaterne fra afrapporteringen)

Konklusion på omkostnings- og budgetkonsekvensanalyserne

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

Amgros' afrapportering - Inkrementelle omkostninger per patient

Behandling med brigatinib (Alunbrig) er forbundet med meromkostninger sammenlignet med alectinib (Alecensa).

I tabel 2 ses de inkrementelle omkostninger for brigatinib (Alunbrig) og alectinib (Alecensa) i SAIP.

Amgros' hovedanalyse resulterer i gennemsnitlige meromkostninger per patient for brigatinib (Alunbrig) sammenlignet med alectinib (Alecensa) på ca. [redacted] DKK. I analysen er behandlingslængden for brigatinib (Alunbrig) sat til 22,03 måneder og 16,78 måneder for alectinib (Alecensa). Behandlingslængderne beregnet som gennemsnitlig behandlingslængde for en gennemsnitlig patient.

Tabel 2: Gennemsnitlige årlige omkostninger af brigatinib (Alunbrig) sammenlignet med alectinib (Alecensa), SAIP, DKK

	Brigatinib (Alunbrig)	Alectinib	Inkrementelle omkostninger
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Hospitalsomkostninger	22.996	17.362	5.634
Patientomkostninger	4.156	3.274	882
Totale omkostninger	[redacted]	[redacted]	[redacted]

Hvis analysen udføres på baggrund af AIP, bliver de inkrementelle omkostninger for brigatinib (Alunbrig) sammenlignet med alectinib (Alecensa) på ca. 250.000 DKK.

Amgros' afrapportering – Budgetkonsekvenser

Ansøger antager, da det er patienter der har modtaget crizotinib og dermed er en patientgruppe der ikke kan tåle alectinib, vil ca. 5 patienter årligt kandiderer til behandlingen. Ansøger antager at hvis brigatinib (Alunbrig) anbefales vil alle 5 patienter modtage brigatinib (Alunbrig). Ansøger beregner år 1 til kun at inkluderer 6 måneder, grundet tidspunkt for vurderingen. Patientantal forskydes således et halvt år. Da patienter behandles i knap to år, vil forskydningen resulterer i at flest patienter behandles i år 3.

Budgetkonsekvenserne hvis brigatinib (Alunbrig) anbefales ligger på meromkostninger på ca. [redacted] DKK ca [redacted] DKK år 2, ca [redacted]. DKK år 3 og ca. [redacted] DKK i år 4 og 5, se tabel 3. Laves analysen med AIP, vil budgetkonsekvenser hvis brigatinib (Alunbrig) anbefales ligge på ca. -1,4 mio. DKK år 1, ca. 1,8 mio. DKK år 2, ca. 2,3 mio. DKK år 3 og ca. 1,3 mio. DKK i år 4 og 5.

Tabel 3: Totale budgetkonsekvenser hvis brigatinib (Alunbrig) anbefales, mio. DKK, SAIP, 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' afrapportering – følsomhedsanalyse med ens behandlingslængde

I tabel 4 ses følsomhedsanalyse baseret på ens behandlingslængde og de inkrementelle omkostninger for brigatinib (Alunbrig) sammenlignet med alectinib (Alecensa) i SAIP.

Følsomhedsanalysen resulterer i gennemsnitlige inkrementelle omkostninger per patient for brigatinib (Alunbrig) sammenlignet med alectinib (Alecensa) på ca. [redacted] DKK.

Tabel 4: Inkrementelle omkostninger baseret på følsomhedsanalyse med ens behandlingslængde, SAIP, DKK

Ens behandlingslængde (16,78 måneder)	Brigatinib (Alunbrig)	Alectinib	Inkrementelle omkostninger
Totale omkostninger	[redacted]	[redacted]	[redacted]

BRIGATINIB (ALUNBRIG)

ALK-POSITIV IKKE-SMÅCELLET LUNGEKRÆFT

AMGROS 5. juli 2019

AMGROS

OPSUMMERING

Baggrund

Brigatinib (Alunbrig) er som monoterapi indiceret til behandling af voksne patienter med fremskreden anaplastisk lymfom-kinase(ALK)-positiv, ikke-småcellet lungekræft (NSCLC), som tidligere har fået behandling med crizotinib. Omkring 0-5 patienter per år kandiderer årligt til behandling af den ansøgte indikation i Danmark. Amgros' vurdering tager udgangspunkt i dokumentation indsendt af Takeda.

Analyse

I analysen estimeres de inkrementelle omkostninger forbundet med behandling med brigatinib (Alunbrig) sammenlignet med alectinib til patienter med uhelbredelig ALK-positiv NSCLC, som tidligere har fået behandling med crizotanib.

Inkrementelle omkostninger og budgetkonsekvenser

Amgros har vurderet de gennemsnitlige meromkostninger per patient ved brug af brigatinib (Alunbrig) sammenlignet med alectinib. De inkrementelle omkostninger er angivet i SAIP.

I scenariet Amgros mener er mest sandsynligt, er de gennemsnitlige meromkostninger for brigatinib (Alunbrig) ca. [redacted] sammenlignet med alectinib til nævnte indikation. Hvis analysen udføres med AIP bliver de inkrementelle omkostninger til sammenligning 248.000 DKK per patient.

Amgros vurderer, at budgetkonsekvenserne for regionerne per år ved anbefaling af brigatinib (Alunbrig) som standardbehandling vil være ca. [redacted] i år 5. Hvis analysen udføres med AIP, er budgetkonsekvenser ca. 1,3 mio. DKK i år 5.

Konklusion

Behandling med brigatinib (Alunbrig) er forbundet med meromkostninger sammenlignet med behandling med alectinib. De inkrementelle meromkostninger er udelukkende drevet af en længere PFS og dermed en længere behandlingslængde.

Liste over forkortelser

AIP	Apotekernes indkøbspris
ALK	Anaplastisk lymfom-kinase
DKK	Danske kroner
DRG	Diagnose Relaterede Grupper
NSCLC	Ikke-småcellet lungecancer
SAIP	Sygehusapotekernes indkøbspriser

INDHOLD

LOG

Ansøgning	
Lægemiddelfirma:	Takeda
Handelsnavn:	Alunbrig
Generisk navn:	Brigatinib
Indikation:	Monoterapi til behandling af voksne patienter med fremskreden anaplastisk lymfom-kinase(ALK)-positiv, ikke-småcellet lungekræft (NSCLC), som tidligere har fået behandling med crizotinib.
ATC-kode:	L01XE43

Proces	
Ansøgning modtaget hos Amgros:	28-03-2019
Endelig rapport færdig:	05-07-2019
Sagsbehandlingstid fra endelig ansøgning:	99 dage
Arbejdsgruppe:	**Louise Greve Dal** Line Brøns Jensen Lianna Geertsen Mark Friborg Pernille Winther Johansen

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

1 BAGGRUND

Brigatinib (Alunbrig) er indiceret som monoterapi til voksne patienter med fremskreden ALK-positiv, ikke-småcellet lungecancer (NSCLC), som tidligere har fået behandling med crizotinib(1). Takeda (herefter omtalt som ansøger) er markedsføringstilladelsesindehaver af brigatinib (Alunbrig) og har den 28.03.2019 indsendt en ansøgning til Medicinrådet om anbefaling af brigatinib (Alunbrig) som standardbehandling på danske hospitaler af den nævnte indikation. Som et led i denne ansøgning vurderer Amgros, på vegne af Medicinrådet de økonomiske analyser, ansøger har sendt som en del af den samlede ansøgning til Medicinrådet. Denne rapport er Amgros' vurdering af de fremsendte økonomiske analyser (herefter omtalt som analysen).

1.1 Problemstilling

Formålet med analysen er at estimere de gennemsnitlige inkrementelle omkostninger per patient og de samlede budgetkonsekvenser for regionerne ved anbefaling af brigatinib (Alunbrig) som standardbehandling på danske hospitaler af den nævnte indikation. I analyserne sammenlignes behandling med brigatinib (Alunbrig) med behandling med alectinib.

1.2 Patientpopulation

I 2017 blev 4.856 danskere diagnoseret med lungekræft, og dermed er lungekræft en af de hyppigst forekommende kræftsygdomme i Danmark. Af de diagnosticerede har ca. 85% NSCLC(1). I slutningen af 2015 levede knap 10.450 personer med lungekræft, mens cirka 3.700 personer årligt dør af lungekræft. Lungekræft har således en høj dødelighed med den seneste opgjorte etårs overlevelse i Danmark på 50,8% for samtlige nydiagnosticerede patienter(1).

Lungekræft inddeles i fire stadier(I-IV) afhængigt af udbredelsesgrad. Stadie III betyder, at tumor enten har en vis størrelse, indvækst i nærliggende struktur eller spredning til regionale lymfeknuder(1). Metastatisk lungekræft betegnes som stadie IV, der som udgangspunkt betragtes som uhelbredelig. Nogle patienter med NSCLC i stadie III betragtes også som havende uhelbredelig lungekræft og behandles som patienter i stadie IV(1).

Man kender mange biomarkører, hvoraf enkelte har betydning for behandlingen. En af dem er ALK-translokation. I 2016 var andelen af patienter med ALK-translokation 1,7% (svarende til 35 patienter) hos patienter med adenokarcinom m.fl. dette skal ses i lyset af, at ALK-status ikke blev registreret hos omkring hver femte patient diagnosticeret med adenokarcinom m. fl.(1).

Mange patienter med ALK-positiv NSCLC vil med tiden ofte få progression i centralnervesystemet (CNS). Generelt beskrives incidensen af hjernemetastaser blandt patienter med ALK-positiv NSCLC som værende høj og studier har vist, at 35-50% af de inkluderede patienter havde hjernemetastaser. Lungekræft patienter med hjernemetastaser oplever betydelig morbiditet og reduceret livskvalitet, ofte med neurologiske dysfunktioner og kognitive ændringer og med en median overlevelse på 3-6 måneder(1).

1.3 Nuværende behandling

Crizotinib har tidligere været anbefalet som 1. linebehandling til uhelbredelig ALK-positiv NSCLC. Den 30. maj 2018 anbefalede Medicinrådet imidlertid alectinib som mulig standardbehandling i 1. linje, og tilsvarende beskriver Dansk Lunge Cancer Gruppe (DLCG)s kliniske retningslinjer alectinib som 1. linjebehandling til patienter med uhelbredelig ALK-positiv NSCLC(1).

Brigatinib kan ifølge EMA indikationen kun anvendes til patienter, der har fået behandling i 1. linje med crizotinib(1). Størstedelen af danske patienter behandles nu i 1. linje med alectinib. Fagudvalget for lungekræft vurderer, at gruppen af danske patienter, der er kandidater til brigatinib i 2. linje efter crizotinib, omfatter 0-5 patienter årligt.(1) Dette kan f.eks. dreje sig om patienter, der enten indledte behandling med crizotinib før alectinib blev anbefalet af Medicinrådet som mulig standardbehandling i 1. linje, eller patienter som ikke tåler alectinib(1).

1.4 Behandling med brigatinib (Alunbrig)

Indikation

Brigatinib (Alunbrig) er indiceret som monoterapi til behandling af voksne patienter med fremskreden ALK-positiv NSCLC, som tidligere har fået behandling med crizotinib(1).

Virkningsmekanisme

Brigatinib (Alunbrig) er en tyrosinkinasehæmmer med specifik aktivitet mod blandt andet ALK. Ved at hæmme ALK reduceres aktiviteten af centralt placerede molekyler i signaleringskaskader af betydning for cellulær overlevelse, vækst og proliferation(1).

Dosering

Brigatinib (Alunbrig) administreres oralt som en enkelt tablet dagligt indtil sygdomsprogression. Efter en syv-dages indkøringsperiode med 90 mg én gang dagligt, øges dosis til 180 mg én gang dagligt.(1)

1.4.1 Komparator

Medicinrådet har defineret alectinib som komparator for nævnte population(1).

Tabel 1: Definerede population og komparator.

Population	Komparator
Voksne patienter med uheldbredelig ALK-positiv NSCLC, som tidligere har fået behandling med crizotinib i 1. linje.	Alectinib

1.5 Medicinrådets kliniske spørgsmål

Medicinrådet har vurderet den kliniske merværdi af brigatinib (Alunbrig) som monoterapi til patienter med uhelbredelig ALK-positiv NSCLC, som tidligere har fået behandling med crizotinib udfra følgende spørgsmål.(1)

- *Hvad er den kliniske merværdi af brigatinib (Alunbrig) til patienter med uhelbredelig ALK-positiv NSCLC, som tidligere har fået behandling med crizotinib?*

2 VURDERING AF INDSENDT ØKONOMISK ANALYSE

I analysen af inkrementelle omkostninger per patient sammenlignes behandling med brigatinib (Alunbrig) med behandling med alectinib til 2. linjebehandling af ikke-småcellet lungekræft med ALK-positiv mutation. Analysen inkluderer omkostninger til lægemidler, monitorering, patienttid og transport.

Amgros havde indvendinger til ansøgers første analyse. Det er kun seneste indsendte analyse som præsenteres.

2.1 Model, metode og forudsætninger

2.1.1 Modelbeskrivelse

Ansøger har indsendt en simpel analyse der sammenligner brigatinib (Alunbrig) med alectinib på baggrund af studierne ALTA for brigatinib (Alunbrig)(2) og ALUR for alectinib(3). Ansøger har ekstrapoleret "tid i behandling" (Time of treatment, TOT) for begge lægemidler, og beregnet den gennemsnitlige behandlingslængde, som ses i tabel 2. Det argumenteres at progressionsfri overlevelse (PFS) også ville være mulig til at estimere behandlingslængden, men da den gennemsnitlige tid til behandlingsophør er længere, benyttes denne. TOT og PFS er næsten identiske.
Efter behandling med brigatinib (Alunbrig) eller alectinib antages behandlingen at være ens og patienterne modtager platinbaseret kemoterapi.
Ansøger anvender kun forløbsdata til behandlingslængden, da de mener en simpel analyse bedst afspejler omkostningerne. Omkostningerne er derfor kun afspejlet i den tid patienterne er i behandlingen, hvor omkostninger til monitorering, patienttid og transport er inkluderet.

Tabel 2: Estimerede behandlingslængder for behandling med brigatinib (Alunbrig) og alectinib

Behandling	Gennemsnitlig behandlingslængde
Brigatinib (Alunbrig)	22,03 måneder
Alectinib	16,78 måneder

Amgros' vurdering

Amgros har bedt ansøger indsende forløbsdata på PFS og overlevelse (OS) og de parametriske fit, der angiver en sandsynlighed for længere PFS og OS for brigatinib (Alunbrig). TOT og PFS er næsten ens, og TOT afspejler bedst den tid patienterne vil befinde sig i behandlingen. Da der ikke eksisterer head-to-head studier der sammenligner brigatinib (Alunbrig) med alectinib er TOT en indirekte sammenligning. Ansøger argumenterer derfor for, ikke at anvende OS og PFS på grund af de usikkerheder der er forbundet med dette.
Der er desuden i Medicinrådets protokol valgt at sammenligne brigatinib (Alunbrig) med alectinib og ikke efterfølgende behandlinger, hvormed ekskludering af efterfølgende kemoterapi fra ansøgers side også er relevant.

Amgros vælger at accepterer ansøgers modeltilgang.

2.1.2 Analyseperspektiv

Ansøger har indsendt en omkostningsanalyse med et begrænset samfundsperspektiv. Analysen har en tidshorisont der afspejler behandlingslængden for lægemidlerne, der ligger inden for 2 år. Ansøger har ikke diskonteret omkostninger der ligger efter år 1.

Amgros' vurdering

Analysens begrænsede samfundsperspektiv er i tråd med Amgros' retningslinjer og accepteres. Da ansøger ikke har diskonteret omkostninger efter år 1, udarbejder Amgros en ny analyse hvor omkostninger efter år 1 diskonteres med 4%.

2.1.3 Omkostninger

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

Lægemiddelomkostninger

Ansøger har inkluderet omkostninger til lægemidler. Anvendte doser er hentet i de respektive produkters SPC'er og priserne er fra Amgros, se tabel 1(4,5).

Tabel 1: Anvendte lægemiddelpriser, SAIP.

Lægemiddel	Styrke	Mg/dosis pr. dag	Pakningsstørrelse	Pris [DKK]	Kilde
Brigatinib (Alunbrig) første 7 dage	90 mg	90	7 stk.	[redacted]	Amgros
Brigatinib (Alunbrig) efterfølgende cyklus	180 mg	180	28 stk.	[redacted]	
Alectinib (Alecensa)	150 mg	1200	28 stk.	[redacted]	

Amgros' vurdering

Amgros accepterer ansøgers lægemiddelomkostninger.

Hospitalsomkostninger

Da brigatinib (Alunbrig) og alectinib administreres oralt, har ansøger ikke inkluderet nogle administrationsomkostninger. Ansøger antager lægebesøg og CT-scanning foretages hver 3. måned under behandlingen. Se tabel 4 og 5.

Tabel 4: Omkostninger til monitorering

	Enhedsomkostning [DKK]	Kode	Kilde
Ambulant besøg	672	BG50A	Ambulante DAGS-takser 2017
CT-scanning, kompliceret	2.033	PG14F	Ambulante DAGS-takser 2017

Tabel 5: Monitoreringsantal og omkostninger for brigatinib (Alunbrig) og alectinib for hele behandlingsperioden

	Brigatinib (Alunbrig)	Alectinib
Antal besøg	8	6
Totale omkostninger per patient	**16.264 DKK**	**12.198 DKK**

Amgros' vurdering

Ansøger har anvendt DAGS-takster fra 2017 uden at fremskrive disse til 2019-priser. Jævnfør Amgros' metodeguidelines skal enhedsomkostninger svare til nutidens værdier. Amgros fremskriver dermed ansøgers takster til 2019. Ansøger antager desuden at det ambulante besøg er inkluderet taksten CT-scanningen og ekskluderer

denne omkostning. På baggrund af klinikere inkluderer Amgros det ambulante besøg, da dette ikke er inkluderet i taksten for CT-scanning.

Ansøgers tilgang accepteres, men Amgros fremskriver DAGS-taksterne fra 2017 til 2019-værdier. Amgros inkluderer ligeledes ambulant besøg.

Omkostninger til bivirkninger

Ansøger har undersøgt omkostninger til behandlingsrelaterede bivirkninger. Ansøger har gjort dette gennem dialog med klinkere om 3- og 4-grads bivirkninger rapporteret i EPAR'en for brigatinib (Alunbrig) og alectinib.(6,7) Her er der argumenteret for hvilke bivirkninger der ville være omkostningsdrevne. Ansøger har ud fra dette vurderet at bivirkningerne for lægemidlerne ikke er behandlingskrævende udover dosisreducering. Ansøger medtager ikke dosisreducering i deres analyse. Ansøger ekskluderer omkostninger relateret til bivirkninger på baggrund af dette. Se tabel 6 og 7 for bivirkninger.

Tabel 6: Bivirkningsfrekvenser for brigatinib (Alunbring)

	[%]
Neoplastisk progression	8,2
Stigning i blod-kreatin-fosfokinase	14,5
Hypertension	10
Stigning i lipase	5,5
Pneumoni	5,5

Tabel 2: Bivirkningsfrekvenser for alectinib

	[%]
Influenza	0,8
Lungeinfektion	0,8
Pneumoni	0,8
Pulmonær embolisme	1,2
Dyspnø	1,2
Hæmoptyse	0,8

Amgros' vurdering

Ansøger har medtaget bivirkninger der forekommer med en frekvens over 5%. Da ingen bivirkninger for alectinib forekommer med en frekvens på over 5%, er disse ikke undersøgt. Amgros mener der er stor usikkerhed omkring ansøgers antagelse af de udvalgte bivirkninger ikke er behandlingskrævende. Amgros mener pneumoni kan være behandlingskrævende med et ressourceforbrug på 36.462 kr. for 2019 DRG- taksten 04MA14. Det kan derfor tyde på der generelt vil være højere omkostninger forbundet med bivirkninger ved brug af brigatinib (Alunbrig). Da studierne for brigatinib (Alunbrig) og alectinib er baseret på en naiv sammenligning, og opgjort forskellig i studierne, er det svært at vurdere forskellen i bivirkninger mellem de to lægemidler.
Yderligere er der i Medicinrådets vurderingsrapport angivet en ikkedokumenterbar klinisk merværdi i forbindelse med bivirkninger, men at data tyder på negativ værdi er grundlaget er for usikkert(8).

Amgros accepterer ansøgers tilgang, da omkostninger til bivirkninger har en meget lille betydning for det samlede resultat og er forbundet med stor usikkerhed grundet forskellig opgørelse af bivirkninger.

Patientomkostninger

Ansøger har valgt at inkludere omkostninger til patienttid. Dette er gjort på baggrund af lægemiddelmonitorerings besøg på hospitalet og inkluderer den effektive tid på hospitalet, ventetid og transporttid. Ansøgers estimerede patienttid kan ses i tabel.

Tabel 8: Ansøgers estimat af effektiv patienttid.

	Patienttid per besøg [minutter]
Konsultation	60
CT-scanning	30
Hospitalsbesøg	20
Patienttransporttid	90

Lægebesøg og CT-scanning antages af ansøger at ske ved samme. Ansøger anvender omkostninger til patienttransport på 100 DKK per besøg og 180 DKK per time for patienttiden. I tabel 3 er ansøgers estimerede patientomkostninger per måned vist.

Tabel 3: Ansøgers estimerede patientomkostninger i hele behandlingsperioden

	Brigatinib (Alunbrig)	Alectinib
Antal besøg i alt	9	7
Totale patientomkostninger [DKK]	**4.230**	**3.310**

Amgros' vurdering

Ansøgers metode er i overensstemmelse med Amgros' katalog for enhedsomkostninger. Amgros accepterer ansøger tilgang.

2.2 Følsomhedsanalyser

Ansøger har udarbejdet en række følsomhedsanalyser, hvor effekten af behandlingslængden, TOT, varieres med +/- 25%.

Ansøger har yderligere indsendt følsomhedsanalyser der sammenligner de inkrementelle omkostninger med ens behandlingslængde (baseret på alectinibs gennemsnitlige behandlingslængde) og de inkrementelle omkostninger per måned, for at vise betydningen af ens behandlingslængder.

Amgros' vurdering

Amgros mener ansøger følsomhedsanalyse er relevant, da behandlingslængden er den mest omkostningsdrevne faktor.

Amgros præsenterer ansøgers følsomhedsanalyser med ens behandlingslængde samt månedlige inkrementelle omkostning per patient, da vurderingsrapporten henviser til en ikkedokumenterbar klinisk merværdi jf. PFS, der definerer behandlingslængderne for brigatinib (Alunbrig) og alectinib(8). Amgros præsenterer de to følsomhedsanalyser i Amgros' følsomhedsanalyse baseret på Amgros' antagelser i hovedanalysen.

3 RESULTATER

3.1 Ansøgers hovedanalyse

Resultaterne fra ansøgers hovedanalyse præsenteres i tabel 4.

Ansøger estimerer i analysen de inkrementelle omkostninger per patient for brigatinib (Alunbrig) sammenlignet med alectinib til at være ca. [redacted], baseret på forskellige behandlingslængder jf. tabel 2.

Tabel 4: Resultatet af ansøgers hovedanalyse, DKK, SAIP

	Brigatinib (Alunbrig)	alectinib	Inkrementelle omkostninger
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Hospitalsomkostninger	16.264	12.198	4.066
Patientomkostninger	4.230	3.310	920
Totale omkostninger	[redacted]	[redacted]	[redacted]

Amgros' vurdering

Amgros accepterer de antagelser der ligger til grund for ansøgers hovedanalyse.

Amgros inkluderer dog ambulant besøg ved monitorering samt fremskriver DRG-takster til 2019-værdier. Amgros diskonterer omkostninger der ligger efter år 1. Ansøger har desuden antaget en måned på 30-dage. Amgros anvender i stedet 30,41 dage som gennemsnitlig antal dage på en måned.

3.2 Ansøgers følsomhedsanalyse

Resultaterne for ansøger følsomhedsanalyse, der viser inkrementelle omkostninger per patient, hvor behandlingslængden på begge lægemidler varierer med +/- 25%, præsenteres i tabel 11. Analysen er foretaget på lægemiddelomkostninger.

Tabel 11: Resultatet af ansøgers følsomhedsanalyse, hvor behandlingslængden varierer med +/- 25%, DKK, SAIP

	Brigatinib (Alunbrig)	Alectinib	Inkrementelle omkostninger
Hovedanalyse	[redacted]	[redacted]	[redacted]
+ 25 %	[redacted]	[redacted]	[redacted]
- 25 %	[redacted]	[redacted]	[redacted]

*Kun inkluderet lægemiddelomkostninger

3.3 Amgros' hovedanalyse

Amgros udarbejder egen hovedanalyse. Forudsætningerne er som i ansøgers analyse bortset fra følgende:

- Ambulant besøg inkluderes

- DAGS-takster fremskrives til 2019-værdier
- Omkostninger efter år 1 diskonteres med 4%
- Amgros anvender 30,41 dage som gennemsnitlig antal dage i en måned

Resultaterne fra Amgros' hovedanalyse præsenteres i tabel 12.

Amgros' hovedanalyse resulterer i gennemsnitlige meromkostninger per patient for brigatinib (Alunbrig) sammenlignet med alectinib på ca. [redacted].

Hvis analysen udføres på baggrund af AIP, bliver lægemiddelomkostningerne for brigatinib (Alunbrig) ca. 1 mio. DKK, mens de total inkrementelle omkostninger bliver ca. 248.000 DKK per patient.

Tabel 12: Resultatet af Amgros' hovedanalyse ved sammenligning med alectinib, DKK, SAIP

	Brigatinib (Alunbrig)	Alectinib	Inkrementelle omkostninger
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Hospitalsomkostninger	22.996	17.362	5.634
Patientomkostninger	4.156	3.274	882
Totale omkostninger	[redacted]	[redacted]	[redacted]

3.4 Amgros' følsomhedsanalyse

Amgros' følsomhedsanalyser ses i tabel 13 og 14.

Tabel 13 viser de inkrementelle omkostninger per patient, hvor behandlingslængden er ens mellem behandlingerne, baseret på de 16,78 måneder (den gennemsnitlige behandlingslængde for alectinib).

Tabel 13: Resultatet af Amgros' følsomhedsanalyse, hvor behandlingslængderne er ens, DKK, SAIP

	Brigatinib (Alunbrig)	Alectinib	Inkrementelle omkostninger
Ens behandlingslængde (16,78 måneder)	[redacted]	[redacted]	[redacted]

*kun lægemiddelomkostninger, da monitoreringsomkostninger er antaget ens per måned

Tabel 14 viser de inkrementelle omkostninger per patient per måned.

Tabel 14: Resultatet af Amgro's følsomhedsanalyse, inkrementelle omkostninger per patient per måned, DKK, SAIP

	Brigatinib (Alunbrig)	Alectinib	Inkrementelle omkostninger
Totale omkostninger per måned (DKK)	[redacted]	[redacted]	[redacted]

*Kun baseret på lægemiddelomkostninger

4 BUDGETKONSEKVENSER

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

- Brigatinib (Alunbrig) bliver anbefalet som standardbehandling af Medicinrådet til indikationen, som denne analyse omhandler
- Brigatinib (Alunbrig) bliver ikke anbefalet som standardbehandling

Budgetkonsekvenserne bliver differencen mellem budgetkonsekvenserne i de to scenarier.

4.1 Ansøgers estimater

4.1.1 Patientpopulation og markedsandel

Tabel 15 viser ansøgers estimat af antal patienter årligt.
Ansøger antager, da det er patienter der har modtaget crizotinib og dermed er en patientgruppe der ikke kan tåle alectinib, ca. vil være 5 patienter årligt som kandiderer til behandlingen. Ansøger antager at hvis brigatinib (Alunbrig) anbefales vil alle 5 patienter modtage brigatinib (Alunbrig). Ansøger beregner år 1 til kun at inkluderer 6 måneder, grundet tidspunkt for vurderingen. Patientantal forskydes således et halvt år. Da patienter behandles i knap to år, vil forskydningen resulterer i at flest patienter behandles i år 3.

Tabel 15: Ansøgers estimat af antal nye patienter per år.

	Anbefales som standardbehandling						Anbefales ikke som standardbehandling				
	År 1	År 2	År 3	År 4	År 5		År 1	År 2	År 3	År 4	År 5
Brigatinib (Alunbrig)	5	5	5	5	5		0	0	0	0	0
Alectinib	0	0	0	0	0		5	5	5	5	5

Amgros' vurdering af estimeret antal patienter

Ud fra Medicinrådet protokol, vurderes at ansøgers estimat af patientantal er det maksimale antal patienter, der sandsynligvis vil behandles per år(1).

Amgros accepterer ansøgers tilgang til budgetkonsensanalysen.

4.1.2 Estimat af budgetkonsekvenser

Ansøger har inkluderet de samme omkostninger i budgetkonsekvensanalysen, som der er inkluderet i omkostningsanalysen.
Med de indlagte antagelser estimerer ansøger, at anvendelse af brigatinib (Alunbrig) vil resultere i budgetkonsekvenser på ca. [redacted] i år 5.
Ansøgers estimat af budgetkonsekvenserne fremgår af tabel 16.

Tabel 16: Ansøgers hovedanalyse for totale budgetkonsekvenser, mio. DKK, SAIP, 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' vurdering

Amgros accepterer ansøgers budgetkonsekvensanalyse.

4.2 Amgros' estimater af budgetkonsekvenser

Amgros anvender ansøgers budgetkonsekvens analyse baseret på Amgros' hovedanalyse.

Amgros estimerer budgetkonsekvenser, ved anvendelse af brigatinib (Alunbrig) til ca. [redacted] i år 5. Se tabel 17.

Hvis analysen udføres med AIP bliver budgetkonsekvenserne ca. 1,3 mio. DKK i år 5 og efterfølgende år.

Tabel 17: Amgros' analyse af totale budgetkonsekvenser, mio. DKK, SAIP, 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]

5 DISKUSSION

Behandling med brigatinib (Alunbrig) er forbundet med betydelige meromkostninger sammenlignet med behandling med alectinib. Meromkostningerne er næsten udelukkende drevet af lægemiddelomkostningerne og behandlingslængden for brigatinib (Alunbrig) og alectinib. Derfor afhænger estimatet af de inkrementelle meromkostninger i altovervejende grad af behandlingslængden baseret på PFS for de to behandlinger.

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Høringssvar til Medicinrådet

Vedrørende udkastet til Medicinrådets vurdering af klinisk merværdi for Alunbrig® til behandling af ALK-positiv ikke-småcellet lungekræft

Kære Jane Skov,

Takeda takker for muligheden for, at komme med bemærkninger til Medicinrådets vurdering af klinisk merværdi af Alunbrig® til behandling af ALK-positiv ikke-småcellet lungekræft. Vi har ingen indvendinger i forhold til den tildelte kategorisering af merværdi.

Derimod ønsker Takeda at benytte lejligheden til, at understrege vigtigheden af, at Alunbrig® stilles til rådighed for den indikationsbestemte patientgruppe hurtigst muligt. Indikationen er målrettet en patientgruppe som befinder sig i et fremskredent sygdomsstadie, og givet, at sygdommen er uhelbredelig er der derfor et uopsætteligt behov for effektiv behandling nu og her. Takeda har og har haft en hurtig godkendelse af lægemidlet som standardbehandling til denne patientgruppe som sin øverste prioritet. Af denne grund stillede vi tidligere i ansøgningsprocessen forslag om, hvorledes processen kunne afsluttes med 12 ugers sagsbehandlingstid. Dette af hensyn til patienterne, lægerne, Medicinrådets ressourcer og Takedas mulighed for, at stille lægemidler til rådighed på det danske marked.

Takeda ønsker derudover, at pointere, at der er afgørende forskel i, hvordan Medicinrådets og Amgros anvender endepunktet progressionsfri overlevelse (PFS) som beslutningsgrundlag i processen.

Medicinrådet konkluderer, som forventet, at der er en ikkedokumenterbar merværdi forbundet med de i ansøgningen vurderede endepunkter. Årsagen hertil er, at evidensen kun understøtter absolutte værdier og dermed udelader relative værdier og konfidensinterval. Modsat fastholder Amgros, på trods af, at Medicinrådet har konkluderet, at den reelle PFS for Alunbrig® ikke kan dokumenteres præcist, at anvende en fastlåst middel PFS på ca. 22 måneder, vurderet imod godt 17 måneders gennemsnitlig PFS for Alecensa®.

Konsekvensen er, at Alunbrig® på et ikke transparent beslutningsgrundlag fremhæves som værende omkostningsmæssigt tungere, sammenlignet med Alecensa®.

Takeda præsenterede i den sundhedsøkonomiske evidens, meromkostningerne fra tre vinkler. De totale behandlingsrelaterede omkostninger (PFS på hhv. 22 og 17 måneder), de ligestillede omkostninger (PFS på hhv. 17 vs. 17 måneder) og endeligt de marginale omkostninger (PFS-forlængelse på 5 måneder for Alunbrig®).

[redacted]

Med venlig hilsen

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Medicinrådet

Medicinrådets vurdering af klinisk merværdi for brigatinib til behandling af ALK-positiv ikke-småcellet lungekræft

Versionsnr.: 1.0

Medicinrådet

Om Medicinrådet

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

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

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

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

Om vurderingen af klinisk merværdi

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

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

Lægemidlet vurderes efter Metodehåndbog for Medicinrådets arbejde med at udarbejde fælles regionale vurderinger af nye lægemidlers og nye indikationers kliniske merværdi – version 1. Se Medicinrådets metodehåndbog for yderligere information.

Dokumentoplysninger	
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Indhold

1 Lægemiddelinformationer

Lægemidlets oplysninger	
Handelsnavn	Alunbrig
Generisk navn	Brigatinib
Firma	Takeda Pharma
ATC-kode	L01XE43
Virkningsmekanisme	Anaplastisk Lymfom Kinase (ALK)-hæmmer
Administration/dosis	Tablet 90 mg én gang dagligt i de første syv dage og derefter 180 mg én gang dagligt.
EMA-indikation	Alunbrig er indiceret som monoterapi til behandling af voksne patienter med fremskreden anaplastisk lymfom-kinase (ALK)-positiv, ikke-småcellet lungecancer (NSCLC), som tidligere har fået behandling med crizotinib.

2 Medicinrådets konklusion vedrørende klinisk merværdi

Medicinrådet vurderer, at brigatinib til patienter med ALK-positiv ikke-småcellet lungekræft, som tidligere er behandlet med crizotinib, giver en **ikkedokumenterbar klinisk merværdi** sammenlignet med alectinib. Evidensens kvalitet kan ikke defineres.

Medicinrådet kategoriserer lægemidlers kliniske merværdi i en af følgende kategorier:

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

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

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

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

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

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

3 Forkortelser

ALK:	Anaplastisk lymfom kinase (*Anaplastic Lymphoma Kinase)*
ARR:	Absolut risikoreduktion
CI:	Konfidensinterval
CNS:	Centralnervesystem
EMA:	Det Europæiske Lægemiddelagentur (*European Medicines Agency)*
EORTC QLQ-C30:	*European Organisation for Research and Treatment of Cancer Quality-of-life Questionnaire-Core 30*
EORTC QLQ-L13:	*European Organisation for Research and Treatment of Cancer Quality-of-life Questionnaire-Lung Cancer 13*
EPAR:	*European public assessment report*
GRADE:	System til vurdering af evidens (*Grading of Recommendations Assessment, Development and Evaluation*)
HR:	*Hazard ratio*
ITT:	*Intention to treat*
MAIC:	*Matched adjusted indirect comparison*
NSCLC:	Ikke-småcellet lungekræft (*Non Small Cell Lung Cancer)*
OR:	*Odds ratio*
OS:	Overlevelse (*overall survival)*
ORR:	Objektiv responsrate
PFS:	Progressionsfri overlevelse (*Progression-Free Survival)*
RR:	Relativ risiko
TKI:	Tyrosinkinasehæmmer

4 Formål

Formålet med Medicinrådets vurdering af klinisk merværdi af brigatinib til patienter med ALK-positiv ikke-småcellet lungekræft, som tidligere er behandlet med crizotinib, er at vurdere den kliniske merværdi i forhold til et eller flere lægemidler til samme patientgruppe.

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

5 Baggrund

Lungekræft

I 2017 blev 4.856 danskere diagnosticeret med lungekræft [1], og dermed er lungekræft en af de hyppigst forekommende kræftsygdomme i Danmark [2]. Af de diagnosticerede har ca. 85 % ikke-småcellet lungekræft (NSCLC) [3]. I slutningen af 2015 levede knap 10.450 personer med lungekræft, mens cirka 3.700 personer årligt dør af lungekræft [4]. Lungekræft har således en høj dødelighed med den senest opgjorte etårs-overlevelse i Danmark på 50,8 % for samtlige nydiagnosticerede patienter [1].

Lungekræft inddeles i fire stadier (I-IV) afhængigt af udbredelsesgrad [5]. De epidemiologiske data i dette afsnit stammer fra Tumor Node Metastasis (TNM) 7-klassifikationen. Der er efterfølgende indført TNM 8-klassifikation i såvel Danmark som internationalt. Stadie III betyder, at tumor enten har en vis størrelse, indvækst i nærliggende struktur eller spredning til regionale lymfeknuder. Metastatisk lungekræft betegnes som stadie IV, der som udgangspunkt betragtes som uhelbredelig. Nogle patienter med NSCLC i stadie III betragtes også som havende uhelbredelig lungekræft og behandles som patienter i stadie IV.

Man kender mange biomarkører, hvoraf enkelte har betydning for behandlingen. En af dem er anaplastisk lymfom kinase (ALK)-translokation [6]. I 2016 var andelen af patienter med ALK-translokation i Danmark 1,7 % (svarende til 35 patienter) hos patienter med adenokarcinom m.fl. [1]. Dette skal ses i lyset af, at ALK-status ikke blev registreret hos omkring hver femte patient diagnosticeret med adenokarcinom m.fl. [1].

Mange patienter med ALK-positiv NSCLC vil med tiden få progression i centralnervesystemet (CNS) [7]. Generelt beskrives incidensen af hjernemetastaser blandt patienter med ALK-positiv NSCLC som værende høj. Således havde ca. 70 % af de patienter, som indgik i det pivotale studie af brigatinib, hjernemetastaser ved studiets begyndelse [8]. Lungekræftpatienter med hjernemetastaser oplever betydelig morbiditet og reduceret livskvalitet, ofte med neurologiske dysfunktioner, kognitive ændringer og en forringet overlevelse [7,9].

5.1 Nuværende behandling

Crizotinib har tidligere af KRIS været anbefalet som førstelinjebehandling til uhelbredelig ALK-positiv NSCLC. Den 30. maj 2018 anbefalede Medicinrådet imidlertid alectinib som mulig standardbehandling i første linje [10] foretrukket frem for crizotinib. Tilsvarende beskriver Dansk Onkologisk Lungecancer Gruppes (DOLG) kliniske retningslinjer alectinib som førstelinjebehandling til patienter med uhelbredelig ALK-positiv NSCLC [11].

Brigatinib kan ifølge EMA-indikationen kun anvendes til patienter, der har fået behandling i første linje med crizotinib. Størstedelen af danske patienter behandles nu i første linje med alectinib. Fagudvalget vurderer, at gruppen af danske patienter, der er kandidater til brigatinib i anden linje efter crizotinib, omfatter 0-5

patienter årligt. Dette kan eksempelvis dreje sig om patienter, der enten indledte behandling med crizotinib før alectinib blev anbefalet af Medicinrådet som mulig standardbehandling i første linje, eller patienter, som ikke tåler alectinib.

5.2 Brigatinib

Brigatinib er en tyrosinkinasehæmmer (TKI) med specifik aktivitet mod blandt andet ALK. Ved at hæmme ALK reduceres aktiviteten af centralt placerede molekyler i signaleringskaskader af betydning for cellulær overlevelse, vækst og proliferation [12].

Brigatinib har EMA-indikation som monoterapi til behandling af voksne patienter med fremskreden ALK-positiv NSCLC, som tidligere har fået behandling med crizotinib.

Brigatinib administreres oralt som en enkelt tablet dagligt indtil sygdomsprogression eller uacceptable bivirkninger. Efter en syv-dages indkøringsperiode med 90 mg én gang dagligt, øges dosis til 180 mg én gang dagligt.

6 Metode

De præspecificerede metoder i protokollen er udarbejdet af Medicinrådet. Ansøgningen er valideret af Medicinrådet.

Ansøger har anvendt og fulgt den præspecificerede metode, jf. protokollen, som blev godkendt i Medicinrådet den 4. februar 2019.

I protokollen opstillede fagudvalget følgende kliniske spørgsmål, som vil blive besvaret i denne rapport:

Hvad er den kliniske merværdi af brigatinib til patienter med uhelbredelig ALK-positiv ikke-småcellet lungekræft, som tidligere har fået behandling med crizotinib?

Den endelige ansøgning blev modtaget den 27. marts 2019.

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

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

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

7 Litteratursøgning

Ansøger har foretaget litteratursøgning, jf. protokollens beskrivelse. Søgningen er udført den 20. marts 2019 i PubMed- og Cochrane Central-databaserne. Ansøger har identificeret otte artikler:

Tabel 1. Publikationer identificeret af ansøger

	Reference	Klinisk forsøg	Indgår direkte i datagrundlag for denne vurdering
1	Gettinger SN, Bazhenova LA., Langer CJ, et al., Activity and safety of brigatinib in ALK- rearranged non-small-cell lung cancer and other malignancies: a single-arm, open-label, phase 1/2 trial. Lancet Oncol 2016; 17:1683-96 [13]	Brigatinib til forskellige typer kræft	Nej, grundet det lave antal relevante patienter
2	Kim DW, Tiseo M, Ahn MJ, et al, Brigatinib in patients with crizotinib-refractory anaplastic lymphoma kinase-positive non-small-cell lung cancer: a randomized, multicenter phase II trial, J Clin Oncol 2017, 35:2490-98 [14]	Brigatinib i to doseringer til NSCLC (fase II)	Ja
3	Shaw AT. Gandhi L, Gadgeel S et al, Alectinib in ALK-positive, crizotinib-resistant, non-small-cell lung cancer; a single-group, multicentre. phase 2 trial, Lancet Oncol 2015, 17(2); 234-42 [15]	Alectinib (fase II)	Ja
4	Ou SH, Ahn JS, De Petris L, et al, Alectinib in crizotinib-refractory ALK-rearranged non-small-cell lung cancer: a phase II global study, J Clin Oncol 2016, 34;661-68 [16]	Alectinib (fase II)	Ja
5	Novello S, Mazieres J, de Castro J et al, Alectinib versus chemotherapy in crizotinib-pretreated anaplastic lymphoma kinase (ALK)-positive non-small-cell lung cancer: results from the phase III ALUR study, Ann Oncol 2018, 29(6);109-16 [17]	Alectinib vs. kemoterapi (fase III)	Ja
6	Gadgeel SM, Shaw AT, Govindan R, et al, Pooled analysis of CNS response to alectinib in two studies of pretreated patients with ALK-positive non-small cell lung cancer, J Clin Oncol 2016, 34;4079-85 [18]	Poolede data vedr. alectinib	Indgår for effektmålet CNS-progression
7	Camidge DR, Kim DW, Tiseo M, et al, Exploratory analysis of brigatinib activity in patients with anaplastic lymphoma kinase-positive non-small cell lung cancer and brain metastases in two clinical trials, J Clin Oncol 2018, 36(26);2693-2701 [19]	Poolede data vedr. brigatinib	Indgår for effektmålet CNS-progression
8	Reckamp K, Lin HM, Huang M, et al, Comparative efficacy of brigatinib versus ceritinib and alectinib in patients with crizotinib-refractory anaplastic lymphoma kinase-positive non-small cell lung cancer, Current Medical Research and Opinion 2019, 35(4); 569-76 [20]	Indirekte *matched* analyse af brigatinib vs. andre lægemidler	Nej, men bruges som supplement

Ansøger har fundet to artikler, som dækker to separate studier af brigatinib, tre artikler, som dækker tre studier af alectinib, og tre artikler, som samler flere af disse studier.

Fagudvalget har valgt at inkludere publikation nr. 2 for data angående effekten af brigatinib, da dette studie (ALTA) inkluderede patienter i den relevante målgruppe og undersøger den beskrevne dosering af brigatinib. Fagudvalget har ekskluderet publikation nr. 1, da der kun indgår 42 patienter med ALK-translokation, som tidligere er behandlet med crizotinib, og kun 24 patienter får relevant dosering. Da antallet af relevante patienter i dette studie er markant lavere end i fire andre studier (ét af brigatinib og tre af alectinib), er usikkerhederne på estimaterne også større, og data er derfor ikke inkluderet i den narrative syntese.

For alectinib er alle tre artikler inkluderet. Herudover er data fra artikel 6 anvendt til vurdering af effektmålet CNS-progression.

MAIC-analysen fra artikel 8 indgår som supplement til den narrative analyse.

Der er udover de ovenstående artikler anvendt data fra EPAR'en for brigatinib [8] og alectinib [21] (ref.) (version fra 2016) til vurdering af data angående sikkerhed af lægemidlerne og data med længere opfølgningstid end i de publicerede artikler.

8 Databehandling

Narrativ syntese

Ansøger har udført en narrativ syntese af data fra kliniske studier og suppleret med en publiceret såkaldt *matched adjusted indirect comparison* (MAIC-analyse). MAIC-analysen betragtes som et supplement til den narrative syntese og ikke som et formelt sammenligningsgrundlag. Dette skyldes, at datagrundlaget i MAIC-analysen er mindre end i den narrative syntese, og at oplysninger om vægtninger i MAIC-analysen ikke har været tilgængelige (se bilag 1).

Tidshorisont

Der er data tilgængeligt med opfølgningstid på op til 24,3 måneder for brigatinib og mellem 6,5 og 21 måneder for alectinib i de respektive studier. Dette er nærmere beskrevet i studiekarakteristika og for de enkelte effektmål, hvor det er relevant.

Vurdering af datagrundlag

Medicinrådets sekretariat og fagudvalget finder, at vurderingen af klinisk merværdi kan foretages på baggrund af de indsendte analyser med følgende bemærkninger:

- Det understreges, at lægemidlerne er sammenlignet med en narrativ syntese, hvilket er lavere i evidenshierarkiet end en direkte eller indirekte sammenligning.
- MAIC-analysens resultater indgår kun som et supplement til den narrative syntese og ikke som et formelt sammenligningsgrundlag. Vurderingerne af klinisk merværdi er baseret på den narrative syntese. En beskrivelse af MAIC-analysen er vedlagt som bilag 1. I ansøgers endelige ansøgning beskrives flere MAIC-analyser (med forskellige tidshorisonter), og der indgår også en MAIC-analyse i EMAs EPAR. Medicinrådets sekretariat og fagudvalget har baseret beskrivelsen på den MAIC-analyse, der er publiceret i artikelform [20].
- En mindre del af ansøgers endelige ansøgning er baseret på upublicerede data, hvorfor fagudvalget ser bort fra disse.

- For de to effektmål 'behandlingsophør grundet uønskede hændelser' og 'alvorlige uønskede hændelser grad 3-4' har ansøger angivet resultater, som er forskellige fra de tal, som er i EPAR og publikationer for brigatinib. Forskellen er, at ansøger har udeladt '*neoplasm progression',* fordi denne hændelse skyldes en progression af selve sygdommen. Fagudvalget vurderer, at det ikke påvirker kategoriseringen af de relevante effektmål, om disse hændelser indgår eller ej.
- På effektmålet alvorlige uønskede hændelser grad 3-4 har ansøger indleveret data for alvorlige uønskede hændelser grad 3-5, hvilket fagudvalget har accepteret.
- Der er data for brigatinib fra mange forskellige cut-offs, og tidspunktet for aflæsning af data har stor betydning, især for effektmål for overlevelse og sikkerhed. Medicinrådets sekretariat og fagudvalget har i størst muligt omfang forsøgt at basere de narrative sammenligninger på publicerede data med længst mulig opfølgningstid. I denne vurderingsrapport har usikkerhederne grundet tidshorisonter mindre betydning for effektmålene PFS, ORR og CNS-progression.

Medicinrådets sekretariat har ikke fundet anledning til at foretage ændringer af beregninger foretaget af ansøger eller supplere med yderligere beregninger.

9 Klinisk merværdi

9.1 Konklusion klinisk spørgsmål 1

Hvad er den kliniske merværdi af brigatinib til patienter med uhelbredelig ALK-positiv ikke-småcellet lungekræft, som tidligere har fået behandling med crizotinib?

Fagudvalget vurderer, at brigatinib til patienter med ALK-positiv ikke-småcellet lungekræft, som tidligere er behandlet med crizotinib, giver en **ikkedokumenterbar merværdi** sammenlignet med alectinib. Evidensens kvalitet kan ikke defineres.

9.1.1 Gennemgang af studier

Karakteristika:

For brigatinib indgår én publiceret artikel på baggrund af et randomiseret fase II-studie (NCT02094573, ALTA), hvor i alt 222 patienter blev randomiseret til to forskellige doseringer af brigatinib [14]. Kun den behandlingsarm (n = 110), som modtog den relevante dosering (90-180 mg), indgår i denne vurdering. Patienterne havde progredieret på crizotinib, og tidligere behandling med kemoterapi var tilladt. Patienterne blev stratificeret efter hjernemetastaser og bedste respons på crizotinib. Det primære endepunkt var objektiv responsrate (ORR) bestemt af investigator. Andre relevante endepunkter var ORR bestemt af en central uafhængig komité, CNS-respons, progressionsfri overlevelse (PFS), overall survival (OS), sikkerhed og livskvalitet.

I denne vurdering benyttes data fra EMAs EPAR i stort omfang angående dette kliniske studie, da de har en længere opfølgningstid. I EPAR'en indgår data fra forskellige cut-offs med mellem 10,8 og 24,3 måneders median opfølgning.

For alectinib indgår tre publicerede artikler:

I et fase II-studie udført i USA og Canada (NCT01871805) blev 87 patienter inkluderet. Patienterne havde progredieret på crizotinib, og tidligere behandling med kemoterapi var tilladt. Det primære endepunkt var

ORR bestemt af en uafhængig komite. Andre relevante endepunkter var CNS-respons, sikkerhed og PFS [15]. For dette studie er der data med en median opfølgningstid på 17 måneder i EPAR'en.

I et globalt fase II-studie (NCT01801111) blev 138 patienter inkluderet. Patienterne havde progredieret på crizotinib. Det primære endepunkt var ORR bestemt af en uafhængig komité. Andre relevante endepunkter var sikkerhed, PFS og OS [16]. For dette studie er der data med en median opfølgningstid på 21 måneder i EPAR'en.

I et randomiseret fase III-ublindet studie i Europa og Asien (NCT0260430342) blev 107 patienter randomiseret 2:1 til alectinib (n = 72) eller kemoterapi. Patienter i kemoterapi-armen indgår ikke i denne vurdering. Patienterne havde progredieret på crizotinib og modtaget kemoterapi. Patienterne blev stratificeret efter hjernemetastaser, performance status (PS), og om de havde modtaget radioterapi på hjernen. Det primære endepunkt var PFS bestemt af *investigator*. Andre relevante endepunkter var ORR, PFS bestemt af en uafhængig komité, CNS-progression og OS [17]. For dette studie er der data med en median opfølgningstid på 6,5 måneder i den publicerede artikel.

Populationer

Af tabel 2 fremgår baselinekarakteristika for patientpopulationerne i de inkluderede studier:

Tabel 2: Baselinekarakteristika for studiepopulationerne

	Brigatinib NCT02094573 ALTA Arm B (90 mg – 180 mg)	Alectinib 1 NCT01871805	Alectinib 2 NCT01801111	Alectinib 3 NCT0260430342 (alectinib-arm)
	N = 110	N = 87	N = 138	N = 72
Alder (median, range)	56,5 (20-81)	54 (29-76)	51,5 (11,1)*	55,5 (21-82)
Mænd (%)	42	45	44	41
ECOG Performance Status 0-1/2 (%)	92/8	83/10	91/9	92/8
Hjernemetastaser (%)	67	52	84	47
Tidligere behandling med kemoterapi (%)	74	74	80	100

*middelværdi og standardafvigelse

Fagudvalget finder, at studiepopulationerne generelt er sammenlignelige angående de beskrevne baselinekarakteristika, omend der er forskel på andel af patienter med hjernemetastaser imellem de tre alectinib- studier.

Fagudvalget bemærker, at de fleste patienter tidligere er behandlet med kemoterapi udover behandlingen med crizotinib, hvilket ikke er i overensstemmelse med aktuel dansk klinisk praksis, men at det ikke har nogen betydning for vurderingen af brigatinib vs. alectinib.

9.1.2 Resultater og vurdering

Resultater og vurdering af de effektmål, som fagudvalget har præspecificeret som hhv. kritiske og vigtige, følger nedenfor.

Overlevelse (kritisk)

Forbedret samlet overlevelse (OS) med mindst mulig toksicitet er det optimale mål for behandling af NSCLC. OS er derfor et kritisk effektmål. Fagudvalget vurderer, at et lægemiddel, der medfører en median forlængelse af levetiden med mindst 3 måneder, har en positiv klinisk merværdi vedrørende dette effektmål.

Tabel 3: Vurdering af klinisk merværdi: Overlevelse

	Forhåndsdefineret grundlag for vurdering	Brigatinib vs. alectinib
Absolutte forskelle	3 måneder	34,1 måneder vs. 22,7 måneder, 26,0 måneder og 12,6 måneder
Evidensens kvalitet	Kan ikke defineres	

For brigatinib er den mediane overlevelse 34,1 måneder [27,7; ikke opnået] [20] og 80,1 % var i live efter 12 måneder. På det tidspunkt hvor median overlevelse blev opgjort i EMAs EPAR, var 40 ud af 110 patienter døde.

I de tre studier af alectinib var den mediane OS henholdsvis 22,7 måneder [17,2; ikke opnået] [21], 26,0 måneder [21,5; ikke opnået] [21] og 12,6 måneder [9,7; ikke opnået] [17]. Data stammer fra EPAR'en for de to fase II-studier, og den publicerede artikel for fase III-studiet. For sidstnævnte er data i artiklen angivet som ikke-modne, eftersom der kun var 20 % døde i alectinib-armen. Derfor er den naive sammenligning med dette studie ikke meningsfuld. Den umiddelbare forskel mellem brigatinib og alectinib (min. 8 måneder) overstiger således den mindste klinisk relevante forskel på 3 måneder.

I de sammenligninger, der indgår i den supplerende MAIC-analyse (se bilag 1), er der data for brigatinib efter en opfølgningstid på 18,6 måneder. Her er den mediane overlevelse ved behandling med brigatinib angivet som 27,6 måneder, hvilket er henholdsvis 4,9 og 1,6 måneder længere end for alectinib i de to studier, der sammenlignes med. Størrelsen på den angivne mediane overlevelse er afhængig af opfølgningstid, hvilket skyldes censureringer. Spekulativt kunne OS for alectinib således også ændre sig, hvis data analyseres ved et senere opfølgningstidspunkt. Dette demonstrerer, hvor stor usikkerheden er ved denne naive sammenstilling. Selvom brigatinib umiddelbart forekommer at give en stor gevinst på effektmålet overlevelse, når tabel 3's tal sammenlignes, må disse tolkes med væsentlige forbehold.

Fagudvalget vurderer, at brigatinib har en ikkedokumenterbar klinisk merværdi på effektmålet overlevelse sammenlignet med alectinib. Evidensens kvalitet kan ikke defineres.

Behandlingsophør grundet uønskede hændelser (kritisk)

Fagudvalget finder, at ophør med en effektiv behandling er kritisk for patienterne. Derfor sættes behandlingsophør grundet uønskede hændelser som et kritisk effektmål. Fagudvalget vurderer, at den mindste klinisk relevante forskel er 5 % sammenlignet med alectinib.

Tabel 4. Vurdering af klinisk merværdi: Behandlingsophør grundet bivirkninger

	Forhåndsdefineret grundlag for vurdering	Brigatinib vs. alectinib
Absolutte forskelle	ARR 5 %	10,9 % vs. 2,3 %, 8,7 % og 5,5 %
Evidensens kvalitet	Kan ikke defineres	

Ifølge ansøgers endelige ansøgning [22] var der 10,9 % af patienterne i ALTA-studiet (12 ud af 110), som i løbet af 24,3 måneder stoppede med brigatinib på grund af en uønsket hændelse. I de tre studier af alectinib var der henholdsvis 2,3 [21], 8,7 [21] og 5,7 % [17] af patienterne, som stoppede med behandlingen grundet uønskede hændelser (18 ud af 295 og samlet 6,1 %) i løbet af de 17/21/6,5 måneder. Data vedr. alectinib stammer fra EPAR'en for de to fase II-studier, og den publicerede artikel for fase III-studiet. Der er en stor usikkerhed på denne naive sammenligning grundet de forskellige udviklingsprogrammer og især forskellig opfølgningstid i studierne.

Den naive sammenstilling viser en absolut forskel, der samlet set er lavere end den forhåndsdefinerede mindste klinisk relevante forskel.

Fagudvalget gør opmærksom på, at uønskede hændelser ikke er opgjort ens i de to lægemidlers udviklingsprogrammer (for brigatinib indgår progression af kræftsygdom som en uønsket hændelse), og at opfølgningstiden er længere for brigatinib. Ansøger angiver i den endelige ansøgning, at kun 9,1 % af patienterne i ALTA-studiet stoppede med brigatinib på grund af en uønsket hændelse, hvis data renses for de patienter, der progredierede [22].

Fagudvalget vurderer, at der er en ikkedokumenterbar klinisk merværdi for brigatinib sammenlignet med alectinib, da forskelle i opfølgningstid og opsamling af data om behandlingsophør er forskellige i studierne. Evidensens kvalitet kan ikke defineres.

CNS-progression (kritisk)

Da ALK-positiv NSCLC ofte metastaserer til centralnervesystemet med betydelig morbiditet og reduceret livskvalitet til følge, anser fagudvalget *CNS-progression* som et vigtigt effektmål. Fagudvalget vurderer, at en forskel i median på 3 måneder er klinisk relevant.

Tabel 5: Vurdering af klinisk merværdi: CNS-progression

	Forhåndsdefineret grundlag for vurdering	Brigatinib vs. alectinib
Absolutte forskelle	3 måneder	18,4 måneder vs. 8,3 måneder
Evidensens kvalitet	Kan ikke defineres	

Den mediane CNS-PFS for brigatinib er 18,4 måneder [12,8; ikke opnået] [22]. I en poolet analyse af to ud af de tre studier af alectinib var den samlede mediane CNS-PFS 8,3 måneder [5,9; 11,2] [18] (fase III-studiet af alectinib indgik ikke i den publicerede opgørelse af CNS-respons).

Den umiddelbare forskel mellem lægemidlerne (ca. 10 måneder) overstiger således den mindste klinisk relevante forskel på 3 måneder, men størrelsen af effektforskellen er usikker grundet den naive sammenligning.

Fagudvalget vurderer, at brigatinib har en ikkedokumenterbar klinisk merværdi på effektmålet CNS-progression sammenlignet med alectinib. Med ikkedokumenterbar mener fagudvalget angående dette effektmål, at der på det eksisterende datagrundlag ser ud til at være en positiv merværdi af brigatinib, men at størrelsen af denne ikke kan vurderes. Evidensens kvalitet kan ikke defineres.

Progressionsfri overlevelse (PFS, vigtig)

PFS anvendes til vurdering af sygdomsprogression og er et relevant og ofte benyttet effektmål i onkologiske studier. Fagudvalget vurderer, at et lægemiddel, der medfører en median forlængelse af PFS på mindst 3 måneder, har en positiv klinisk merværdi vedrørende PFS.

Tabel 6: Vurdering af klinisk merværdi: PFS

	Forhåndsdefineret grundlag for vurdering	Brigatinib vs. Alectinib
Absolutte forskelle	3 måneder	16,7 måneder vs. 8,2 måneder, 8,9 måneder og 7,1 måneder
Evidensens kvalitet	Kan ikke defineres	

Den mediane PFS for brigatinib er på 16,7 måneder [11,6; ikke opnået] i EPAR'en [8]. I de tre studier af alectinib var den mediane PFS henholdsvis 8,2 [6,3; 12,6] [21], 8,9 [5,6; 12,8] [21] og 9,6 måneder [6,9; 12,2] [17]. Data stammer fra EPAR'en for de to fase II-studier, og den publicerede artikel for fase III-studiet. Den naive forskel mellem lægemidler (min. 7 måneder) overstiger således den mindste klinisk relevante forskel på 3 måneder men er usikker grundet manglende konfidensinterval.

Data for PFS for brigatinib er i mindre grad end data for OS påvirket af forskellene i opfølgningstid for brigatinib, hvilket kan tilskrives, at medianen for PFS er tættere på den mediane opfølgningstid end den mediane overlevelse er. Den usikkerhed, som sås for overlevelse grundet forskelle i opfølgningstid, er altså mindre for PFS.

Således ser der for dette effektmål ud til at være en konsistent og stor umiddelbar forskel mellem brigatinib og alle tre studier af alectinib. Data tyder på en positiv merværdi af brigatinib på dette effektmål.

Fagudvalget vurderer, at brigatinib har en ikkedokumenterbar klinisk merværdi på effektmålet PFS sammenlignet med alectinib. Med ikkedokumenterbar mener fagudvalget angående dette effektmål, at der på det eksisterende datagrundlag ser ud til at være en positiv merværdi af brigatinib, men at størrelsen af denne ikke kan vurderes. Evidensens kvalitet kan ikke defineres.

Alvorlige uønskede hændelser (grad 3-4, vigtig)

Forekomst af alvorlige uønskede hændelser grad 3-4 er et udtryk for bl.a. alvorlig toksicitet af lægemidlet [23]. Fagudvalget anser grad 3-4 alvorlige uønskede hændelser som et vigtigt effektmål og vurderer, at lægemidlet har en negativ klinisk merværdi vedrørende effektmålet, hvis det medfører alvorlige uønskede hændelser hos mere end 5 % af patienterne i forhold til placebo.

Ansøger har indleveret data for uønskede hændelser grad 3-5, hvor fatal toksicitet indgår, hvilket fagudvalget har accepteret.

Tabel 7: Vurdering af klinisk merværdi: Alvorlige uønskede hændelser

	Forhåndsdefineret grundlag for vurdering	Brigatinib vs. alectinib
Absolutte forskelle	ARR 5 %	70,9 % vs. 41,4 %, 39,9 % og 25,7 %
Evidensens kvalitet	Kan ikke defineres	

I ALTA-studiet oplevede 70,9 % af patienterne en alvorlig uønsket hændelse grad 3-5, ifølge EPAR'en for brigatinib, i løbet af 24,3 måneder [8]. I dette tal indgår *neoplasm progression* (forværring af kræftsygdom) som en uønsket hændelse. For alectinib oplevede henholdsvis 41,4 % [21], 39,9% [21] og 25,7% [17] af patienterne en alvorlig uønsket hændelse i løbet af 17/21/6,5 måneder. Data stammer fra EPAR'en for de to fase II-studier og den publicerede artikel for fase III-studiet.

Fagudvalget gør opmærksom på, at uønskede hændelser ikke er opgjort ens i de to lægemidlers udviklingsprogrammer (for brigatinib indgår progression af kræftsygdom som en uønsket hændelse), og at opfølgningstiden er længere for brigatinib. Ansøger angiver i den endelige ansøgning, at 63 % af patienterne i ALTA-studiet oplevede en alvorlig uønsket hændelse, hvis data korrigeres for progression af kræftsygdom [22].

Den naive sammenstilling tyder på, at der er en absolut forskel i alvorlige uønskede hændelser ved brigatinib sammenlignet med alectinib, som overstiger de 5 %, der er defineret som den mindste klinisk relevante forskel. Denne forskel ses også, hvis ansøgers korrigerede data anvendes.

Ud fra de kvantitative data vurderer fagudvalget, at brigatinib har en ikkedokumenterbar merværdi på effektmålet alvorlige uønskede hændelser sammenlignet med alectinib. Med ikkedokumenterbar mener fagudvalget, at data tyder på en negativ merværdi, men grundlaget er usikkert. Evidensens kvalitet kan ikke defineres.

Kvalitativ vurdering af uønskede hændelser

I EPAR´en for brigatinib beskrives bivirkningsprofilen som forventelig for en ALK-TKI, med undtagelse af lungerelaterede uønskede hændelser. Det kliniske udviklingsprogram af brigatinib har identificeret et sikkerhedssignal, som også er beskrevet i EPAR´en og ansøgers endelige ansøgning, såkaldt *Early Onset Pulmonary Events*, som er en pneumonitits med mulig dødelig udgang. De fleste af disse reaktioner ses i begyndelsen af behandlingen og er rationalet bag den beskrevne dosering med opstart med 90 mg.

Baseret på både den kvantitative og den kvalitative vurdering af uønskede hændelser vurderer fagudvalget, at data tyder på, at brigatinib har en negativ merværdi på effektmålet alvorlige uønskede hændelser sammenlignet med alectinib. Grundlaget er dog så usikkert, at brigatinib kategoriseres med en ikkedokumenterbar klinisk merværdi. Evidensens kvalitet kan ikke defineres.

Livskvalitet

Livskvalitet kan for NSCLC-patienter måles med flere forskellige instrumenter. De to mest velegnede instrumenter er her nævnt i prioriteret rækkefølge: European Organisation for Research and Treatment of Cancer Quality-of-life Questionnaire-Core 30 (EORTC QLQ-C30) eller det sygdomsspecifikke EORTC QLQ-Lung Cancer 13 (EORTC QLQ-LC13) [24–26]. Ansøger har fremsendt data målt med EORTC QLQ-C30 fra ALTA-studiet.

EORTC QLQ-C30 består af fem funktionsskalaer, tre symptomskalaer og en "global" livskvalitetsskala. Der anvendes en scoringsskala fra 0-100. En høj score på de fem funktionsskalaer repræsenterer et højt/positivt

funktionsniveau. En høj score for global helbredsstatus repræsenterer høj livskvalitet, mens en høj score på de tre symptomskalaer repræsenterer høj forekomst af symptomer/problemer [25]. Den mindste klinisk relevante forskel baserer sig på en lille ændring defineret som 5-10 point på den globale skala. En moderat ændring er 10-20 point, og en stor ændring er > 20 point [27]. Fagudvalget har defineret den mindste klinisk relevante forskel som 10 point, da dette vil overstige grænsen for en lille ændring.

I ansøgers endelige ansøgning fremgår det, at der er livskvalitetsdata angående brigatinib fra ALTA-studiet, hvor der ses forbedringer på den globale skala EORTC QLQ-C30 [14]. Der er data fra et enkelt studie af alectinib, hvor der blev rapporteret en klinisk betydende forbedring på samme skala [15].

Disse data kan indikere, at der er forbedringer i livskvalitet ved både alectinib og brigatinib, men det kan ikke vurderes, om der er forskelle mellem de to lægemidler.

På denne baggrund vurderer fagudvalget, at brigatinib har ikkedokumenterbar klinisk merværdi på effektmålet livskvalitet sammenlignet med alectinib. Evidensens kvalitet kan ikke defineres.

Objektiv responsrate (ORR)

ORR (defineret som partielt eller komplet respons) anvendes til belysning af behandlingsrespons. Fagudvalget vurderer, at tumorreduktion medfører en periode med forbedring eller ingen forværring af symptomer fra kræftsygdommen. Fagudvalget vurderer derfor, at responsraten er et vigtigt effektmål. Fagudvalget finder, at den mindste klinisk relevante forskel er en ARR på 5 %.

Tabel 8: Vurdering af klinisk merværdi: ORR

	Forhåndsdefineret grundlag for vurdering	Brigatinib vs. Alectinib
Absolutte forskelle	ARR 5 %	56,4 % vs. 52,2 %, 50,0 % og 37,5 %
Evidensens kvalitet	Kan ikke defineres	

I det publicerede ALTA-studie var ORR (bedømt af investigator) 54 % [14]. I EMAs EPAR er tallet opgivet som 56,4 % [8]. Ifølge EPAR'en for alectinib havde henholdvsis 52,2 % (bedømt af uafhængig komite), 50,0 % (bedømt af uafhængig komite) og 37,5 % (bedømt af investigator) af patienterne et objektivt respons [21].

Den naive sammenstilling dokumenterer ikke en absolut og konsistent forskel i ORR ved brigatinib sammenlignet med alectinib, som overstiger de 5 %, der er defineret som den mindste klinisk relevante forskel.

Baseret på den narrative syntese af ORR for de to lægemidler, vurderer fagudvalget, at brigatinib har en ikkedokumenterbar klinisk merværdi på effektmålet sammenlignet med alectinib. Evidensens kvalitet kan ikke defineres.

9.1.3 Evidensens kvalitet

Der er tale om en narrativ syntese uden kvantitative sammenligninger ud fra især fase II-data. Derfor er evidensen iht. GRADE som udgangspunkt af lav kvalitet. Der er som minimum basis for at nedgradere til meget lav kvalitet på grund af *indirectness*.

Da fagudvalget derudover ikke har mulighed for at kategorisere merværdien ved de enkelte effektmål grundet manglende evidens, kan den samlede evidenskvalitet ikke defineres. Der er ikke foretaget en formel vurdering af evidensens kvalitet.

9.1.4 Konklusion

Fagudvalget vurderer, at brigatinib til patienter med ALK-positiv ikke-småcellet lungekræft, som tidligere er behandlet med crizotinib, giver en ikkedokumenterbar klinisk merværdi sammenlignet med alectinib.

Den samlede kategorisering af det kliniske spørgsmål er baseret på gennemgangen af de enkelte effektmål, som er opsummeret i nedenstående tabel.

Tabel 9. Samlet vurdering af klinisk merværdi

Effektmål	Vigtighed	Merværdi	Evidensens kvalitet
Overlevelse	Kritisk	Ikkedokumenterbar	Kan ikke defineres
Behandlingsophør grundet uønskede hændelser	Kritisk	Ikkedokumenterbar	Kan ikke defineres
CNS-progression	Kritisk	Ikkedokumenterbar	Kan ikke defineres
Progressionsfri overlevelse	Vigtig	Ikkedokumenterbar	Kan ikke defineres
Alvorlige uønskede hændelser grad 3-4	Vigtig	Ikkedokumenterbar	Kan ikke defineres
Livskvalitet	Vigtig	Ikke dokumenterbar	Kan ikke defineres
Objektiv responsrate	Vigtig	Ikkedokumenterbar	Kan ikke defineres
Samlet		Ikkedokumenterbar	Kan ikke defineres

Der forekommer umiddelbart i de naive sammenligninger en markant forskel i overlevelse, men det kan ikke udelukkes, at denne skyldes forskelle i opfølgningstid mellem studierne af alectinib og brigatinib. Usikkerheden på dette effektmål er så væsentlig, at størrelsen på forskellen mellem de to lægemidler ikke kan vurderes.

Størrelsen af forskellene i det kritiske effektmål CNS-progression og det vigtige effektmål PFS tyder begge på, at brigatinib har en klinisk merværdi ift. alectinib, men grundet manglende relative effektestimater og manglende konfidensintervaller er der stor usikkerhed om den sande størrelse af effektforskellen. Usikkerheden er dog mindre for disse effektmål end for OS.

Data for det kritiske effektmål ”behandlingsophør pga. uønskede hændelser” tyder ikke på forskel mellem lægemidlerne og trækker derfor hverken op eller ned i vurderingen, hvorimod data for det vigtige effektmål ”alvorlige uønskede hændelser” tyder på en negativ merværdi, som trækker ned i vurderingen. For de øvrige vigtige effektmål tyder data ikke på forskelle mellem lægemidlerne og vægter derfor hverken positivt eller negativt.

Samlet set vurderer fagudvalget den kliniske merværdi derfor som ”ikkedokumenterbar”.

I bilag 1 beskrives en publiceret MAIC-analyse, hvor brigatinib sammenlignes med alectinib. Fagudvalget har brugt denne som supplement til de naive sammenligninger og finder ikke, at den ændrer konklusionerne.

10 Andre overvejelser

Fagudvalget gør opmærksom på, at patientpopulationen, som kandiderer til behandling med brigatinib, er yderst begrænset og sandsynligvis kun er eksisterende i en kort tidsperiode, da patienter nu modtager alectinib som førstelinjebehandling i stedet for crizotinib. Fagudvalget skønner, at 0-5 patienter i Danmark årligt vil komme i betragtning til behandling med brigatinib. Dette kan eksempelvis være patienter, som ikke kan tåle alectinib og derfor får førstelinjebehandling med crizotinib.

Fagudvalget gør opmærksom på, at data behandlet i denne vurderingsrapport primært stammer fra fase II-forsøg. Vurderingen er baseret på naive sammenligninger, og sammenligningerne mellem lægemidler er behæftet med stor usikkerhed.

11 Fagudvalgets vurdering af samlet klinisk merværdi og samlet evidensniveau

Fagudvalget vurderer, at brigatinib til patienter med ALK-positiv ikke-småcellet lungekræft, som tidligere er behandlet med crizotinib, giver en **ikkedokumenterbar klinisk merværdi** sammenlignet med alectinib. Evidensens kvalitet kan ikke defineres.

12 Rådets vurdering af samlet klinisk merværdi og samlet evidensniveau

Medicinrådet vurderer, at brigatinib til patienter med ALK-positiv ikke-småcellet lungekræft, som tidligere er behandlet med crizotinib, giver en **ikkedokumenterbar klinisk** merværdi sammenlignet med alectinib. Evidensens kvalitet kan ikke defineres.

13 Relation til eksisterende behandlingsvejledning

Medicinrådet har besluttet at udarbejde to fælles regionale behandlingsvejledninger for terapiområdet NSCLC for henholdsvis første- og andenlinjebehandling. Brigatinib vil blive vurderet i behandlingsvejledningen vedr. andenlinjebehandling, såfremt crizotinib bliver standardbehandling i første linje.

14 Bilag 1 – beskrivelse af MAIC-analyse

Matching adjusted indirect comparison (MAIC) er en statistisk metode, der bruges til indirekte sammenligninger af to kliniske studier, også i tilfælde hvor der ikke er en fælles komparator (en såkaldt *unachored* analyse). Denne analyse kan benyttes til at sammenligne to *single-arm*-studier, som er datagrundlaget i dette tilfælde. Til en MAIC-analyse skal der være individuelle patientdata tilgængelige for én men ikke nødvendigvis begge grupper af patienter, der sammenlignes. I dette tilfælde er der individuelle data for patienter behandlet med brigatinib og aggregerede data for patienter behandlet med alectinib.

Patienterne behandlet med brigatinib bliver i analysen vægtet på udvalgte prognostiske faktorer, således at deres vægtede gennemsnit svarer til gennemsnittet af patienter fra studiet af alectinib. Vægtningen medfører, at resultater for nogle patienter tæller mindre end 1 i analysen, hvorfor datagrundlaget samlet bliver mindre. Formålet med vægtningen er at gøre populationerne sammenlignelige på de udvalgte faktorer.

I den publicerede MAIC-analyse er brigatinib sammenlignet med to forskellige studier af alectinib (benævnt 1 og 2 i tabel 1) [20]. Data for brigatinib stammer fra et andet cut-off (efter en median opfølgningstid på 18,6 måneder) end det senest tilgængelige. Derfor er den mediane overlevelse for patienter behandlet med brigatinib (27,6 måneder) kortere end den, som er benyttet i den naive sammenligning i Medicinrådets vurderingsrapport. For alectinib havde data en median opfølgningstid på hhv. 17 og 21 måneder, og den mediane overlevelse er den samme, som er benyttet i den naive sammenligning (22,7 og 26,0 måneder).

Vægtningen betyder, at datagrundlaget for brigatinib bliver mindre (det ændres fra n = 110 til n = 77,5 og n = 70,5 i de to sammenligninger). Information om de enkelte vægtninger er ikke inkluderet i artiklen eller publiceret som supplement.

Der er altså en række usikkerheder i forbindelse med den publicerede MAIC-analyse:

- Kortere opfølgning end data med længst opfølgning på brigatinib
- Resultaterne relaterer til en mindre population end studiet af brigatinib som helhed
- Mangel på information om vægtningerne.

Derfor har Medicinrådets sekretariat valgt ikke at benytte den publicerede MAIC-analyse som et formelt grundlag for de kvantitative sammenligninger, men resultaterne indgår som supplement til de naive sammenligninger. Der er MAIC-data på de tre effektmål: ORR, OS og PFS.

Overlevelse

Nedenstående tabel stammer fra ansøgers endelige ansøgning og er modificeret fra den publicerede MAIC-analyse.

	NPNP28761			NP28673		
	Alectinib (N=87)	Brigatinib Naive (N = 110)	Brigatinib MAIC (ESS = 78)	Alectinib (N=138)	Brigatinib Naive (N = 110)	Brigatinib MAIC (ESS = 71)
Median OS, Months (95% CI)	22.7 (17.2, NA)	27.6 (27.6, NA)	27.6 (27.6, NA)	26.0 (21.5, NA)	27.6 (27.6, NA)	27.6 (27.6, NA)
OS, HR (95% CI) Cox-regression	--	0.60 (0.37, 0.97)	0.70 (0.42, 1.16)	--	0.69 (0.45, 1.06)	0.66 (0.39, 1.09)
P-value	--	0.037	0.163	--	0.091	0.104
12-month Survival % (95% CI)	69.3 (58.2; 78.0)	80.1 (71.1; 86.6)	75.3 (64; 83.5)	74.7 (66.4; 81.2)	80.1 (71.1; 86.6)	79.5 (67.7; 87.3)
24-month Survival % (95% CI)	47.3 (31.2; 61.8)	69.4 (59.3; 77.5)	66 (53.6; 75.8)	56.5 (47.3; 64.6)	69.4 (59.3; 77.5)	71.5 (67.7; 87.3)

TABLE 12: NAIVE AND MAIC ADJUSTED OS-DATA FROM [1]. EES: EFFECTIVE SAMPLE SIZE.

Fagudvalget bemærker, at den mediane overlevelse for patienter behandlet med brigatinib er uændret efter matching med to studier af alectinib (benævnt 1 og 2, i tabel 1) [20]. Den absolutte forskel mellem brigatinib og alectinib er henholdsvis 4,9 måneder og 1,6 måneder for de to sammenligninger (mellem brigatinib og hhv. alectinib 1 og alectinib 2). Der er udregnet relative risikoestimater, som begge er statistik insignifikante. Data fra den publicerede MAIC dokumenterer altså ikke relative eller absolutte forskelle mellem lægemidlerne og er samtidig baseret på data med en kortere opfølgningstid end den naive sammenstilling. Fagudvalget tillægger denne analyse mindre betydning end den naive sammenligning.

PFS

Nedenstående tabel stammer fra ansøgers endelige ansøgning og er modificeret fra den publicerede MAIC-analyse.

	NP28761			NP28673		
	Alectinib (N=87)	Brigatinib Naive (N = 110)	Brigatinib MAIC (ESS = 78)	Alectinib (N=138)	Brigatinib Naive (N = 110)	Brigatinib MAIC (ESS = 71)
Median PFS, Months (95% CI)	8.2 (6.3, 12.6)	16.7 (11.6, NA)	17.6 (11.1, NA)	8.9 (5.6, 12.8)	16.7 (11.6, NA)	17.6 (11.1, NA)
PFS, HR (95% CI) Cox-regression	--	0.59 (0.40, 0.87)	0.56 (0.36, 0.86)	--	0.64 (0.45, 0.92)	0.61 (0.40, 0.93)
P-value	--	0.009	0.009	--	0.015	0.023

TABLE 16. NAIVE AND MAIC-ADJUSTED PFS FROM [1].

Den mediane PFS for brigatinib er angivet som 16,7 måneder, hvilket svarer til medianen i den naive sammenligning. Fagudvalget bemærker, at efter matching med to studier af alectinib (benævnt 1 og 2 i tabel 1) bliver den mediane PFS for patienter behandlet med brigatinib ikke lavere [20]. Den absolutte forskel mellem brigatinib og alectinib er større end 7 måneder for hver af de to sammenligninger. Der er udregnet hazard ratios, som er statistisk signifikante og til fordel for brigatinib. Fagudvalget tillægger denne analyse mindre betydning end den naive sammenligning.

ORR

Nedenstående tabel stammer fra ansøgers endelige ansøgning og er modificeret fra den publicerede MAIC-analyse.

	NP28761			NP28673		
	Alectinib (N=87)	Brigatinib Naive (N = 110)	Brigatinib MAIC (ESS = 78)	Alectinib (N=138)	Brigatinib Naive (N = 110)	Brigatinib MAIC (ESS = 71)
ORR (95% CI)	40 (30; 51)	55 (45; 64)	53 (42; 64)	45 (37; 53)	55 (45; 64)	54 (42; 66)
ORR OR (95% CI)	--	1.78 (1.01; 3.17	1.69 (0.91 ; 3.15	--	1.47 (0.89 ; 2.44)	1.44 (0.81 ; 2.58
P-value	--	0.047	0.096	--	0.133	0.212

TABLE 19. NAIVE AND MAIC-ADJUSTED IRC-ASSESSED ORR IN THE ITT-POPULATION, FROM [1].

I den publicerede MAIC-analyse [20] indgår lavere tal for ORR for alectinib (hhv. 40 % og 45 %) end de tal, der anvendes til den naive sammenstilling (52,2 % og 50 %). ORR for brigatinib er opgivet som 55 % (tallet er 54 % i den publicerede artikel og 56,4 % i EMAs EPAR). I MAIC-analysen ses både før og efter matching en absolut forskel mellem brigatinib og alectinib, der overstiger den definerede mindste klinisk relevante forskel til fordel for brigatinib. Der er også udregnet statistisk signifikante relative risici til fordel for brigatinib. Fagudvalget tillægger denne analyse mindre betydning end den naive sammenligning.

Samlet vurdering

Fagudvalget og Medicinrådets sekretariat vurderer, at MAIC-analysens resultater må tages med meget store forbehold. Det fremgår, at de justerede resultater for brigatinib ikke adskiller sig væsentlig fra de ikke-justerede på nogen af de tre effektmål. Vægtningen har altså først og fremmest medført, at datagrundlaget er ca. 30 % mindre.

Ansøger angiver i sin endelige ansøgning, at der er udført en MAIC-analyse baseret på det seneste cut-off for brigatinib, men denne er ikke taget i betragtning, da den er baseret på upublicerede data.

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16 Sammensætning af fagudvalg og kontaktinformation til Medicinrådet

Medicinrådets fagudvalg vedrørende lungekræft

Formand	**Indstillet af**
Christa Haugaard Nyhus Overlæge	Lægevidenskabelige Selskaber
Medlemmer	**Udpeget af**
Udpegning i gang	Region Nordjylland
Halla Skuladottir Overlæge, dr.med.	Region Midtjylland
Stefan Starup Jeppesen Overlæge, ph.d	Region Syddanmark
Jeanette Haar Ehlers Overlæge	Region Sjælland
Lotte Engell-Nørregård Afdelingslæge, ph.d.	Region Hovedstaden
Henrik Hager Overlæge	Inviteret af formanden
Nille Behrendt Overlæge	Dansk Patologiselskab
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Annie Lorenzen Farmaceut	Dansk Selskab for Sygehusapoteksledelse
Finn Klausen Patient/patientrepræsentant	Danske Patienter
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17 Versionslog

Version	Dato	Ændring
1.0	19. juni 2019	Godkendt af Medicinrådet.

Application for the assessment of clinically added value of brigatinib as monotherapy for the treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC) previously treated with crizotinib

Contents

General information

This is a template of the application form to be submitted to the Danish Medicines Council (*Medicinrådet*) for the assessment of the clinically added value of new medicines and new indications. The purpose of the form is to provide an overview of the basic information, literature search, study, and analysis results that will serve as the basis for the assessment. It indicates the minimum required information needed for the assessment.

The assessment of the pharmaceutical will be based on the outcomes defined in the protocol. Results for all critical and important outcomes (*kritiske og vigtige effektmål*) must be addressed in the application. The results of less important outcomes (*mindre vigtige effektmål*) do not need to be addressed. For all the data provided, a reference is mandatory.

During the completion of this form, elements should not be removed from the document. All sections should be filled in (if a section is not applicable, state "not applicable" and explain why). Table examples are provided in the form. Layout may deviate from the template to accommodate data; however, all requested information must be stated. We accept submission of appendices. Audits of data analyses and literature searches will occur.

In order to minimize any translation errors between the application and the assessment report, submission in the Danish language is preferred.

If confidential data are submitted, highlight the data in yellow and write the expected publication date in a comment. If confidential data are submitted in an appendix, the document must in addition be watermarked as "confidential."

The application will be published simultaneously with the final assessment and recommendation report on the Danish Medicines Council's web page (www.medicinraadet.dk). Any data that will be considered in the assessment report will be published with the final application.

Checklist before submitting the application form:

- Are all relevant fields in the application form filled in?
- Is the application explicit and self-explanatory?
- Does the application meet the general requirements defined in the *Process and Methods Guide* of the Danish Medicines Council for new medicines and new indications?
- Does the application meet the specific requirements in the protocol?
- Are deviation(s) from the protocol (if any) described?
- Are deviation(s) from the protocol (if any) justified?

1 Basic information

TABLE 1: CONTACT INFORMATION

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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)	Film-coated tablet
Mechanism of action	Brigatinib is a TKI inhibitor with specific activity on ALK, IGF-1R, ROS1 and EGFR proteins. Inhibition of the ALK protein reduces the activity of centrally placed molecules in certain signaling pathways impacting cellular survival, growth and proliferation.
Dosage regimen	The recommended starting dose of Brigatinib is 90 mg once daily for the first 7 days, then 180 mg once daily. If Brigatinib is interrupted for 14 days or longer for reasons other than adverse reactions, treatment should be resumed at 90 mg once daily for 7 days before increasing to the previously tolerated dose. If a dose is missed or vomiting occurs after taking a dose, an additional dose should not be administered and the next dose should be taken at the scheduled time. Treatment should continue as long as clinical benefit is observed.
Therapeutic indication relevant for assessment (as defined by the European Medicines Agency, EMA)	Brigatinib is indicated as monotherapy for the treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC) previously treated with crizotinib.

Other approved therapeutic indications	Not relevant
Will dispensing be restricted to hospitals?	Yes. (BEGR.) Treatment with Brigatinib should be initiated and supervised by a physician experienced in the use of anticancer medicinal products. ALK-positive NSCLC status should be known prior to initiation of Brigatinib therapy. A validated ALK assay is necessary for the selection of ALK-positive NSCLC patients. Assessment for ALK-positive NSCLC should be performed by laboratories with demonstrated proficiency in the specific technology being utilised.
Combination therapy and/or co-medication	Not relevant
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
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
IRC: Independent Review Committee
ITT: Intention To Treat (Population)
KM: Kaplan-Meier
MedDRA: Medical Dictionary for Regulatory Activities
NA: Not Applicable
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
QD: once daily
PK: Pharmacokinetics
PS: (Eastern Cooperative Oncology Group) Performance Status
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

AIM: to assess the added clinical value of brigatinib as monotherapy for the treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC) previously treated with crizotinib; compared to monotherapy with alectinib.

METHODS: in accordance with the protocol defined by the Medicines Council the outcome measures evaluated were*: Overall Survival (OS), rate of Discontinuation due to Adverse Events (AEs), Central Nervous System Progression Free Survival (CNS PFS), Progression Free Survival (PFS), rate of grade 3-4 AEs as well a qualitative summary of known Adverse Drug Reactions, Quality of Life (QoL), and Objective Response Rate (ORR)*. Two comprehensive literature databases (CENTRAL and MedLine) were searched for clinical trials allowing for a direct or indirect comparison of the efficacy of brigatinib against alectinib. These searches yielded a total of 149 publications. Of these 149 publications eight publications representing five phase II clinical trials fulfilled the criteria defined in the protocol provided by the Medicines Council. Additionally, the two relevant EPARs were included in the literature that forms the basis for this application. As none of the trials identified contain a direct comparison between alectinib and brigatinib, the comparative analysis is primarily narrative supported by Match Adjusted Indirect Comparisons [1] and indirect comparisons of naïve data, where relevant.

RESULTS: Numerically, brigatinib consistently had clinically meaningful, longer OS, CNS PFS, and PFS as well as higher ORR than alectinib; PFS was statistically significant longer. The rate of discontinuation due to AEs was found to be statistically and clinically comparable between alectinib and brigatinib, while the rate of grade 3-4 AEs was found to be statistically and clinically higher for brigatinib. The limited Quality of Life data available suggested that brigatinib and alectinib both improved QoL.

CONCLUSION: in total all the efficacy outcome measures (OS, CNS PFS, PFS, and ORR) demonstrated numerical superiority of brigatinib compared to alectinib, discontinuation rates due to AEs were found to be similar, the rate of grade 3-4 AEs were higher for brigatinib, and Quality of Life was found to be similar.

4 Literature search

Databases and search strategies

All searches were conducted in MEDLINE and CENTRAL via Pubmed and Cochrane Library respectively.

The searches were conducted on March 20th, 2019.

All searches were performed as temporally unrestricted searches and were performed using free text and MESH-qualified texts. The CENTRAL database was searched at the "*Title, Abstract, Keywords"* level.

The individual searches were imported to EndNote X8, which automatically excluded duplicate entries.

No MeSH-terms were identified for alectinib/alcensa/CH5424802 and brigatinib/alunbrig/AP26113, in the CENTRAL database. A search on the MeSH descriptor [Carcinoma, non-small-cell lung] with the qualifier [therapy – TH] was therefore performed. The results from the *Trials*-tab were retrieved to Word, where an automatic search for "alectinib"/"alecensa"/"CH5424802" and "brigatinib"/" alunbrig"/"AP26113". This search did not yield any results, Figure 1 and 2.

Direct Comparison

Initially, searches of MEDLINE and CENTRAL, aimed at identifying any randomized controlled trials between alectinib and brigatinib in non-small cell lung cancer patients, were conducted, figure 1.

MEDLINE

MEDLINE was searched through Pubmed using the free text search string *((Brigatinib OR alunbrig) AND (alectinib OR alecensa)) AND non-small lung cancer* which is automatically translated to

((("AP26113"[Supplementary Concept] OR "AP26113"[All Fields] OR "brigatinib"[All Fields]) OR alunbrig[All Fields]) AND (("CH5424802"[Supplementary Concept] OR "CH5424802"[All Fields] OR "alectinib"[All Fields]) OR alecensa[All Fields])) AND ("carcinoma, non-small-cell lung"[MeSH Terms] OR ("carcinoma"[All Fields] AND "non-small-cell"[All Fields] AND "lung"[All Fields]) OR "non-small-cell lung carcinoma"[All Fields] OR ("non"[All Fields] AND "small"[All Fields] AND "cell"[All Fields] AND "lung"[All Fields] AND "cancer"[All Fields]) OR "non small cell lung cancer"[All Fields])

by Pubmed and thus include both free-text and MeSH-qualifed search terms.

CENTRAL

CENTRAL was searched through the Cochrane Library using the below search string

#1	(alectinib OR alcensa OR CH5424802):ti,ab,kw
#2	(brigatinib OR alunbrig OR AP26113):ti,ab,kw
#3	#1 AND #2
#4	[mh "Carcinoma, Non-Small-Cell Lung"]
#5	lung:ti,ab

#6	(cancer* or carcin* or neoplasm* or tumour* or tumor*):ti,ab
#7	(non-small or nonsmall):ti,ab
#8	#5 and #6 and #7
#9	nsclc:ti,ab,kw
#10	#4 OR #8 OR #9
#11	#3 AND #10

These searches did not yield any publications which compared the two drugs directly, figure 1.

Searches aimed at indirect comparisons were thus performed, as described below.

Indirect Comparison

Next, searches aimed at identifying Clinical Trials of alectinib and brigatinib in non-small cell lung cancer patients, were performed, with the aim of allowing an indirect comparison.

MEDLINE

MEDLINE was searched through Pubmed using the free text search string *((Brigatinib OR alunbrig) OR (alectinib OR alecensa)) AND non-small lung cancer* which is automatically translated to

((("AP26113"[Supplementary Concept] OR "AP26113"[All Fields] OR "brigatinib"[All Fields]) OR alunbrig[All Fields]) OR (("CH5424802"[Supplementary Concept] OR "CH5424802"[All Fields] OR "alectinib"[All Fields]) OR alecensa[All Fields])) AND (non-small[All Fields] AND ("lung neoplasms"[MeSH Terms] OR ("lung"[All Fields] AND "neoplasms"[All Fields]) OR "lung neoplasms"[All Fields] OR ("lung"[All Fields] AND "cancer"[All Fields]) OR "lung cancer"[All Fields]))

by Pubmed and thus include both free-text and MeSH-qualifed search terms.

CENTRAL

CENTRAL was searched through the Cochrane Library using the below search string

#1	(alectinib OR alcensa OR CH5424802):ti,ab,kw
#2	(brigatinib OR alunbrig OR AP26113):ti,ab,kw
#3	#1 OR #2
#4	[mh "Carcinoma, Non-Small-Cell Lung"]
#5	lung:ti,ab
#6	(cancer* or carcin* or neoplasm* or tumour* or tumor*):ti,ab
#7	(non-small or nonsmall):ti,ab

#8	#5 and #6 and #7
#9	nsclc:ti,ab,kw
#10	#4 OR #8 OR #9
#11	#3 AND #10

Combined, these searches yielded 8 publications which fulfilled the criteria laid out in the protocol, figure 2.

Four of these publications are single arm phase I or II trials of relevance for this application [2-5].
One publication is a randomized phase III trial, which includes an alectinib arm that is relevant for the current proposal [6].
Two peer-reviewed publications specifically summarize CNS-related data for both brigatinib [7] and alectinib [8].
One publication is a matching adjusted indirect comparison of alectinib and brigatinib in crizotinib refractory patients [1].

EPARs and Summary Publications of CNS-efficacy

The publications identified through database searches report data that is relatively immature.
To assess the most up-to-date data possible the respective EPARs of brigatinib and alectinib [9, 10] were included as well, Figure 2, as these reports summarize data that is more mature, insofar it comes from later data cut-offs.

Finally, relevant data from the eligible clinical studies, their peer-reviewed summaries and EPARs were extracted into a pre-designed data extraction tables, tables A3a-g. The extracted data were verified by a second reviewer and any disputes were resolved through discussion.

PRISMA Flow Diagram Direct Comparison

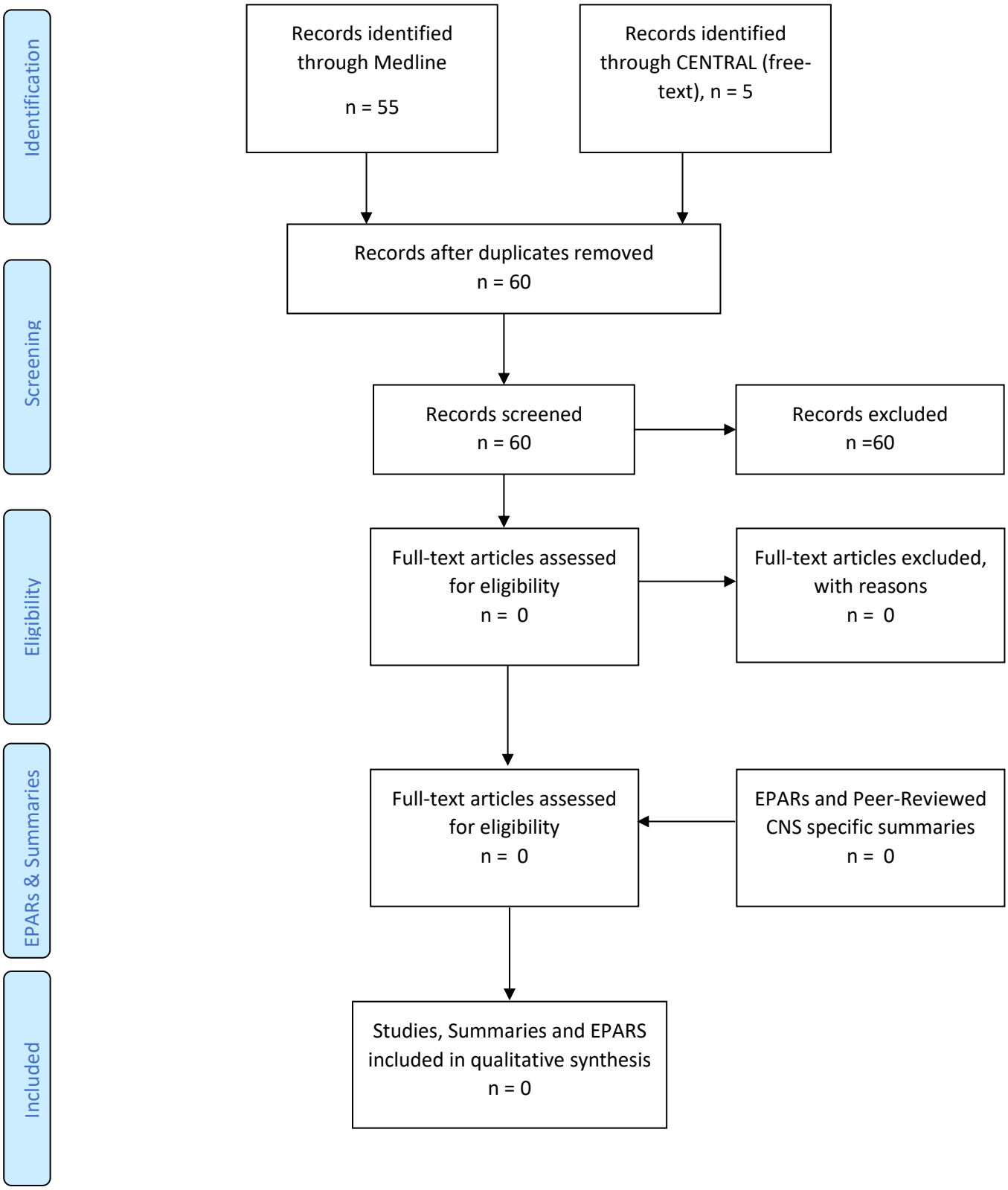


FIGURE 1: PRISMA FLOW DIAGRAM FOR DIRECT COMPARISON.

PRISMA Flow Diagram Indirect Comparison

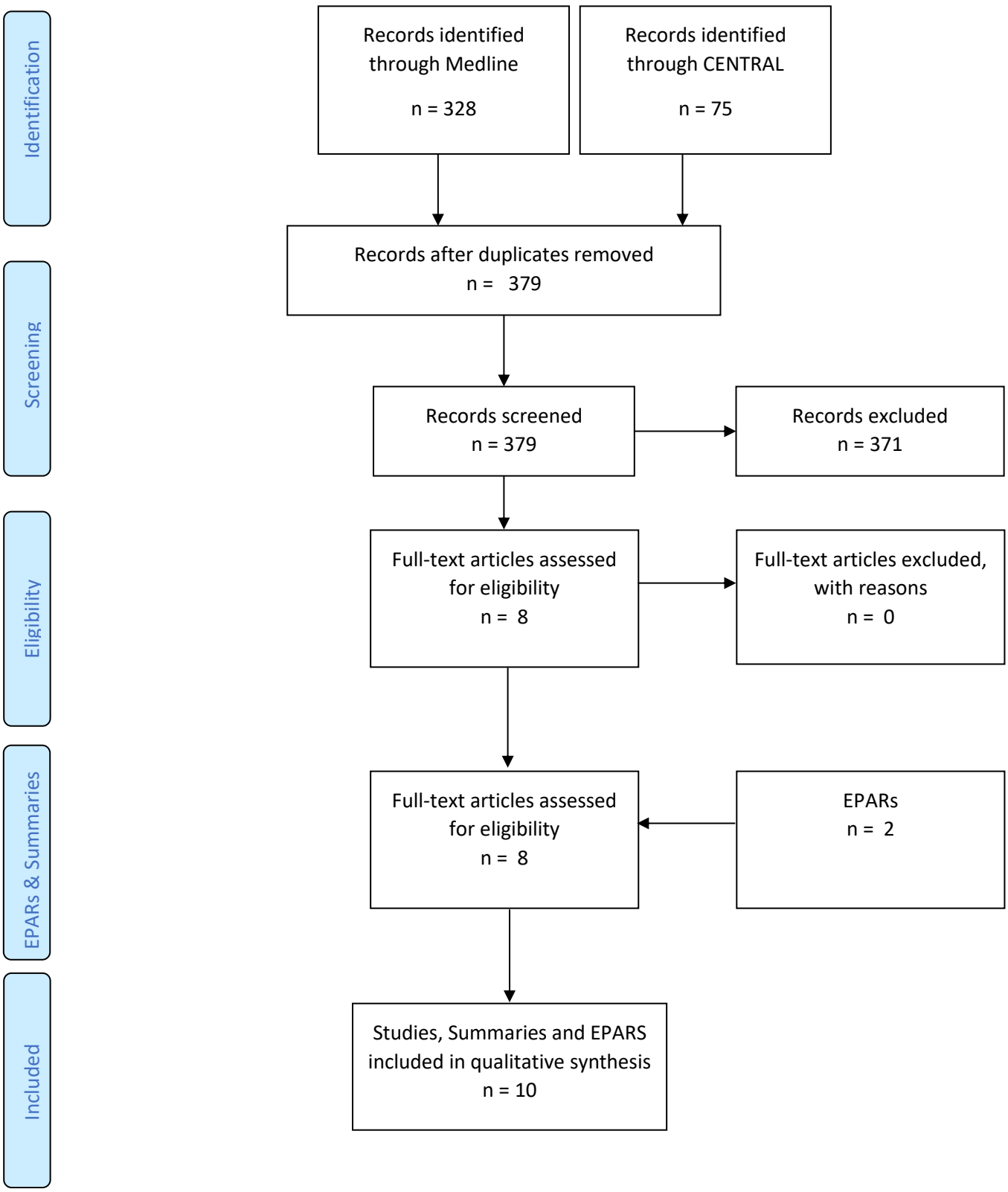


FIGURE 2: PRISMA FLOW DIAGRAM FOR INDIRECT COMPARISON.

4.1 Relevant studies

Table 3 summarizes the articles identified through the literature search by type, while table 4 describe each individual publication in detail (excluding EPARs).

Type of Publications	Number of Publications
Primary report of phase II and phase III trials	5
Articles summarizing CNS-efficacy	2
MAIC based comparison of brigatinib and alectinib	1
EPARs	2

TABLE 3: SUMMARY OF PUBLICATIONS INCLUDED IN THE ASSESSMENT BY TYPE.

TABLE 4: 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
Title Activity and safety of brigatinib in ALK-rearranged non-small-cell lung cancer and other malignancies: a single-arm, open-label, phase 1/2 trial **Authors** Gettinger, S. N. Bazhenova, L. A. Langer, C. J. Salgia, R. Gold, K. A. Rosell, R. Shaw, A. T. Weiss, G. J. Tugnait, M. Narasimhan, N. I. Dorer, D. J. Kerstein, D. Rivera, V. M. Clackson, T. Haluska, F. G. Camidge, D. R. **Journal** Lancet Oncol **Publication year** 2016	A Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Preliminary Anti-Tumor Activity of the Oral Anaplastic Lymphoma Kinase (ALK)/Epidermal Growth Factor Receptor (EGFR) Inhibitor Brigatinib (AP26113)	NCT01449461	Start: September 20th, 2011 End: November 16th, 2015(Primary endpoint)	Hvad er den kliniske merværdi af brigatinib til patienter med uhelbredelig ALK-positiv NSCLC, som tidligere har fået behandling med crizotinib?

Title Brigatinib in Patients with Crizotinib-Refractory Anaplastic Lymphoma Kinase-Positive Non-Small-Cell Lung Cancer: A Randomized, Multicenter Phase II Trial **Authors** Kim, D. W. Tiseo, M. Ahn, M. J. Reckamp, K. L. Hansen, K. H. Kim, S. W. Huber, R. M. West, H. L. Groen, H. J. M. Hochmair, M. J. Leighl, N. B. Gettinger, S. N. Langer, C. J. Paz-Ares Rodriguez, L. G. Smit, E. F. Kim, E. S. Reichmann, W. Haluska, F. G. Kerstein, D. Camidge, D. R. **Journal** Journal of Clinical Oncology **Publication Year** 2017	**ALTA** A Study to Evaluate the Efficacy of Brigatinib (AP26113) in Participants With Anaplastic Lymphoma Kinase (ALK)-Positive, Non-small Cell Lung Cancer (NSCLC) Previously Treated With Crizotinib.	NCT02094573	Start: June 4th, 2014 End: Februrary 29th, 2016 (Primary Endpoint) Estimated end: September 21st, 2020	Hvad er den kliniske merværdi af brigatinib til patienter med uhelbredelig ALK-positiv NSCLC, som tidligere har fået behandling med crizotinib?
Title Alectinib in ALK-positive, crizotinib-resistant, non-small-cell lung cancer: a single-group, multicentre, phase 2 trial **Authors** Shaw, A. T. Gandhi, L.	A Study of Alectinib (CH5424802/RO5424802) in Participants With Anaplastic Lymphoma Kinase (ALK)-Rearranged Non-Small Cell Lung Cancer (NSCLC)	NCT01871805	Start: September 30th, 2013 End: August 31st, 2017	Hvad er den kliniske merværdi af brigatinib til patienter med uhelbredelig ALK-positiv NSCLC, som tidligere har fået behandling med crizotinib?

Gadgeel, S. Riely, G. J. Cetnar, J. West, H. Camidge, D. R. Socinski, M. A. Chiappori, A. Mekhail, T. Chao, B. H. Borghaei, H. Gold, K. A. Zeaiter, A. Bordogna, W. Balas, B. Puig, O. Henschel, V. Ou, S. I. study, investigators **Journal** Lancet Oncol **Publication Year** 2015				
Title Alectinib in Crizotinib-Refractory ALK-Rearranged Non-Small-Cell Lung Cancer: A Phase II Global Study **Authors** Ou, S. H. Ahn, J. S. De Petris, L. Govindan, R. Yang, J. C. Hughes, B. Lena, H. Moro-Sibilot, D. Bearz, A. Ramirez, S. V. Mekhail, T. Spira, A. Bordogna, W. Balas, B. Morcos, P. N. Monnet, A. Zeaiter, A. Kim, D. W. **Journal** Journal of Clinical Oncology	A Study of Alectinib (RO5424802) in Participants With Non-Small Cell Lung Cancer Who Have Anaplastic Lymphoma Kinase (ALK) Mutation and Failed Crizotinib Treatment	NCT01801111	Start: June 20th, 2013 End: October 27th, 2017	Hvad er den kliniske merværdi af brigatinib til patienter med uhelbredelig ALK-positiv NSCLC, som tidligere har fået behandling med crizotinib?

Publication Year 2016				
Title Alectinib versus chemotherapy in crizotinib-pretreated anaplastic lymphoma kinase (ALK)-positive non-small-cell lung cancer: results from the phase III ALUR study **Authors** Novello, S. Mazieres, J. Oh, I. J. de Castro, J. Migliorino, M. R. Helland, A. Dziadziuszko, R. Griesinger, F. Kotb, A. Zeaiter, A. Cardona, A. Balas, B. Johannsdottir, H. K. Das-Gupta, A. Wolf, J. **Journal** Ann Oncol **Publication Year** 2018	**ALUR** Alectinib Versus Pemetrexed or Docetaxel in Anaplastic Lymphoma Kinase (ALK)-Positive Advanced Non-Small Cell Lung Cancer (NSCLC) Participants Previously Treated With Platinum-Based Chemotherapy and Crizotinib	NCT02604342	*Start: November 3rd, 2015* *End: August 13th, 2018*	Hvad er den kliniske merværdi af brigatinib til patienter med uhelbredelig ALK-positiv NSCLC, som tidligere har fået behandling med crizotinib?
Title Pooled Analysis of CNS Response to Alectinib in Two Studies of Pretreated Patients With ALK-Positive Non-Small-Cell Lung Cancer **Authors** Gadgeel, S. M. Shaw, A. T. Govindan, R. Gandhi, L. Socinski, M. A. Camidge, D. R.	A Study of Alectinib (CH5424802/RO5424802) in Participants With Anaplastic Lymphoma Kinase (ALK)-Rearranged Non-Small Cell Lung Cancer (NSCLC) A study of RO5424802) in Participants With Non-Small Cell Lung Cancer Who Have Anaplastic Lymphoma Kinase (ALK) Mutation and Failed Crizotinib Treatment	NCT01871805 NCT01801111	NA: the publication summarizes results from two different trials	Hvad er den kliniske merværdi af brigatinib til patienter med uhelbredelig ALK-positiv NSCLC, som tidligere har fået behandling med crizotinib?

De Petris, L. Kim, D. W. Chiappori, A. Moro-Sibilot, D. L. Duruisseaux, M. Crino, L. De Pas, T. Dansin, E. Tessmer, A. Yang, J. C. Han, J. Y. Bordogna, W. Golding, S. Zeaiter, A. Ou, S. I. **Journal** Journal of Clinical Oncology **Publication Year** 2016				
Title Exploratory Analysis of Brigatinib Activity in Patients With Anaplastic Lymphoma Kinase-Positive Non-Small-Cell Lung Cancer and Brain Metastases in Two Clinical Trials **Authors** Camidge, D. R. Kim, D. W. Tiseo, M. Langer, C. J. Ahn, M. J. Shaw, A. T. Huber, R. M. Hochmair, M. J. Lee, D. H. Bazhenova, L. A. Gold, K. A. Ou, S. I. West, H. L. Reichmann, W. Haney, J. Clackson, T. Kerstein, D. Gettinger, S. N.	A Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Preliminary Anti-Tumor Activity of the Oral Anaplastic Lymphoma Kinase (ALK)/Epidermal Growth Factor Receptor (EGFR) Inhibitor Brigatinib (AP26113) A study to Evaluate the Efficacy of Brigatinib (AP26113) in Participants With Anaplastic Lymphoma Kinase (ALK)-Positive, Non-small Cell Lung Cancer (NSCLC) Previously Treated With Crizotinib.	NCT01449461 NCT02094573	NA: the publication summarizes results from two different trials	Hvad er den kliniske merværdi af brigatinib til patienter med uhelbredelig ALK-positiv NSCLC, som tidligere har fået behandling med crizotinib?

Journal Journal of Clinical Oncology **Publication Year** 2018				
Title Comparative efficacy of brigatinib versus ceritinib and alectinib in patients with crizotinib-refractory anaplastic lymphoma kinase-positive non-small cell lung cancer **Authors** Reckamp, Karen Lin, Huamao M. Huang, Joice Proskorovsky, Irina Reichmann, William Krotneva, Stanimira Kerstein, David Huang, Hui Lee, Joseph **Journal** Current Medical Research and Opinion **Publication Year** 2018	ALTA NP28761 NP28673	NA	NA: the publication summarizes results from three different trials	Hvad er den kliniske merværdi af brigatinib til patienter med uhelbredelig ALK-positiv NSCLC, som tidligere har fået behandling med crizotinib?
**when multiple clinical questions are defined in the protocol*				

4.2 Main characteristics of included studies

See Table A2 in the appendix.

5 Clinical questions

5.1 What is the clinically added value of brigatinib for patients with incurable ALK-positive NSCLS who have previoulsy been treated with crizotinib?

5.1.1 Presentation of relevant studies

5.1.1.1 General considerations

In total, five studies were identified as having generated data that is relevant for this application:

- Two phase I/II trials
- Two phase II trials
- One phase III trial

These five trials generated a total of eight relevant publications [1-8].

Five of these publication reported data from the initial data-cut [2-4, 6, 11]; CNS PFS from four of the trials were published separately from the main publication and with longer follow-up times [7, 8], and one article sought to assess the relative efficacy of brigatinib and alectinib based on the published data of the trials [1].

Additionally, the majority of the trials generated additional data at dosages and/or in patient populations that are outside the scope of the present application and only subset of the data from these trials are therefore relevant for the application. Only the relevant data will be presented.

5.1.1.2 Study 101 A Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Preliminary Anti-Tumor Activity of the Oral Anaplastic Lymphoma Kinase (ALK)/Epidermal Growth Factor Receptor (EGFR) Inhibitor Brigatinib (AP26113)

The phase 1/2 trial was a first-in human, single-arm, nonrandomized, uncontrolled, multicentre, open-label study (NCT01449461) conducted in adult patients with advanced malignancies in the US and Spain [2].
A total of 137 patients (79 [58%] of whom had ALK+ NSCLC) were enrolled and treated with brigatinib.
Of the 79 patients with ALK+ NSCLC, 71% had received prior crizotinib [10].

The phase 1, dose-finding portion of the phase 1/2 trial enrolled patients with advanced malignancies (except leukaemia). The phase 2 proof-of-concept portion enrolled patients into 5 expansion cohorts, which were histologically and molecularly defined (Figure 3).

- Cohort 1: patients with ALK+ NSCLC who were naïve to ALK-targeted therapies
- Cohort 2: patients with ALK+ NSCLC who were resistant to crizotinib (i.e., had experienced disease progression while on crizotinib)
- Cohort 3: patients with NSCLC with documented EGFR T790M mutation and resistance to 1 previous epidermal growth factor receptor (EGFR) inhibitor
- Cohort 4: patients with any cancers with abnormalities in ALK, EGFR, ROS1, or other targets against which Brigatinib is active

- Cohort 5: patients with ALK+ NSCLC with active brain metastases who were naïve or resistant to crizotinib (added in a protocol amendment to explore activity against central nervous system [CNS] metastases)

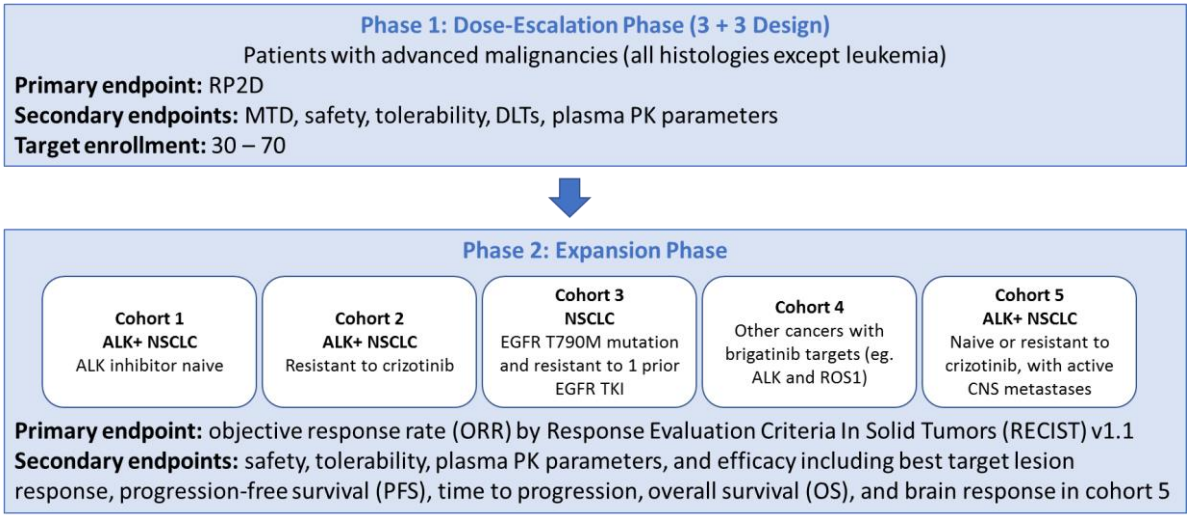


Figure 3: Phase 1/2 Trial Schema. ALK, anaplastic lymphoma kinase; CNS, central nervous system; DLT, dose-limiting toxicity; EGFR, epidermal growth factor receptor; MTD, maximum tolerated dose; NSCLC, non-small cell lung cancer; PK, pharmacokinetics; ROS1, c-ros 1 oncogene; RP2D, recommended phase 2 dose; TKI, tyrosine kinase inhibitor

Patients in the phase 1 dose-escalation portion of the study received brigatinib orally at daily doses ranging from 30 to 300 mg. In the phase 2 expansion portion, patients received 1 of the following Brigatinib regimens: 90 mg once daily (n = 18), 180 mg once daily with a 7-day lead in at 90 mg once daily (90 mg → 180 mg once daily; n = 32), or 180 mg once daily (n = 48.
Patients from the phase 1 cohort were combined with those from phase 2 for the efficacy analysis.

Application relevant population
In total 25 patients who had previously received crizotinib were treated with the 90 mg → 180 mg dose [10] that is relevant for the current application.

5.1.1.3 ALTA

The ALTA study is an ongoing open-label, multicentre, international, noncomparative, 2 arm, randomized, dose-finding, phase II trial conducted in adult patients with locally advanced or metastatic ALK+ NSCLC that have progressed on crizotinib.

Patients were stratified by baseline brain metastases (present *vs*. absent) and best investigator-assessed response to crizotinib (complete response or partial response *vs.* other or unknown) and were randomly assigned (1:1) to 90 mg once daily or 180 mg once daily with a 7-day lead-in at 90 mg once daily (90 mg → 180 mg). Treatment continued until disease progression requiring alternative systemic therapy, intolerable toxicity, or consent withdrawal, Figure 4.

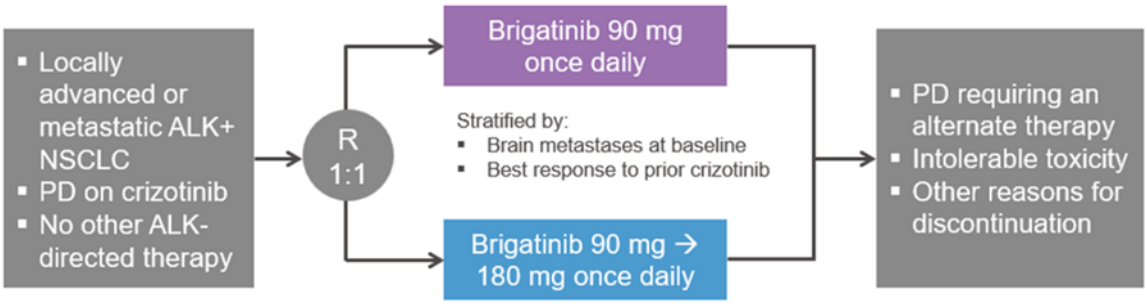


FIGURE 4: STUDY SCHEMATICS OF ALTA

Treatment in either arm could be continued at the investigator's discretion after progression. Patients in arm A could receive Brigatinib 180 mg once daily after objective progression at 90 mg once daily.
Dose interruptions or reductions were allowed in order to manage treatment-related AEs, on the basis of the investigator's judgment.
In total 222 patients were included in the study.

The trial has had numerous data read-outs spanning from the initial extraction at February 29th, 2016, with a median follow-up of 8.3 months in patients treated with 90 mg → 180 mg, over February 2017, to the latest data extraction date of September 29th, 2017, with a median follow up of 24.3 months in the 90 mg → 180 mg arm.

Application relevant population
The current application is supported by the data from the 90mg → 180 mg arm, which contained 110 patients. This study-population represents the approved dose of brigatinib.

5.1.1.3 Study NP28761: A Phase I/II Study of the ALK Inhibitor alectinib (CH5424802/RO5424802) in patients with ALK-rearranged Non-Small Cell Lung Cancer previously treated with Crizotinib.

The following information is compiled from the alectinib EPAR [9] and the publication reporting the trial [5].

Study NP28761 is an on-going multi-centre, single arm, open-label, dose escalation study to determine the safety, tolerability and activity of alectinib as a single agent in patients with either locally advanced (AJCC Stage IIIB) and not amenable to curative therapy or metastatic (Stage IV) ALK+ NSCLC who had experienced disease progression on crizotinib with or without prior chemotherapy.
Alectinib was administered to the patient orally BID starting on Day 1 through Day 21 of each 21-day treatment cycle. Patients were treated continuously until disease progression, death, or withdrawal for any other reason.
As the trial was single-armed, no randomization occurred.
The RP2D determined in Phase I was 600 mg BID. In total 87 patients were enrolled at this dose and assessed for efficacy and safety.

5.1.1.4 NP28673: An open-label, non-randomized, multicentre Phase I/II trial of alectinib (RO5424802) given orally to Non-Small Cell Lung Cancer patients who have ALK mutation and who have failed crizotinib treatment.

The following information is compiled from the alectinib EPAR [9] and the publication reporting the trial [4].

This study was conducted in three parts:
● Phase I, Part 1: A dose-escalation phase with the objective of assessing the safety, tolerability, and PK of alectinib 600 mg BID and 900 mg BID dose regimens. During the conduct of Part 1 for this study, the RP2D (600 mg BID) was confirmed in study NP28761 and Part 1 and Part 2 were combined.
● Phase II, Part 2: A safety and efficacy evaluation phase
● Phase II, Part 3: A post-progression treatment phase

Alectinib as a single agent was administered orally at a dose of 600 mg BID within 30 minutes after meals in the morning and evening. Patients received alectinib at the stated dose for 5 cycles (28 days) continuously, starting on Cycle 1, Day 1. Patients in Part 2 that were considered by the investigator to still benefit from treatment, could be included in the treatment beyond progression in Part 3, where they could continue to receive alectinib alone. Thus, the study effectively evaluated treatment until progression, intolerable toxicities of withdrawal or consent [4].
The response evaluable (RE) population comprised patients with measurable disease at baseline who had a baseline tumor assessment and who had received at least one dose of alectinib at the RP2D of 600 mg twice daily.
Radiologic assessments were performed at screening and every 8 weeks in the first year, every 12 weeks in the second year and every 16 weeks subsequently until disease progression.
As the trial was single-armed, no randomization occurred.

5.1.1.5 ALUR

The following information is based on the publication reporting the ALUR trial [6]

ALUR: a randomized, multi-center, open-label, phase III trial of alectinib versus chemotherapy in advanced/metastatic ALK-positive NSCLC patients previously treated with platinum-based doublet chemotherapy and crizotinib.
Patients were randomized 2 : 1 to receive alectinib 600 mg twice daily or chemotherapy (pemetrexed 500 mg/m2 or docetaxel 75 mg/m2, both every 3 weeks) until disease progression, death, or withdrawal.
Primary end point was investigator-assessed progression-free survival (PFS).
Randomization was carried out using the following stratification factors:

- ECOG PS (0/1 versus 2); baseline CNS metastases (yes/no)
- For patients with baseline CNS metastases, brain radiotherapy history (yes/no)

At the investigators' discretion, alectinib could be continued beyond radiologic progression until loss of clinical benefit.
Disease was assessed at screening and every 6 weeks until progression. Response (RECIST v1.1) was assessed by investigators using physical examinations, computed tomography scans, and magnetic resonance imaging.
Crossover from chemotherapy to alectinib was permitted following progression.
This was an open-label study. While the investigators and patients were unblinded, the Sponsor and the study team performing the primary analysis were blinded to randomized treatment assignments until after database lock. The following steps were taken to keep the study team blinded: no aggregate review of patients indicating the treatment allocation was performed, and open review outputs for independent data monitoring committee were not split by treatment arm but presented in a pooled manner. All tumor assessments performed by an Independent Review Committee (IRC) were blinded.

5.1.1.6 Overview of disease and treatment specific patient characteristics and considerations of inter study difference

SIMILARITIES

All five trials are remarkable homogenous in their study design and disease- and prior treatment specific inclusion/exclusion criterias (table 5).
All studies included NSCLC patients with stage IIIB and IV disease. All five studies had a requirement for failure of/progression on prior crizotinib treatment and a tolerance for prior chemotherapy. Slight differences were noted when it came to the symptom burden and activity of brain metastasis, with the alectinib trials being slightly more restrictive than the brigatinib trials, table 5.

	Brigatinib		**Alectinib**		
Study	ALTA	Study 101 ALK+ NSCLS patients with prior crizotinb treatment	NP28673	NP28761	ALUR
Disease	Stage IIIB or IV ALK+ NSCLC	Stage IIIB or IV ALK+ NSCLC	Stage IIIB or IV ALK+ NSCLC	Stage IIIB or IV ALK+ NSCLC	Stage IIIB or IV ALK+ NSCLC
Crizotinib	Must have progressed on Crizotinb	Failure of crizotinib	Must have failed Crizotinib treatment	Prior treatment with crizotinib and progression according to RECIST	Two prior systemic lines of therapy, which must have included one line of platinum-based chemotherapy and one line of crizotinib
Prior Chemotherapy	Allowed	Allowed	Allowed	Allowed	Platinum based required
ECOG PS	0-2	0-1	0-2	0-2	0-2
Brain Metastais	Active and Inactive Symptomatic – if neurologically stable and not requiring increasing doses corticosteroids	Active and Inactive Except neurologically unstable or requiring anticonvulsants or increasing doses of corticosteroids	Active and Inactive Non-symptomatic and non-treatment requiring	Active and Inactive Non-symptomatic and non-treatment requiring	Active and Inactive Asymptomatic or symptomatic and ineligible for radiotherapy.
Treatment Duration	Until progression, intolerable toxicities or withdrawal of consent	Until progression, intolerable toxicities or withdrawal of consent	Until progression, intolerable toxicities or withdrawal of consent	Until progression, intolerable toxicities or withdrawal of consent	Until progression, intolerable toxicities or withdrawal of consent

TABLE 5 OVERVIEW OF THE MAIN DISEASE AND TREATMENT SPECIFIC PATIENT CHARACTERISTICS ALLOWED PER PROTOCOL IN THE STUDIES INCLUDED IN THE APPLICATION.

This homogeneity of inclusion criteria is reflected in the patient's characteristics (Table 5). The key demographic parameter median age is 56.5, 57.0, 52.0, 54.0, and 55.5 across the three trials. Similarly, key disease descriptors such as the rate of patients with ECOG PS 0-1, brain metastasis, and prior chemotherapy are, with a few exceptions, well balanced across the trials.
The rates of patients with ECOG PS 0-1 were 91.8, 100, 90.6, 89.7, and 91.7, while the rates of patients with prior chemotherapy were 73.6, 68.0, 79.7, 74.0, and 100. Notably, an inclusion criterion in the ALUR trial

was to have received prior chemotherapy.
Interestingly, at 67.3% and 68.0% the rate of brain metastases is slightly higher in the two brigatinib trials than in the alectinib trials at 61.0%, 59.8%, and 65.3%. This is in accordance with the slightly less restrictive inclusion criterion for brain metastases in the brigatinib trials and suggests that the patients in the brigatinib trials were slightly more progressed than in the alectinib trials.
For a full overview of the baseline patient characteristics, please refer to table 6,

	Brigatinib		**Alectinib**		
Study	ALTA (Arm B 90→180mg)	Study 101 (ALK+, NSCLC, post-crizotinib, 90→180mg cohort)	NP28673	NP28761	ALUR
No. of patients	110	25	138	87	72
Age					
Median	56.5	57.0	52.0	54.0	55.5
Range	20-81	32-73	22-79	29-79	21-82
65+, N (%)	30 (27.3)	5 (20.0)	NR	NR	12 (16.7)
Gender					
Male	46 (41.8)	14 (56.0)	61 (44.0)	39 (45.0)	41 (56.9)
Female	64 (58.2)	11 (44.0)	77 (56.0)	48 (55.0)	31 (43.1)
Race					
Asian	30 (27.3)	3 (12.0)	36 (26.0)	7 (8.0)	5 (6.9)
White	76 (69.1)	20 (80.0)	93 (67.0)	73 (84.0)	61 (84.7)
Other	2 (1.8)	2 (8.0)	9 (7.0)	7 (8.0)	1 (1.5)
Unknown	2 (1.8)	0 (0)	0 (0)	0 (0)	5 (6.9)
ECOG PS					
0	45 (40.9)	10 (40.0)	44 (31.9)	30 (34.5)	NR
1	56 (50.9)	15 (60.0)	81 (58.7)	48 (55.2)	NR
0 or 1	101 (91.8)	25 (100)	125 (90.6)	78 (89.7)	66 (91.7)
2	9 (8.2)	0 (0)	13 (9.4)	9 (10.3)	6 (8.3)
2+	9 (8.2)	0 (0)	13 (9.4)	9 (10.3)	6 (8.3)
3+	0 (0)	0 (0)	0 (0)	0 (0)	NR
Missing	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Smoking status		NR			
Never	63 (57.3)		96 (70.0)	54 (62.0)	35 (48.6)
Former	43 (39.1)		39 (28.0)	33 (38.0)	35 (48.6)
Current	4 (3.6)		3 (2.0)	0 (0)	2 (2.8)
Unknown	0 (0)		0 (0)	0 (0)	0 (0)
Histology class					
Adenocarcinoma	108 (98.2)	24 (96.0)	133 (96.4)	82 (94.3)	72 (100)
Adenosquamous	0 (0)	1 (4.0)	2 (1.4)	2 (2.3)	0 (0)
Large-cell	1 (0.9)	0 (0)	3 (2.2)	1 (1.1)	0 (0)
Squamous cell	1 (0.9)	0 (0)	0 (0)	1 (1.1)	0 (0)
Other	0 (0)	0 (0)	0 (0)	1 (1.1)	0 (0)
Disease stage at study entry					NR
IV	108 (98.2)	25 (100)	NR	86 (99.0)	
Other	2 (1.8)	0 (0)		1 (1.0)	

Metastatic sites					
Brain	74 (67.3)	17 (68.0)	84 (61.0)	52 (59.8)	47 (65.3)
Lung	93 (84.5)	NR	NR	NR	NR
Bone	38 (34.5)	NR	NR	NR	NR
Liver	23 (20.9)	NR	NR	NR	NR
Prior therapy					
Crizotinib	110 (100)	25 (100)	138 (100)	87 (100)	72 (100)
Chemo (no plat.)	1 (0.9)	NR	NR	NR	NR
Platinum-based	80 (72.7)	NR	NR	NR	72 (100)
Any chemo	81 (73.6)	17 (68.0)	110 (79.7)	64 (74.0)	72 (100)
Prior radiotherapy to brain	46 (41.8)	7 (28.0)	61 (44.2)	34 (39.1)	23 (31.9)
Prior last treatment crizotinib	106 (96.3)	22 (88.0)	NR	NR	NR
Time from prior crizotinib therapy to the first dose of TKI					
Median (days)					NR
Range	6 3-642	5 4-247	15 7-676	15 7-733	

TABLE 6 CHEMO, CHEMOTHERAPY; CR, COMPLETE RESPONSE, ECOG PS, EASTERN COOPERATIVE ONCOLOGY GROUP PERFORMANCE STATUS; NR, NOT REPORTED; PD, PROGRESSIVE DISEASE; PLAT, PLATINUM THERAPY; PR, PARTIAL RESPONSE; SD, STABLE DISEASE; TKI, TYROSINE KINASE INHIBITOR.

DIFFERENCES

A substantial difference in how AEs are captured analyzed is suggested by the observation that the alectinib development program does not have a single *Neoplasm progression* AE, while this class of AE is common in the brigatinib developmental program.
The cause and implications of this will be expanded upon in the relevant AE-parts of the comparative analysis section.
The ALTA trial reported the more stringent *Confirmed* Objective Response Rate and not the Objective Response Rate, while the NP28761 and NP28673 trials reported (non-confirmed) Objective Response Rates.

All trials assessed response according to RECIST v1.1.
However, the ALTA trial reported IRC-assessed (confirmed) ORR based on the ITT-population, while the NP28761 and NP28673 trials reported IRC-assessed (non-confirmed) ORRs based on the "response evaluable" population.
RECIST v1.1 stipulates that non-evaluable tumors can only obtain a response in the case of a *complete response*. The obvious consequence of omitting non-evaluable tumors from the primary endpoint assessment is an increase in the response rate, as tumors that would otherwise be scored as non-responsive are absent from the dataset.

5.1.2 Results per study

All protocol specified outcome measures are reported in table A3a through A3f.

Study specific summaries are provided in the following sections.

Data are from the primary publications and the EPARs when the EPARs contain data with longer follow-up.

5.1.2.1 Study 101: A Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Preliminary Anti-Tumor Activity of the Oral Anaplastic Lymphoma Kinase (ALK)/Epidermal Growth Factor Receptor (EGFR) Inhibitor Brigatinib (AP26113)

ANALYSIS POPULATIONS

All treated patients (who received at least 1 dose of brigatinib) comprise the main population for efficacy and safety analyses. Since treatment assignment in the study was not performed through an intention-to-treat (ITT) method, such as randomization, the definition of an ITT population is not relevant.

APPLICATION-RELEVANT POPULATION

The study enrolled 137 patients who were treated with doses of brigatinib ranging from 30 mg QD to 300 mg QD, see section 5.1.1.2 for further details [12]. Of these 137 patients, only 25 were ALK+ NSCLC patients who had progressed on crizotinib [10].
The following data are representative of these patients, where possible. In order to further enlighten the efficacy and tolerability of brigatinib, data from the application-relevant patient population will be supplemented with relevant data from non-NSCLC patients who received the 90 mg → 180 mg dose.

OS: 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. All patients were followed-up for survival at least every 3 months, up to 2 years after the initial dose of brigatinib.

Results
The median OS for the 25 ALK+ NSCLC patients treated with the 90 mg → 180 mg regimens previously treated with crizotinib was not reached at the data cut-off of May 31st, 2016, as reported in the EPAR [10]. No Kaplan-Meier curve has been generated for this patient population.
The median OS for the ALK+ NSCLC patients treated with 90 mg QD was 34.4 months [13].

DISCONTINUATION DUE TO ADVERSE EVENTS

Neither the EPAR, nor the publication [2, 10] reported discontinuation due to adverse events for the 25 ALK+ NSCLC patients who received the 90 mg → 180 mg dose.
However, in total 32 patients were treated with 90 mg → 180mg: 3 ALK+ NSCLC patients who were TKI-

naïve, one $EGFR^{T790M}$ mutated NSCLC patient, 3 ALK+ patients with *other cancers*, and the 25 ALK+ NSCLC patients that were resistant to crizotinib [2]. Among these 32 patients the rate of discontinuation due to adverse events was 9% (3 patients) [2].

CNS-Progression (CNS-PFS)

Definition and Operationalisation of endpoint:
Progression-Free-Survival is time from randomization until Progressive Disease (PD), or death due to any cause, whichever occurs first.
Disease assessment including imaging of the brain using a contrast-enhanced brain MRI (such as gadolinium) was required for all patients at baseline and for patients who had CNS metastases at follow-up visits. Target and non-target lesions were selected at study start and followed throughout the course of treatment for response assessment according to RECIST v1.1 guidelines. CNS lesions previously treated with SRS were not evaluable and should not have been selected as either target or non-target lesions. All radiographic images (e.g., CT scan, MRI) performed during the study were submitted to and stored by an imaging core laboratory for future independent evaluation as appropriate.
Disease assessment was performed at screening and 8-week intervals. The allowable window for the tumor imaging screening assessment was 21 days prior to Day 1. However, whenever feasible, baseline imaging was performed as close as possible to Cycle 1, Day 1. Imaging assessment was also required to be performed at the End of Treatment. Note: RECIST v1.1-defined responses were confirmed with an imaging assessment that occurred at least 4 weeks after the first response. For patients in Cohort 5 (measurable brain metastases at baseline) cMRI had to reveal at least one measurable brain lesion ($\geqslant$10 mm at the longest diameter) at screening as the target lesion. All imaging scans included a slice thickness of 1 mm, ideally, and up to 5 mm as a maximum.

Results:
With a median follow-up time of 24.9 months (range: 0.2 to 47.6 months) the median CNS PFS was 14.6 months (95% CI: 12.7; 36.8) among *all* ALK+ NSCLC patients with CNS metastases at baseline [7]. Among the ALK+ NSCLC patients who had CNS-metastases at baseline and were treated with 90 mg $\rightarrow$ 180 mg the median CNS-progression-free-survival was not reached at this data cut-off [10].

Progression-Free-Survival, PFS

Definition and Operationalisation of endpoint:
Progression-Free-Survival is time from randomization until Progressive Disease (PD), or death due to any cause, whichever occurs first.
At screening, disease assessment included imaging of the chest, abdomen, pelvis, and brain using appropriate radiological procedures (CT scan, MRI scan) and physical examination (for palpable lesions). A contrast-enhanced brain MRI (such as gadolinium) was required for all patients at baseline and for patients who had CNS metastases at follow-up visits. Target and non-target lesions were selected at study start and followed throughout the course of treatment for response assessment according to RECIST v1.1 guidelines. CNS lesions previously treated with SRS were not evaluable and should not have been selected as either target or non-target lesions. All radiographic images (e.g., CT scan, MRI) performed during the study were submitted to and stored by an imaging core laboratory for future independent evaluation as appropriate.

Disease assessment was performed at screening and 8-week intervals. The allowable window for the tumor imaging screening assessment was 21 days prior to Day 1. However, whenever feasible, baseline imaging was performed as close as possible to Cycle 1, Day 1. Imaging assessment was also required to be performed at the End of Treatment. Note: RECIST v1.1-defined responses were confirmed with an imaging assessment that occurred at least 4 weeks after the first response.

Results:

At the data cut-off on May 31st 2016, the median PFS was 16.3 month (95% CI: 9.2; NR) among the 25 ALK+ NSCLC patients who were treated with 90 mg → 180 mg [10]. The median follow-up for this cohort is not reported [10].

GRADE 3-4 ADVERSE EVENTS

Definition and Operationalisation of endpoint:
Patients were to be followed for all AEs from the date the informed consent was signed until at least 30 Days After the End of Treatment, and for all serious or study drug-related toxicities until the AEs resolved or were considered chronic or stable or until patient contact discontinued. Type, incidence, severity (graded in accordance with the NCI CTCAE Version 4.0), timing, seriousness and relatedness, outcome, action taken with study drug, and treatment were assessed and documented by the investigator throughout the study. Malignancy-related signs and symptoms noted at study entry were recorded as AEs during the study if they worsened in severity or increased in frequency.
The treatment-emergent AEs were those AEs that started at the time of or after the first dose of study drug and no later than 30 days after the last dose date.
Adverse Events do not imply causality with treatment with study drug.

Results:
The rate of grade 3-4 Adverse Events was not reported specifically for the 25 ALK+ NSCLC patients previously treated with crizotinib and treated with 90 mg → 180 mg brigatinib, which are relevant for the current application. However, in total 32 patients were treated with 90 mg → 180mg: 3 ALK+ NSCLC patients who were TKI-naïve, one $EGFR^{T790M}$ mutated NSCLC patient, 3 ALK+ patients with *other cancers*, and the 25 ALK+ NSCLC patients that were resistant to crizotinib [2].
Among these 32 patients the rate of grade 3-4 adverse events was 63% [2].
However, due to a pharmacovigilance technicality *progression of neoplasm* was captured as an AE. Without this class of AEs, the rate was 59%, table A3a and table A4 (see section 5.1.3 for further information and justification).

None of the patients treated with 90 mg → 180 mg experienced grade 5 events.

A study specific complete list of adverse reactions was not reported in the publication [3], the EPAR [10] or the Clinical Study Report.

However, a compiled listing of adverse reactions from study 101 and ALTA is provided in the EPAR and is presented in this application in table 4, section 5.1.2.2.

QUALITY OF LIFE

As this was a phase I/II trial the study did not include QoL measures.

OBJECTIVE RESPONSE RATE

Definition and Operationalisation of endpoint
Patients had tumour imaging with contrast-enhanced CT of the chest and abdomen and contrast-enhanced MRI of the brain at baseline and at 8 weeks intervals during treatment and at the end of treatment. Investigator determined responses (according to RECIST 1.1) were confirmed with additional imaging assessment 4 weeks after the response was recorded.

Results:
The objective Response rate was 80% (95% CI: 59.3; 93.2).
The confirmed objective response rate was 76% (95% CI: 54.9; 90.6).

5.1.2.2 ALTA - A Study to Evaluate the Efficacy of Brigatinib (AP26113) in Participants With Anaplastic Lymphoma Kinase (ALK)-Positive, Non-small Cell Lung Cancer (NSCLC) Previously Treated With Crizotinib

APPLICATION-RELEVANT STUDY POPULATION

The study enrolled 222 ALK+ NSCLC patients who previously had progressed on crizotinib. These patients were randomized to receive one of either 90 mg brigatinib QD or 90 mg QD for seven days followed by an up-dosing to 180 mg brigatinib QD (90 mg → 180 mg) [3]. Of these 222 patients 110 patients were randomized to the 90 mg → 180 mg arm, and are thus relevant for the current application.
The following data are therefore derived from this cohort of patients.

ANALYSIS POPULATIONS

The primary analyses of efficacy (objective response rate, ORR) were based on the ITT population. The ITT population included all patients randomized to each regimen regardless of whether they received study drug or adhered to the assigned dose.
Safety was analyzed using the treated population for each regimen. These populations were comprised of all patients who received at least one dose of study treatment. The prespecified Statistical Analysis Plan specified that, in the case that more than 3 patients were randomized and not treated with study treatment, the primary efficacy analyses should be repeated using the treated population.
Selected secondary endpoints were analysed in the Per-Protocol Population, comprised of all patients in the treated population excluding all patients who did not meet key entry criteria, had no measurable disease at baseline, or had no adequate post-baseline radiographic response assessment.
Specifically, the per-protocol population were the treated patients who also met all the following criteria:

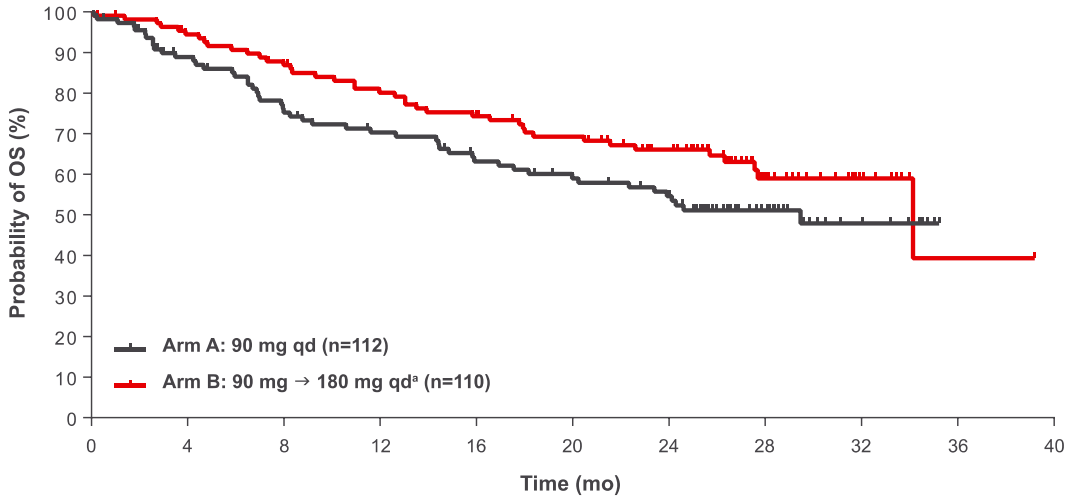
- Histologically or cytologically confirmed locally advanced or metastatic NSCLC
- Confirmed baseline ALK rearrangement by Vysis® FISH test either locally or by central confirmation
- Previously progressed on crizotinib
- At least one measurable target lesion as assessed by the investigator

- At least two adequate post-baseline radiographic response assessments unless the reason for no post-baseline radiographic response assessment were one of the following:
    - Death
    - Discontinuation due to documented disease progression per RECIST v1.1
    - Discontinuation due to AE

OS: 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.
All the randomized patients were included in the primary analysis. OS was defined as the time interval from the date of the first dose of the study treatment until death due to any cause in the ITT population. OS were censored on the date of last contact for patients who were still alive.
For patients who were randomized and not treated, the OS was defined as the time interval from date of randomization to date of death or date of the last contact, if available.
All patients were followed-up for survival at least every 3 months after treatment discontinuation.
Median values and two-sided 95% CIs were estimated using Kaplan-Meier methods.

Results
The latest data cut-off resulted in a median OS of 34.1 months (95% CI: 27.7; NR), as reported in the EPAR [10].
Figure 5 depicts the KM-curves for both the study populations. The application-relevant curve is red.



	Arm A: 90 mg qd	Arm B: 90 mg → 180 mg qd[a]
Median OS, months (95% CI)	29.5 (18.2–NR)	34.1 (27.7–NR)
1-year OS probability, % (95% CI)	70 (61–78)	80 (71–87)
2-year OS probability, % (95% CI)	55 (44–64)	66 (56–74)

[a] 180 mg qd with 7-day lead-in at 90 mg

Figure 5: Kaplan-Meier curves of OS for both study populations.

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 will be 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.

Results:

In total 10.9 % (12/110) of patients discontinued due to adverse events at the data cut-off of September 2017 [10].

A qualitative summary of the adverse events leading to discontinuation from the May 2016 data cut-off is presented in table 7 [10]. It is seen that the disease related AE *Neoplasm Progression* accounts for 18% (2/11) of the total discontinuations. The cause and implications of this, will be further addressed in the relevant paragraph of section 5.1.3.

With-out neoplasm progression rate of discontinuation due to AEs was 9.1%, table 3Ab & table A4

	90 mg QD →180 mg QD
Patients with TEAEs leading to brigatinib discontinuation	11 (10.0)
Pneumonitis	3 (2.7)
Neoplasm progression	2 (1.8)
Pneumonia	2 (1.8)
Angioedema	1 (0.9)
Muscle spasms	1 (0.9)
Radiation pneumonitis	1 (0.9)
Respiratory failure	1 (0.9)

Table 7: Treatment Emergent Adverse Events leading to brigatinib discontinuation – by preferred term, from [10].

CNS-Progression (CNS-PFS)

Definition and Operationalisation of endpoint:

Progression-Free-Survival is time from randomization until Progressive Disease (PD), or death due to any cause, whichever occurs first.

Contrast-enhanced MRI of the brain (such as gadolinium) was required at screening for all patients and was repeated postbaseline for patients with CNS metastases. All radiographic images (e.g., CT scan, MRI) performed during the study were submitted to the imaging core laboratory for central review (Biomedical Systems [BMS], Saint Louis, Missouri).

Disease assessment by CT or MRI scans was performed at screening and at 8-week intervals thereafter (on Day 1 [±3 days] of every odd-numbered cycle) through 15 cycles after the initial dose of brigatinib, and every 3 cycles thereafter until disease progression. More frequent imaging was recommended at any time, if clinically indicated; confirmation of CR or PR might have been performed at least 4 weeks after initial

response. Imaging assessment was also performed at the End-of-Treatment if more than 4 weeks had passed since the last imaging assessment.
Median values and two-sided 95% CIs were estimated using Kaplan-Meier methods.

Results:
With a median follow-up time among all 110 patients of 11.0 months (range: 1.0 to 22.0), the median CNS PFS was 18.4 months (95% CI: 12.8; NR) among all ALK+ NSCLC patients with CNS metastases at baseline [7]. Median CNS PFS among patients with measurable brain metastasis was 18.5 months (95% CI: 4.9; NR) at the September 2017 data cut-off with a median follow-up in the entire population of 24.3 months (range 0.1; 39.2) [10].

PROGRESSION-FREE-SURVIVAL, PFS

Definition and Operationalisation of endpoint:
Progression-Free-Survival is time from randomization until Progressive Disease (PD), or death due to any cause, whichever occurs first.
At screening, disease assessment included imaging of the chest and abdomen (covering adrenal glands), using appropriate radiological procedures (CT scans or MRI with contrast, unless contrast media was contraindicated). Contrast-enhanced MRI of the brain (such as gadolinium) was required at screening for all patients and was repeated postbaseline for patients with CNS metastases. All radiographic images (e.g., CT scan, MRI) performed during the study were submitted to the imaging core laboratory for central review (Biomedical Systems [BMS], Saint Louis, Missouri).
Disease assessment by CT or MRI scans was performed at screening and at 8-week intervals thereafter (on Day 1 [±3 days] of every odd-numbered cycle) through 15 cycles after the initial dose of brigatinib, and every 3 cycles thereafter until disease progression. More frequent imaging was recommended at any time, if clinically indicated; confirmation of CR or PR might have been performed at least 4 weeks after initial response. Imaging assessment was also performed at the End-of-Treatment if more than 4 weeks had passed since the last imaging assessment.
Median values and two-sided 95% CIs were estimated using Kaplan-Meier methods.
PFS was evaluated independently by an IRC and by the investigators

Results:

At the data cut-off of February 2017, the median IRC-determined PFS was 16.7 months (95% CI: 11.6; 21.4), [10], while the investigator-determined PFS was 15.6 months (95% CI: 11.1; 21.0). Median follow-up time was 24.3 (range 0.1; 39.2).
Figure 6 depicts the Kaplan-Meier curve of the investigator-assessed PFS.

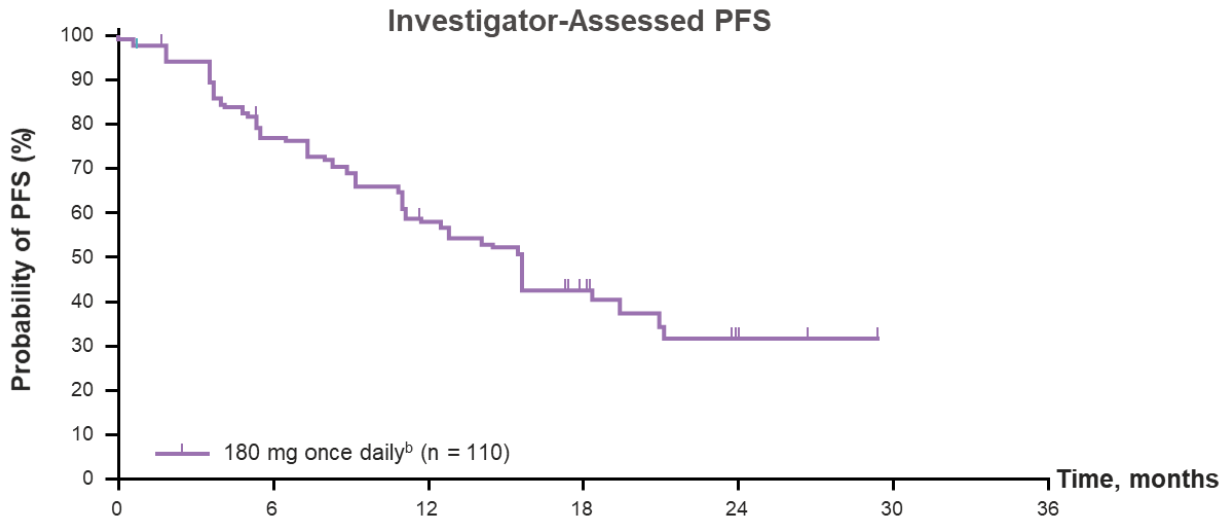


FIGURE 6: INVESTIGATOR-ASSESSED PFS.

GRADE 3-4 ADVERSE EVENTS

Definition and Operationalisation of endpoint:
Patients were to be followed for all AEs from the date the informed consent was signed until at least 30 Days After the End of Treatment, and for all serious or study drug-related toxicities until the AEs resolved or were considered chronic or stable or until patient contact discontinued. Type, incidence, severity (graded in accordance with the NCI CTCAE Version 4.0), timing, seriousness and relatedness, outcome, action taken with study drug, and treatment were assessed and documented by the investigator throughout the study. Malignancy-related signs and symptoms noted at study entry were recorded as AEs during the study if they worsened in severity or increased in frequency.
The treatment-emergent AEs were those AEs that started at the time of or after the first dose of study drug and no later than 30 days after the last dose date.
Adverse Events do not imply causality with treatment with study drug.

Results:
The rate of grade 3-4 adverse events was 70.9% [10]. However, due to a pharmacovigilance technicality, neoplasm progression was captured as an AE (see section 5.1.3 for details). With-out this class of events, the rate of grade 3-4 events was 62%, table A3b & table A4.

A study specific complete list of adverse reactions was not reported in the publication [3], the EPAR [10] or the Clinical Study Report.

However, a compiled listing of adverse reactions from study 101 and ALTA is provided in the EPAR and is presented in this application in table 8, below.

System organ class	Frequency category	Adverse reactions* all grades	Adverse reactions grade 3-4
Infections and infestations	Very common	Pneumonia[a] (15%) Upper respiratory tract infection (13%)	
	Common		Pneumonia[a] (4%)
Blood and lymphatic system disorders	Very common	Anemia (52%) Lymphocyte count decreased (50%) APTT increased (36%) White blood cell count decreased (27%) Neutrophil count decreased (15%) Decreased platelet count (11%)	Lymphocyte count decreased (20%)
	Common		APTT increased (2%) Anemia (1%) Neutrophil count decreased (1%)
Metabolism and nutrition disorders	Very common	Hyperglycemia (66%) Hyperinsulinemia[b] (61%) Hypophosphatemia (38%) Decreased appetite (25%) Hypokalemia (24%) Hypomagnesemia (23%) Hyponatremia (23%) Hypercalcemia (20%)	
	Common		Hypophosphatemia (9%) Hyperglycemia (6%) Hyponatremia (4%) Hypokalemia (1%) Decreased appetite (1%)
Psychiatric disorders	Very common	Insomnia (11%)	
Nervous system disorders	Very common	Headache[c] (44%), Peripheral neuropathy[d] (28%) Dizziness (16%)	
	Common	Memory Impairment (7%) Dysgeusia (5%)	Peripheral neuropathy[d] (2%) Headache[c] (1%)
Eye disorders	Very common	Visual Disturbance[e] (20%)	
	Common		Visual disturbance[e] (2%)
Cardiac disorders	Common	Tachycardia[f] (6%) Electrocardiogram QT prolonged (6%) Bradycardia[g] (5%) Palpitations (4%)	
	Uncommon		Electrocardiogram QT prolonged (0.7%)
Vascular disorders	Very Common	Hypertension (27%)	Hypertension (10%)
Respiratory, thoracic and mediastinal disorders	Very Common	Cough (41%) Dyspnea[h] (29%)	
	Common	Pneumonitis[i] (9%)	Pneumonitis[i] (4%) Dyspnoea[h] (3%)
Gastrointestinal disorders	Very common	Lipase increased (50%) Nausea (49%) Diarrhea[j] (46%) Amylase increased (44%) Vomiting (32%) Constipation (23%) Abdominal pain[k] (19%) Dry mouth (10%) Stomatitis[l] (10%)	Lipase increased (12%)

	Common	Dyspepsia (6%) Flatulence (3%)	Amylase increased (9%) Abdominal pain[k] (1%)
	Uncommon	Pancreatitis (0.7%)	Nausea (0.7%) Dyspepsia (0.7%) Pancreatitis (0.7%)
Hepatobiliary disorders	Very common	AST increased (66%) ALT increased (46%) Alkaline phosphatase increased (39%)	
	Common	Blood lactate dehydrogenase increased (8%) Hyperbilirubinaemia (7%)	ALT increased (4%) AST increased (3%) Alkaline phosphatase
Skin and subcutaneous tissue disorders	Very Common	Rash[m] (35%) Pruritus (13%)	
	Common	Dry skin (4%) Photosensitivity reaction (4%)	Rash[m] (4%) Photosensitivity reaction (1%)
	Uncommon		Dry skin (0.7%)
Musculoskeletal and connective tissue disorders	Very common	Blood CPK increased (50%) Myalgia[n] (41%) Arthralgia (21%)	Blood CPK increased (14%)
	Common	Pain in extremity (9%) Musculoskeletal stiffness (1%)	Pain in extremity (1%)
	Uncommon		Myalgia[n] (0.7%)
Renal and urinary disorders	Very common	Blood creatinine increased (17%)	
General disorders and administration site conditions	Very common	Fatigue[o] (48%) Edema[p] (17%) Pyrexia (12%)	
	Common	Pain (5%) Non-cardiac chest pain (4%) Chest discomfort (4%)	Fatigue[o] (2%)
	Uncommon		Non-cardiac chest pain (0.7%) Pyrexia (0.7%)
Investigations	Common	Weight decreased (7%)	
	Uncommon		Weight decreased (0.7%)

Table 8: Adverse reactions reported in patients treated with Brigatinib in ALTA and Study 101 (per Common Terminology Criteria for Adverse Events (CTCAE) version 4.0) at the 90 mg → 180 mg regimen. **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 paresthesia, peripheral sensory neuropathy, dysesthesia, hyperesthesia, hypoesthesia, neuralgia, neuropathy peripheral, neurotoxicity, peripheral motor neuropathy, polyneuropathy. **e**: includes altered visual depth perception, asthenopia, cataract, color blindness acquired, diplopia, glaucoma, intraocular pressure increased, macular edema, photophobia, photopsia, retinal edema, 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 dyspnea, dyspnea exertional. **i**: includes interstitial lung disease, pneumonitis. **J**: includes diarrhea, diarrhea 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 edema, face edema, localised edema, edema peripheral, periorbital edema, swelling face, generalised edema, peripheral swelling. *****: The frequencies for ADR terms associated with chemistry and hematology laboratory changes were determined based on the frequency of abnormal laboratory shifts from baseline.

Grade 5 AEs were experienced by 11 patients in the 90 mg → 180 mg arm, table 9. Based on a narrative analysis 1 death in the entire study was considered possible related to brigatinib [10].

QUALITY OF LIFE (QOL)

Definition and Operationalisation of endpoint

Patient-reported symptoms and HRQoL were collected by administering the EORTC QLQ-C30 (v3.0) questionnaire. The questionnaire was administered to the patients at baseline and every 4 weeks following baseline, at end-of-treatment and after 30 days follow-up.
The questionnaire was administered to patients in their local language.

The EORTC QLQ-C30 were scored for 5 functional scales (physical, role, cognitive, emotional, and social functioning); 3 symptom scales (fatigue, pain, and nausea/vomiting); and a global health status/QoL scale. Six single-item scales were also included (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties).

For HRQoL measures, raw scores for multi-item scales were calculated by averaging items within scales first. Raw scores were summarized by time point with descriptive statistics for each scale. Raw scores for multi-item scales and single-item measures were linearly transformed to obtain the score ranging from 0 to 100 according to EORTC QLQ-C30 (V3) Scoring Manual [14].
The global health status / QoL scale based upon Q29 and Q30 were used as the overall summary measure. The HRQoL scores including the overall summary measure were summarized at baseline and by time point in evaluable patients overall and by treatment group. The changes from baseline over time were summarized with descriptive statistics and explored using mixed effects models.

Results

No QoL data that addresses mean change from baseline has been published in the EPAR or the peer-reviewed publications.
The following therefore represents non-published data.

The protocol for the assessment of the added clinical value of brigatinib dictates that the minimal clinically relevant difference is a 10% on the Global scale.
This is not in accordance with the minimal clinically important change that was defined for the comparator alectinib roughly one year ago, where the minimal important difference was 5% [15]. This value of 5% improvement represents a score that patients reports as a “little” positive change, e.g. the change is perceptible to the patients [16].

In the ALTA trial, the maximum mean change in Global Health Status score was 11.96, figure 7, **Takeda Data on File**.
Overall, the curve of mean change in Global Health Status / Quality of Life (Global HRQoL) shows a relatively steady improvement in the range of 5-12 percentage points through-out the first 2 years of treatment (figure 5) suggesting that 1) treatment with brigatinib is associated with a perceptible positive change in Global Health Status and 2) this positive change is durable.

Indeed, the mean improvement of Global Health Status is 4.8% at the end of treatment, trending toward 5%.

As the numbers of responders decrease through-out the trial, the 95% CI intervals, predictably, increase.

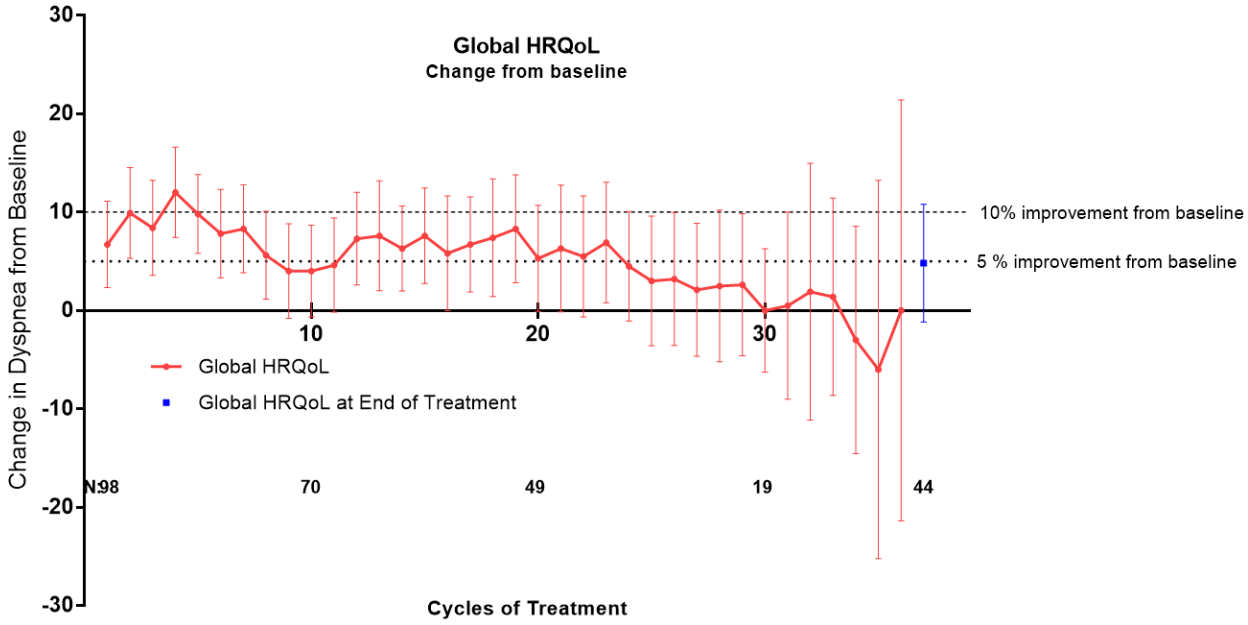


FIGURE 7. MEAN CHANGE FROM BASELINE IN GLOBAL HEALTH STATUS, OUTCOME VARIABLE ARE 95% CI.

To complement these Global Health Status data, Takeda Pharma A/S, has chosen to submit data for the disease-relevant single-item measure dyspnea.

This QoL-domain showed a persistent bettering of score starting at 28 days after the first administration of brigatinib. Thus, the mean improvement in dyspnea from baseline ranged from 5.1% to 19.0%, figure 8, **Takeda Data on File**. The curve shows a relatively steady improvement in the range of 7-12 percentage points through-out the treatment.
Indeed, several of the means show a bettering of ≥ 10% as specified in the protocol, while all the means show a bettering of ≥ 5% as specified in the protocol for evaluation of the comparator, alectinib [15]. Predictably, there is an increasing 95% CI with decreasing responders.

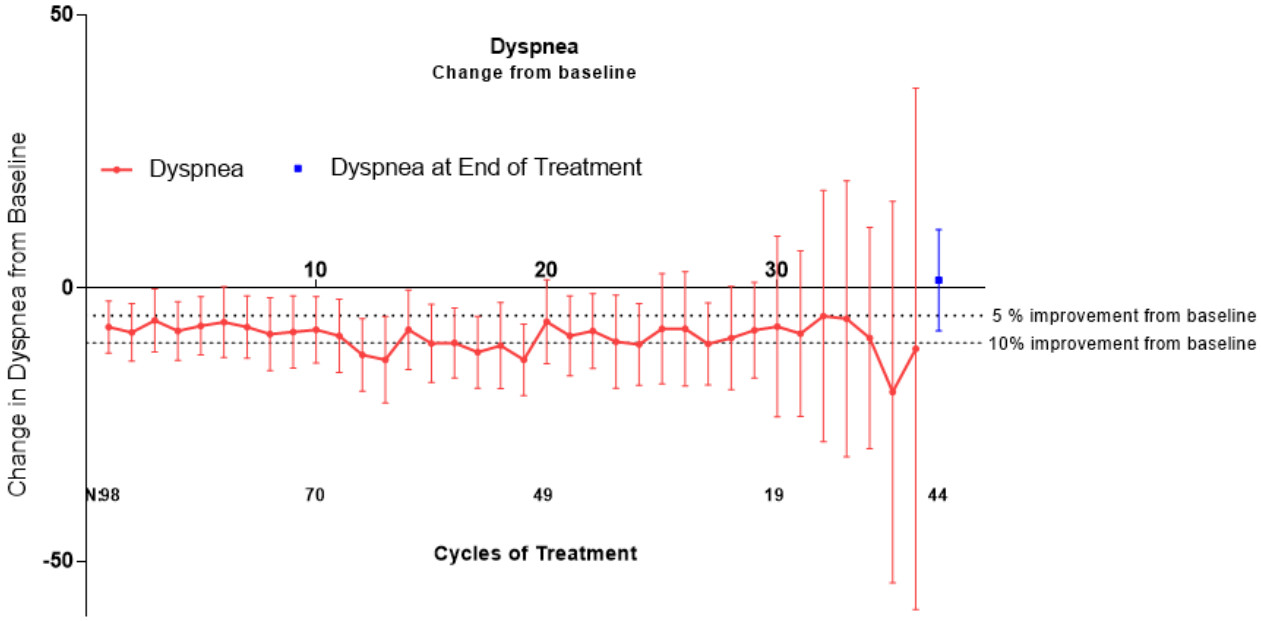


FIGURE 8. MEAN CHANGE FROM BASELINE, IN DYSPNEA RELATED QOL OUTCOME VARIABLES ARE 95% CI.

OBJECTIVE RESPONSE RATE (ORR)

Definition and Operationalisation of endpoint

The protocol for assessment of brigatinib in the Medicines Council stipulates the current efficacy measure as "objective Response Rate." However, no objective response rates have been published for the ALTA trial. Instead, the primary objective "*Confirmed* Objective Response Rate" has been reported in both publications and EPAR [3, 10]. The distinction between the two concepts is that a confirmed response is validated (confirmed) four weeks after the initial response has been recorded. Thus, a confirmed response is a response that is more likely to be true and/or maintained for at least four weeks [17], making confirmed responses more clinically meaningful.

Additionally, the Confirmed ORR is likely to be lower than the ORR.

Tumor response was determined per RECIST v1.1 by the investigator, with a secondary independent radiological review.
Patients had tumor imaging with contrast-enhanced CT of the chest and abdomen and contrast-enhanced MRI of the brain at baseline and at 8 weeks intervals during treatment and at the end of treatment.
Investigator determined responses (according to RECIST 1.1) were confirmed with additional imaging assessment 4 weeks after the response was recorded.
Confidence Intervals was reported at 97.5% and 95.0 % level for investigator assessed and IRC assessed confirmed Objective Response Rates, respectively, and were calculated using the exact binomial method [3].

Results:

As described above, the ALTA trial reports *confirmed* Objective Response Rates, rather than Objective Response Rates.

The confirmed objective response rates were 56.4% (97.5% CI: 45.2; 67.0) and 56.4% (95% CI: 46.6%; 65.8%) as assessed by investigators and IRC, respectively [10].

5.1.2.2 Study NP28761: A Phase I/II Study of the ALK Inhibitor alectinib (CH5424802/RO5424802) in patients with ALK-rearranged Non-Small Cell Lung Cancer previously treated with Crizotinib

ANALYSIS POPULATIONS

For analysis of the primary endpoint and other response endpoints, the primary analysis population was defined as the response-evaluable population—ie, patients with measurable disease at baseline by IRC who received at least one dose of study drug. All other endpoints were assessed in the intention-to-treat population.

OS: 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 [5].

Results
The median OS for the 87 patients treated was 22.7 months (95% CI: 17.2, NE), as reported in the EPAR [9].
No Kaplan-Meier curve is available for this patient population.

DISCONTINUATION DUE TO ADVERSE EVENTS

2% of the patients discontinued the treatment due to AEs [5].
As reported in the publication one patient had a serious, grade 3, drug-induced liver injury. The second patient was diagnosed with grade 3 increased aspartate aminotransferase and alanine aminotransferase and grade 2 increased blood bilirubin.

CNS-PROGRESSION (CNS-PFS)

Neither the primary publication, nor the EPAR reports this endpoint separately for this trial [5, 9]. However, a separate publication reports a pooled analysis of patients with baseline CNS metastasis treated with 600 mg alectinib twice daily from this trial and a similar trial from the development program of alectinib (NP28673) [8].
This endpoint is therefore reported based on this pooled analysis.

Definition and Operationalisation of endpoint:
Progression-Free-Survival is time from randomization until Progressive Disease (PD), or death due to any cause, whichever occurs first.
As described in the publication [8] tumor response and progression, including CNS response and progression, were assessed according to RECIST version 1.1 by IRC. A separate IRC assessing CNS disease consisted of specialist neuroradiologists who were blinded to systemic response.

All patients underwent baseline tumor imaging, including computed tomography of the chest and abdomen, as well as brain imaging. If MRI was not possible, a CT of the head was acceptable.
CNS assessment was performed prospectively by regular brain imaging; magnetic resonance imaging was the most commonly used method; in the pooled population, 85 patients (62.5%) were assessed with magnetic resonance imaging, 38 (27.9%) with computed tomography, and 13 (9.6%) with both methods.
The frequency of response or progression assessments, including brain scans, was the same regardless of baseline CNS metastases status.
However, scans were taken every 6 weeks in the NP28761 study and every 8 weeks in NP28673.

Analysis
CNS end points were assessed in the following two populations: patients with measurable CNS disease at baseline and patients with measurable and/or non-measurable CNS disease at baseline, on the basis of RECIST version 1.1 by IRC. CORR was defined as objective tumor response rate (CR and PR) of CNS lesions in patients who had baseline CNS disease, on the basis of RECIST version 1.1 by IRC. CNS DCR (CDCR) was defined as the percentage of patients who had a best overall CNS response of PR, CR, or stable disease (SD) on the basis of RECIST version 1.1 by IRC.
CDOR was defined as the time from the first observation of a CNS response until the first observation of CNS progression or death from any cause on the basis of RECIST version 1.1 by IRC. For patients with only non-measurable disease, response could be classed as CR, SD, or PD, but not PR.
The Clopper-Pearson method was used to construct 95% CIs for response rates. Kaplan-Meier analysis of time-to-event data (DOR) was used to estimate median event times, and the Brookmeyer-Crowley method was used to calculate two-sided 95% CIs.
The pooled CNS population from the two different trials comprised 136 patients (out of a total of 225 patients, 60%) [8].

Results:
The combined median CNS PFS for the NP28761 and NP28673 trials was 8.3 months (95% CI: 5.9; 11.2) [8].

PROGRESSION-FREE-SURVIVAL, PFS

Definition and Operationalisation of endpoint:
Progression-Free-Survival is time from randomization until Progressive Disease (PD), or death due to any cause, whichever occurs first.
As described in the publication [5], all patients underwent tumor imaging at baseline, including CT of either the chest, abdomen, or pelvis and MRI brain scans.
An independent review committee (IRC) assessed measurable disease at baseline and responses and progressions by RECIST at subsequent visits. This IRC assessed both systemic disease and CNS disease where applicable.
Restaging scans were obtained for all patients, including brain scans, every 6 weeks through cycle six, then every 9 weeks thereafter.
Tumor responses were assessed with RECIST.
Laboratory tests (haematology, serum chemistry, blood coagulation tests, urinalysis, and electrocardiograms) were done on day 1 of every cycle and at the end of treatment.
For the independent review, two different IRC readers read all scans; if no discordance was noted between the two assessments, data from the first reader were used. Any discrepancies between the readers were adjudicated independently by a third reader.

Results:

At per the IRC, the median PFS was 8.2 month (95% CI: 6,3; 12,6) [9]. The median follow-up was 17 months [9].

GRADE 3-4 ADVERSE EVENTS

Definition and Operationalisation of endpoint:

Adverse events were graded according to Common Terminology Criteria for Adverse Events, version 4.0 and were assessed from the start of treatment until 28 days after the final administration of alectinib. Adverse Events do not imply causality with treatment with study drug.

Results:
The EPAR and article [5, 9] reports that

- 41.4% of the patients, corresponding to 36 patients, experienced a grade 3-5 event
- 2,3% (n=2) of the patients died due to an AE, one of which was considered related to alectinib [5].

A study specific complete list of adverse reactions was not reported in the publication [5] or the EPAR [9].

However, a list of Adverse Events occurring with ≥ 10% were reported in the publication [5], and is presented in table 9:

AEs with a frequency ≥ 10% in NP28761	Grade 1–2	Grade 3	Grade 4
Blood creatine phosphokinase increased	12 (14%)	7 (8%)	0
Aspartate aminotransferase increased	14 (16%)	4 (5%)	0
Alanine aminotransferase increased	11 (13%)	5 (6%)	0
Weight increased	14 (16%)	0	0
Blood alkaline phosphatase increased	11 (13%)	0	0
Blood bilirubin increased	6 (7%)	1 (1%)	0
Activated partial thromboplastin time prolonged	4 (5%)	1 (1%)	0
Electrocardiogram QT prolonged	0	1 (1%)	0
Fatigue	29 (33%)	0	0
Peripheral oedema	20 (23%)	0	0
Generalised oedema	0	1 (1%)	0
Constipation	31 (36%)	0	0
Nausea	19 (22%)	0	0
Diarrhoea	18 (21%)	0	0
Vomiting	10 (11%)	0	0

Intestinal obstruction	0	1 (1%)	0
Myalgia	21 (24%)	0	0
Back pain	9 (10%)	0	0
Headache	18 (21%)	0	0
Dizziness	9 (10%)	0	0
Seizure	2 (2%)	1 (1%)	0
Hemiparesis	1 (1%)	1 (1%)	0
Brain oedema	0	0	1 (1%)
Cerebral ventricle dilatation	0	1 (1%)	0
Cerebrovascular accident	0	1 (1%)	0
Embolic stroke	0	0	1 (1%)
Dyspnoea	13 (15%)	3 (3%)	0
Cough	15 (17%)	0	0
Obstructive airways disorder	0	1 (1%)	0
Upper-respiratory-tract infection	9 (10%)	0	0
Lung infection 1 (1%)	1 (1%)	0	
Influenza	0	1 (1%)	0
Staphylococcal sepsis	0	1 (1%)	0
Hypokalaemia	6 (7%)	2 (2%)	0
Hypertriglyceridaemia	5 (6%)	2 (2%)	0
Hypoalbuminaemia	4 (5%)	1 (1%)	0
Hypophosphataemia	2 (2%)	2 (2%)	0
Hypocalcaemia	2 (2%)	1 (1%)	0
Hyponatraemia	2 (2%)	0	1 (1%)
Glucose tolerance impaired	0	1 (1%)	0
Hyperammonaemia	0	1 (1%)	0
Malnutrition	0	1 (1%)	0
Photosensitivity reaction	9 (10%)	0	0
Anaemia	15 (17%)	0	1 (1%)
Neutropenia	3 (3%)	1 (1%)	0

Lymphopenia	1 (1%)	1 (1%)	0
Insomnia	10 (11%)	0	0
Confusional state	0	1 (1%)	0
Drug-induced liver injury	0	1 (1%)	0

TABLE 9 : AES WITH A FREQUENCY ≥ 10% IN THE NP28761 TRIAL

QUALITY OF LIFE

Definition and Operationalisation of endpoint:
Quality of life was assessed on day 1 of cycle one and on day 1 of all subsequent odd cycles, using the European Organisation for Research and Treatment of Cancer (EORTC) Quality-of-Life Questionnaire (QLQ-C30) and its corresponding module for lung cancer (QLQ-LC13) [5].

Results
An improvement in Global Health Status of more than 10 points was recorded in the trial [5].

OBJECTIVE RESPONSE RATE

Definition and Operationalisation of endpoint
ORR was assessed according to RECIST v 1.1 and was assessed in the *response-evaluable population*, meaning the patients who had measurable disease at baseline [5]. This corresponded to 67 out of a total of 87 patients [9].

95% CI was calculated using Clopper-Pearson CI methodology [5]

Results:
The objective Response rate was 52.2% (95% CI: 39.7; 64.6) [9].
No confirmed ORR was reported.

5.1.2.3 *Study NP28673: A Study of Alectinib (RO5424802) in Participants With Non-Small Cell Lung Cancer Who Have Anaplastic Lymphoma Kinase (ALK) Mutation and Failed Crizotinib Treatment*

ANALYSIS POPULATIONS

For analysis of the primary endpoint and other response endpoints, the primary analysis population was defined as the response-evaluable population—ie, patients with measurable disease at baseline by IRC who received at least one dose of study drug. All other endpoints were assessed in the intention-to-treat population.

OS: 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; the Brookmeyer-Crowley method was used to calculate two-sided 95% CIs [4].

Results
The median OS for the 138 patients treated was 26.0 months (95% CI: 21.5, NE), as reported in the EPAR [9].
No Kaplan-Meier curve is available for this patient population.

DISCONTINUATION DUE TO ADVERSE EVENTS

Definition and Operationalisation of endpoint:
Adverse events were graded according to Common Terminology Criteria for Adverse Events, version 4.0 and were assessed from the start of treatment until 28 days after the final administration of alectinib. Adverse Events do not imply causality with treatment with study drug.

Results:
8.7 % of the patients discontinued the treatment due to AEs [9].

CNS-PROGRESSION (CNS-PFS)

Neither the primary publication, nor the EPAR reports this endpoint separately for this trial [5, 9]. However, a separate publication reports a pooled analysis of patients with baseline CNS metastasis treated with 600 mg alectinib twice daily from this trial and a similar trial from the development program of alectinib (NP28673) [8].
This endpoint is therefore reported based on this pooled analysis.

Definition and Operationalisation of endpoint:
Progression-Free-Survival is time from randomization until Progressive Disease (PD), or death due to any cause, whichever occurs first.
As described in the publication [8] tumor response and progression, including CNS response and progression, were assessed according to RECIST version 1.1 by IRC. A separate IRC assessing CNS disease consisted of specialist neuroradiologists who were blinded to systemic response.
All patients underwent baseline tumor imaging, including computed tomography of the chest and abdomen, as well as brain imaging. If MRI was not possible, a CT of the head was acceptable.
CNS assessment was performed prospectively by regular brain imaging; magnetic resonance imaging was the most commonly used method; in the pooled population, 85 patients (62.5%) were assessed with magnetic resonance imaging, 38 (27.9%) with computed tomography, and 13 (9.6%) with both methods.
The frequency of response or progression assessments, including brain scans, was the same regardless of baseline CNS metastases status.
However, scans were taken every 6 weeks in the NP28761 study and every 8 weeks in NP28673.

Analysis
CNS end points were assessed in the following two populations: patients with measurable CNS disease at baseline and patients with measurable and/or nonmeasurable CNS disease at baseline, on the basis of RECIST version 1.1 by IRC. CORR was defined as objective tumor response rate (CR and PR) of CNS lesions in patients who had baseline CNS disease, on the basis of RECIST version 1.1 by IRC. CNS DCR (CDCR) was

defined as the percentage of patients who had a best overall CNS response of PR, CR, or stable disease (SD) on the basis of RECIST version 1.1 by IRC.
CDOR was defined as the time from the first observation of a CNS response until the first observation of CNS progression or death fromany cause on the basis of RECIST version 1.1 by IRC. For patients with only nonmeasurable disease, response could be classed as CR, SD, or PD, but not PR.
The Clopper-Pearson method was used to construct 95% CIs for response rates. Kaplan-Meier analysis of time-to-event data (DOR) was used to estimate median event times, and the Brookmeyer-Crowley method was used to calculate two-sided 95% CIs.
The pooled CNS population from the two different trials comprised 136 patients (out of a total of 225 patients, 60%) [8].

Results:
The combined median CNS PFS for the NP28761 and NP28673 trials was 8.3 months (95% CI: 5.9; 11.2) [8].

PROGRESSION-FREE-SURVIVAL, PFS

Definition and Operationalisation of endpoint:
Progression-Free-Survival is time from randomization until Progressive Disease (PD), or death due to any cause, whichever occurs first.
As described in the publication [5], all patients underwent tumour imaging at baseline, including CT of either the chest, abdomen, or pelvis and MRI brain scans.
An independent review committee (IRC) assessed measurable disease at baseline and responses and progressions by RECIST at subsequent visits. This IRC assessed both systemic disease and CNS disease where applicable.
Restaging scans were obtained for all patients, including brain scans, every 8 weeks.
Tumour responses were assessed with RECIST.
Laboratory tests (haematology, serum chemistry, blood coagulation tests, urinalysis, and electrocardiograms) were done on day 1 of every cycle and at the end of treatment.

Results:

At per the IRC, the median PFS was 8.9 month (95% CI: 5.6; 12,8) [9]. The median follow-up was 21 months [9].

GRADE 3-4 ADVERSE EVENTS

Definition and Operationalisation of endpoint:
Adverse events were graded according to Common Terminology Criteria for Adverse Events, version 4.0 and were assessed from the start of treatment until 28 days after the final administration of alectinib. Safety data are summarized for all patients who received at least one dose of alectinib.

Results:
The EPAR [9] reports that

- 39.9% of the patients, corresponding to 55/138, experienced a grade 3-5 event
- 3.6% (n=5) of the patients died due to an AE.

A study specific complete list of adverse reactions was not reported in the publication [4] or the EPAR [9].

However, a list of Adverse Events occurring in ≥ 10% of patients were reported in the publication[4], and is presented in table 10:

No. (%) of Patients With Adverse Event by Grade					
Adverse Event	Grade 1	Grade 2	Grade 3	Grade	All Grades
Any cause, in ≥ 10% Patients					
Constipation	39 (28)	6 (4)	0	0	45 (33)
Fatigue (1)	26 (19)	8 (6)	2	0	36 (26)
Peripheral edema (1)	27 (20)	6 (4)	1	0	34 (25)
Myalgia (1)	25 (18)	5 (4)	1	0	31 (23)
Asthenia (1)	16 (12)	8 (6)	1	0	25 (18)
Headache (1)	16 (12)	4 (3)	2	0	22 (16)
Cough	15 (11)	4 (3)	0	0	19 (14)
Dyspnea (3)	8 (6)	5 (4)	4	0*	18 (13)
Nausea	13 (9)	3 (2)	0	0	16 (12)
AST elevation (1)	13 (9)	1 (1)	1	1 (1)	16 (12)
Rash	15 (11)	1 (1)	0	0	16 (12)
Vomiting (1)	10 (7)	4 (3)	1	0	15 (11)
Diarrhea (1)	10 (7)	3 (2)	1	0	14 (10)
ALT elevation (1)	7 (5)	5 (4)	1	1 (1)	14 (10)
Diarrhea (1)	6 (4)	0	1	0	7 (5)
*One patient had a grade 5 event that was unrelated to treatment.					

TABLE 10 AES WITH A FREQUENCY ≥ 10% IN THE NP28673 TRIAL

QUALITY OF LIFE

QoL was not reported from this trial in either the publication [4], or the EPAR [9].

OBJECTIVE RESPONSE RATE

Definition and Operationalisation of endpoint

The response evaluable (RE) population comprised patients with measurable disease at baseline who had a baseline tumor assessment and who had received at least one dose of alectinib at the RP2D of 600 mg twice daily.

ORR was defined as the proportion of patients achieving a best response of complete response (CR) or partial response (PR) in the RE population. The RE population comprised 122 patients (out of 138).

95% CI was calculated using Brookmeyer-Crowley CI methodology [4].

Results:
The IRC-assessed objective Response rate in the *response evaluable population* was 50.8% (95% CI: 41.6; 59.9) [4].
No confirmed ORR was reported.

5.1.2.4 ALUR Alectinib Versus Pemetrexed or Docetaxel in Anaplastic Lymphoma Kinase (ALK)-Positive Advanced Non-Small Cell Lung Cancer (NSCLC) Participants Previously Treated With Platinum-Based Chemotherapy and Crizotinib

ANALYSIS POPULATIONS

This was a randomized trial that compared alectinib against chemotherapy post-crizotinib.
The data presented in this application is derived from the alectinib arm of the trial.
The analysis populations for protocol V5 (ITT2, C-ITT2, and mC-ITT2) included patients in the intent-to-treat (ITT), C-ITT (patients in the ITT population with CNS disease at baseline) and mC-ITT (patients in the ITT population with measurable CNS disease at baseline) populations who were randomized from the first randomization to the day when the 90th randomization occurred [6].

OS: 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; Cox model analysis was used to calculate two-sided 95% Cis [6].

Results
The median OS for the 72 patients in the ITT was 12.6 months (95% CI: 9.7, NR), as reported in the trial publication [6]. Median follow-up was not reported; the safety follow-up was short at 6.5 months, and the OS data was immature, with only 22% of events having occurred [6]
No Kaplan-Meier curve is available.

DISCONTINUATION DUE TO ADVERSE EVENTS

Definition and Operationalisation of endpoint:
Safety was monitored by assessing serious and non-serious AEs, safety laboratory tests, vital signs, and electrocardiograms. The incidence, nature, and severity of all AEs were graded according to the CTCAE v4.0.

Results:

5.7 % of the patients discontinued the treatment due to AEs [6].

CNS-Progression (CNS-PFS)

Neither the primary publication, nor the EPAR reports this endpoint for this trial [6, 9].

Progression-Free-Survival, PFS

Definition and Operationalisation of endpoint:
Progression-Free-Survival is time from randomization until Progressive Disease (PD), or death due to any cause, whichever occurs first.
Primary analysis of investigator-assessed PFS (ITT) was carried out sing a stratified Cox model including treatment arm variable and stratification factors. Estimates for PFS were obtained using a Kaplan–Meier Approach.
As described in the publication [6], disease was assessed at screening and every 6 weeks until progression. Response (RECIST v1.1) was assessed by investigators using physical examinations, computed tomography scans, and magnetic resonance imaging.

Results:
As per the IRC, the median PFS was 7.1 months (95% CI: 6.3; 10.8); the investigator assessed PFS was 9.6 months (95% CI: 6.9; 12.2) [6]. The median follow-up was not reported explicitly for the efficacy assessments; the safety follow-up was 6.5 months [6].

Grade 3-4 Adverse Events

Definition and Operationalisation of endpoint:
Safety was monitored by assessing serious and non-serious AEs, safety laboratory tests, vital signs, and electrocardiograms. The incidence, nature, and severity of all AEs were graded according to the CTCAE v4.0. **Importantly, the safety follow-up was very short at 6.5 months.**

Results:
The primary publication [6] reports that

- 27.1% of the patients, corresponding to 18/70, experienced a grade 3-4 event
- None (0%) of the patients died due to an AE.

A study specific complete list of adverse reactions was not reported in the publication [6] or the EPAR [9].

However, a list of Adverse Events occurring in ≥ 10% of patients were reported in the publication[4], and is presented in table 11:

n (%)	All grades	Grade ≥3
Fatigue	4 (5.7)	0
Constipation	13 (18.6)	0
Nausea	1 (1.4)	0

Neutropenia	2 (2.9)	0
Anemia	10 (14.3)	1 (1.4)
Asthenia	7 (10.0)	2 (2.9)

TABLE 11. AES WITH A FREQUENCY ≥ 10% IN THE ALUR TRIAL.

Median safety follow-up in this trial was short at 6.5 months [6].

QUALITY OF LIFE

QoL was not reported from this trial in either the publication [6], or the EPAR [9].

OBJECTIVE RESPONSE RATE

Definition and Operationalisation of endpoint
ORR was defined as the proportion of patients achieving a best response of complete response (CR) or partial response (PR) and was summarized by the number and proportion of responders and non-responders, along with two-sided 95% Clopper–Pearson confidence intervals (CIs) [6].
ORR was assessed in the ITT population.

Results:
The investigator-assessed Objective Response Rate was 37.5%% (95% CI:26 ; 50) [6].
No confirmed or IRC assessed ORRs were reported.

5.1.3 Comparative analyses

DATA SOURCES FOR COMPARATIVE ANALYSIS

A comparative analysis is complicated by the fact that four of the relevant trials for this application do not have a comparator [2-5], and that the last trial has an irrelevant comparator [6].

In effect all the trials are thus uncontrolled single arm trials.

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.

The narrative analysis will be supplemented by MAIC based comparisons, see below, of OS, PFS and ORR between ALTA (brigatinib) & NP28761 (alectinib) and ALTA & NP28673 (alectinib) as well as by statistical analysis of naïve data, where relevant. The outcomes of these analyses are presented in table A4.

Specifically, OS, PFS, and ORR will be compared indirectly through MAIC analysis, while AE-rates and median CNS PFS, will be compared naively, with all the caveats such a comparison necessitates. Mean change in QoL will not be compared, as the data source of the comparator trial only reports changes "above 10 points".

Finally,

- the study-specific values of all outcome measures available are reported in tables A3a-e
- MAIC based comparative data are presented in tables A3f-g
- naïve comparisons of AE-rates and CNS-PFS is presented in table A4.

MAIC ANALYSIS, RECKHAM ET AL, 2018 & UNPUBLISHED ANALYSIS

In the absence of head-to-head studies and common comparators, standard methods such as network meta-analysis are not feasible.

However, a matching adjusted indirect comparison can be used [18, 19]. This type of analysis allows a dataset composed of individual patient data to be compared against a dataset composed by summary patient data [18, 19] and is applicable to compare treatment outcomes such as continuous, categorical and censored time-to-event outcomes [19].
Briefly, the analysis is based on a form of propensity score weighting of individual patient data from the index trial such that their weighted average characteristics match those of subjects in the comparator trial. Following matching, the relative efficacy is estimated across the balanced populations [18, 19].

The method is generally accepted and is generally used by EMA and NICE when approving pharmaceuticals for rare diseases, e.g. [20-23].

Within NSCLC the method has been used to evaluate the treatment of metastatic BRAF V600E mutated NSCLC [24], to evaluate the clinical efficacy of ceritinib in 2. line treatment, and for reimbursement purposes of ceritinib in 1. Line of treatment by NICE [23].

Two different comparative analyses have been prepared:

1. A published MAIC analysis generating relative efficacy estimates between brigatinib and alectinib for ORR, PFS, OS [1]. This analysis was based on the individual patient level data from the ALTA trial being weighed against the summary patient data from the NP28761 and NP28673 trials, respectively [1]. This work is based on an early data cut-off (Februrary 2018), where the overall survival data of brigatinib was immature: median 27.6 months rather than the median 34.1 months registered at the latest data cut-off (September, 2017).
2. A Network Meta-analysis based on three separate MAIC analysis of the individual patient level data from the ALTA trial being weighed against the summary patient data from the NP28761, NP28673, ALUR trials, respectively.

The latter of the two comparative analyses was based on the latest data cut-off of September 2017.

As reported in the publication [1], the baseline characteristics to be matched on included prognostic factors previously identified in the literature such as Asian ethnicity, ECOG performance status, smoking status, and crizotinib as last prior therapy as well as variables with clinical relevance (age, sex, best response to prior crizotinib, previous chemotherapy, prior radiotherapy, number of metastatic sites, and brain metastases). Each MAIC matched on as many of these variables as were available in the comparator trial to limit the potential bias of the unanchored MAIC assumption.

One important aspect of the MAIC methodology is to minimize all confounding aspects in the comparison [19]. The comparison of ORR was therefore based on IRC-assessed ORRs in the ITT-populations of ALTA, NP28761, and NP28673 [1], see section 5.1.1.4

For a full account of the methodology, please see the *Statistical Methods* section of the original publication [1], appendix A6.

OVERALL SURVIVAL, OS

A naïve comparison of the OS data obtained from the five trials relevant for this application consistently demonstrates a numerically longer OS for patients treated with brigatinib.

Indeed, using the longest follow-up available, the median OS was not reached for the application relevant study population of the 101-trial and was 34.1 months in the ALTA trial [10]. This is compared to the median OS in the alectinib trials (NP28761/NP28673/ALUR) of 22.7, 26.0, and 12.6 months, respectively [6, 9], figure 9 and table A3a-e.

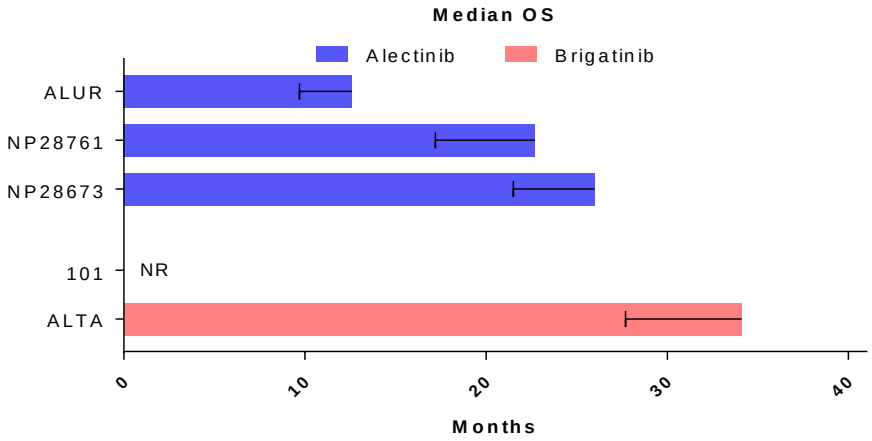


FIGURE 9: MEDIAN OVERALL SURVIVAL AS REPORTED WITH THE LONGEST POSSIBLE FOLLOW-UP [6, 9, 10]. OUTCOME VARIABLES ARE 95% CI. NOTE THAT NONE OF THE TRIALS HAVE REPORTED AN UPPER 95% CI (NOT ESTIMABLE) AND THAT MEDIAN OS WAS NOT REACHED IN THE 101-STUDY.

Consquently, a meta-analysis based on MAICs using this more mature data cut-off has demonstrated an OS HR for ALTA vs. NP28761/NP28673/ALUR of 0,57 (95% CI: 0.43; 0.77), Takeda Data on File.

For the published MAIC analysis [1] the early data cut-off of February 2017 was used for brigatinib. At this point the median OS was 27.6 months [1].

Table 12 summarizes the data from the analysis.

	NPNP28761			NP28673		
	Alectinib (N=87)	**Brigatinib Naive** (N = 110)	**Brigatinib MAIC** (ESS = 78)	**Alectinib** (N=138)	**Brigatinib Naive** (N = 110)	**Brigatinib MAIC** (ESS = 71)
Median OS, Months (95% CI)	22.7 (17.2, NA)	27.6 (27.6, NA)	27.6 (27.6, NA)	26.0 (21.5, NA)	27.6 (27.6, NA)	27.6 (27.6, NA)
OS, HR (95% CI) Cox-regression	--	0.60 (0.37, 0.97)	0.70 (0.42, 1.16)	--	0.69 (0.45, 1.06)	0.66 (0.39, 1.09)
P-value	--	0.037	0.163	--	0.091	0.104
12-month Survival % (95% CI)	69.3 (58.2; 78.0)	80.1 (71.1; 86.6)	75.3 (64; 83.5)	74.7 (66.4; 81.2)	80.1 (71.1; 86.6)	79.5 (67.7; 87.3)
24-month Survival % (95% CI)	47.3 (31.2; 61.8)	69.4 (59.3; 77.5)	66 (53.6; 75.8)	56.5 (47.3; 64.6)	69.4 (59.3; 77.5)	71.5 (67.7; 87.3)

TABLE 12: NAIVE AND MAIC ADJUSTED OS-DATA FROM [1]. EES: EFFECTIVE SAMPLE SIZE.

It is seen, that

- The matching of the brigatinib data results in a significantly smaller study population (Effective Sample Size, ESS) and consequently significantly wider CIs as well as increased p-values.
- Despite relatively equal median and 12-month OS, the HR for OS is relative low and in favor of brigatinib due to the markedly longer 24-month OS rate.

The latter is supported by the KM-curves of OS, Figures 10-11.

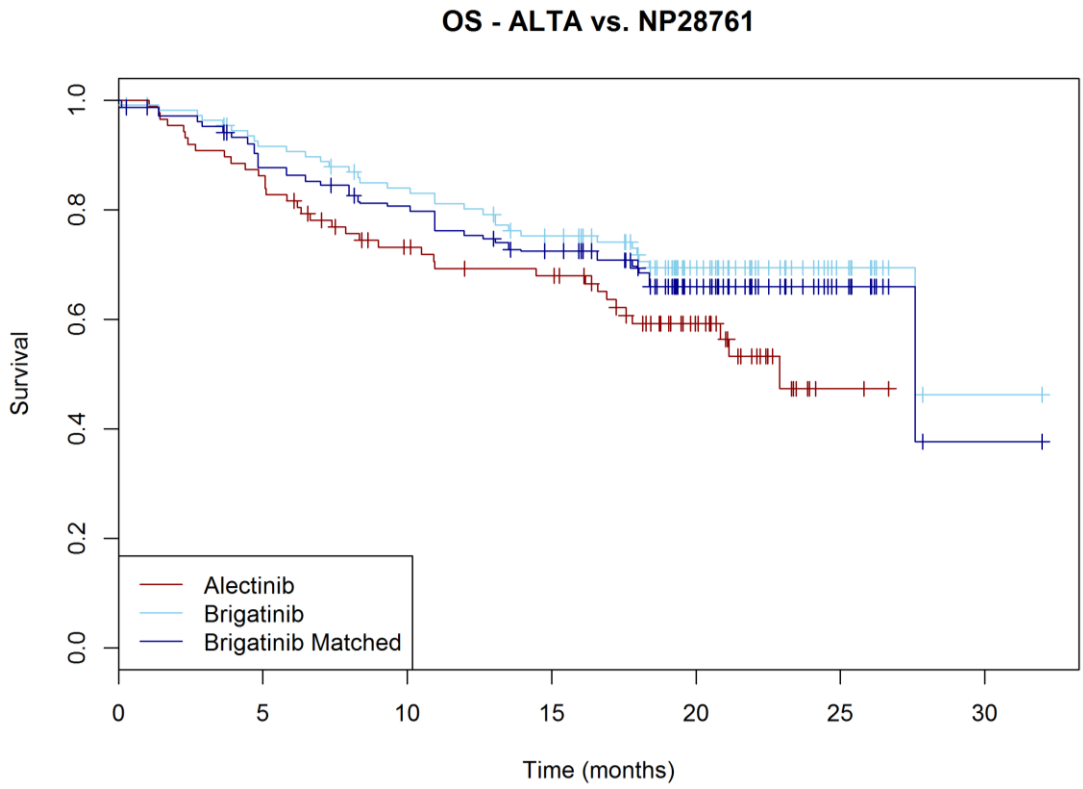


FIGURE 10. KAPLAN-MEIER CURVES OF OVERALL SURVIVAL FROM THE ALTA AND NP28761 TRIALS.

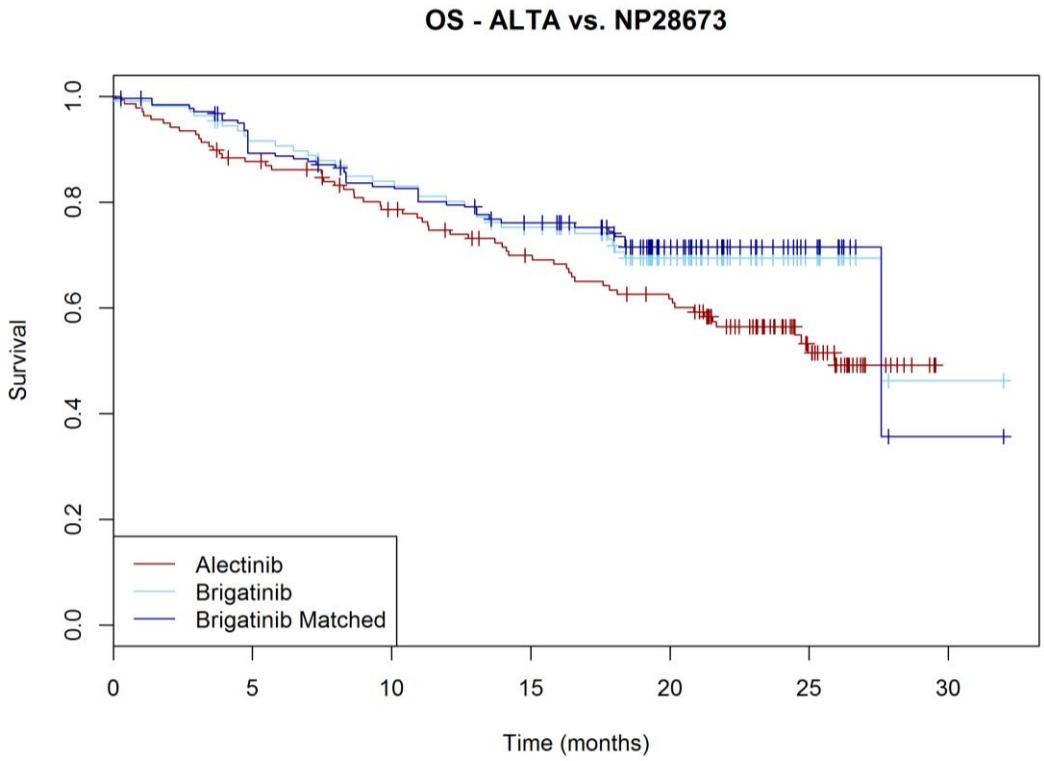


FIGURE 11. KAPLAN-MEIER CURVES OF OVERALL SURVIVAL FROM THE ALTA AND NP28673 TRIALS.

Overall, the above summary of naïve data (figure 9), a meta-analysis of MAIC adjusted data, and MAIC readouts for individual comparisons, table 12 [25], consistently suggest that brigatinib has a favorable impact on OS compared to alectinib.

Indeed, the naïve comparison of the most recent data cut, consistently results in an OS-difference that is higher than the 3 months stipulated as the minimal clinically relevant differences by the Medicines Council, table A3 a-e.

DISCONTINUATION DUE TO ADVERSE EVENTS

The safety populations and corresponding rates of discontinuations due to AEs from the trials relevant for this application is summarized naively below, table 13.

Study and Pharmaceutical	No. of Patients	Discontinuations due to AEs, N (%)	Safety Follow-up, Months	Reference
101 - brigatinib	32	3 (9.4)	17	[10]
ALTA – brigatinib	110	12 (10.9)	24.3	[10]
Total – brigatinib	**142**	**15 (10.6)**	-	-
NP28761- alectinib	87	2 (2.3)	17	[9]
NP28673 – alectinib	138	12 (8.7)	21	[9]
ALUR - alectinib	70	4 (5.7)	6.5	[6]
Total - alectinib	**295**	**18 (6.1)**	-	-

TABLE 13. RELEVANT SAFETY POPULATIONS AND THE CORRESPONDING RATES OF AES LEADING TO DISCONTINUATION FROM THE TRIALS SUPPORTING THIS APPLICATION.

It is naively, seen that the delta in the discontinuation rate is 4.5% points between the developmental programs of brigatinib and alectinib (grey rows). It is also seen that the safety follow-up of the ALUR trial is very short at 6.5 months, table 13 [6].

However, there is reason to believe that the developmental programs between alectinib and brigatinib differ substantially regarding AE-collection and analysis.

Indeed, the protocol of the ALTA trial stipulates, that *Worsening of signs and symptoms of the malignancy under study should be reported as AEs in the appropriate sections of the eCRF* [26]. Consequently, 9/78 (11.5%) of the grade 3+ AEs from the ALTA trial was *Neoplasm progression*, and 2 (1.4%) of the AEs causing discontinuation in the brigatinib developmental program was *Neoplasm progression* [10].

In contrast, a publicly available protocol from the alectinib development program stipulates under the headline "*Lack of Efficacy or Worsening of NSCLC*", that: "*Events that are clearly consistent with the expected pattern of progression of the underlying disease should not be recorded as AEs. These data will be captured as efficacy assessment data only*" [27]. In Agreement with this, *Neoplasm progression* (or similar MedDRA-terms) is not mentioned as an AE in the EPAR or trial publications of alectinib; neither as an AE causing discontinuation, nor as a grade 3-4 AE [4-6, 9].

Given the above, it appears that the inevitable worsening of symptoms and progression of the underlying disease was recorded as an AE in the brigatinib development program, but not in the development program of alectinib.

Table 14, below, thus depicts the data with a similar approach to sign and symptoms of the underlying disease (removal of "neoplasm progression" from the brigatinib data set).

In this analysis, the discontinuation rate due to AEs is 9.4% and 9.1% for the 101-study and the ALTA-trial, respectively, table 14 & table A3a-b. The delta between brigatinib and alectinib using this approach to signs and symptoms of the underlying disease is 3.1%, OR 1.55 (95% CI: 0.74-3.26, p=0.25), table A4.

Study and Pharmaceutical	No. of Patients	Discontinuations due to AEs, N (%)	Safety Follow-up, Months	Reference
101 - brigatinib	32	3 (9.4)	17	[10]
ALTA – brigatinib	110	10 (9.1)	24.3	[10]
Total – brigatinib	**142**	**13 (9.2)**	-	-
NP28761- alectinib	87	2 (2.3)	17	[9]
NP28673 – alectinib	138	12 (8.7)	21	[9]
ALUR - alectinib	70	4 (5.7)	6.5	[6]
Total - alectinib	**295**	**18 (6.1)**	-	-

TABLE 14. RELEVANT SAFETY POPULATIONS AND THE CORRESPONDING RATES OF AES LEADING TO DISCONTINUATION FROM THE TRIALS SUPPORTING THIS APPLICATION, WITH *AES CLEARLY CONSISTENT WITH THE EXPECTED PATTERN OF PROGRESSION OF THE UNDERLYING DISEASE* REMOVED FROM THE DATA SET OF BRIGATINIB IN ACCORDANCE WITH A CLINICAL TRIAL PROTOCOL FROM THE ALECTINIB DEVELOPMENTAL PROGRAM [27].

In sum, brigatinib is associated with a statistically insignificant increase in the rate of discontinuation due to AEs that is well below the 5% clinically meaningful difference stipulated by the Medicines Council as clinically meaningful.

CNS-Progression, CNS PFS

A naïve comparison of the CNS-PFS data obtained from the five trials relevant for this application consistently demonstrates a numerically longer CNS-PFS for patients treated with brigatinib.
The median CNS-PFS reported from the 101, ALTA, NP28761, and NP 28673 trials are summarized in table 15; the difference is summarized in table A4; the ALUR-trial did not report CNS-PFS [6].

Trial	N	Median CNS PFS Months (95% CI)	Reference
101, brigatinib	18§	NR	[10]
ALTA	73	18.4 (12.8; NR)	[7]
NP28761 NP28673 Pooled	136	8,3 (5,9; 11,2)	[8]

Table 15: Median CNS PFS. §:NSCLC patients treated with 90 mg → 180 mg brigatinib with baseline metastasis and previously treated with crizotinib [10].

It is seen from table A4, that the difference in median CNS-PFS is 10.1 months, which is significantly higher than the 3 months clinically meaningful difference stipulated by the Medicines Council.

In further support of this conclusion is the median CNS PFS of all ALK+ NSCLC patients (comprising treatment doses from 90 mg brigatinib QD to 240 brigatinib mg QD) from the dose finding 101-study: 14.6 months (95% cI: 12.7; 36.8) [7].
Thus, all available data demonstrates a numerically longer CNS-PFS for patients treated with brigatinib.

Progression Free Survival, PFS

A naïve comparison of the IRC-assessed PFS data obtained from the five trials relevant for this application consistently demonstrate a numerically longer PFS for patients treated with brigatinib.
Indeed, using the longest follow-up available, the median PFS was 16.3 months for the application relevant study population of the 101-trial and 16.7 months in the ALTA trial [10]. This is compared to the median PFS in the alectinib trials (NP28761/NP28673/ALUR) of 8.2, 8.9, and 7.1 months, respectively [6, 9], figure 12.

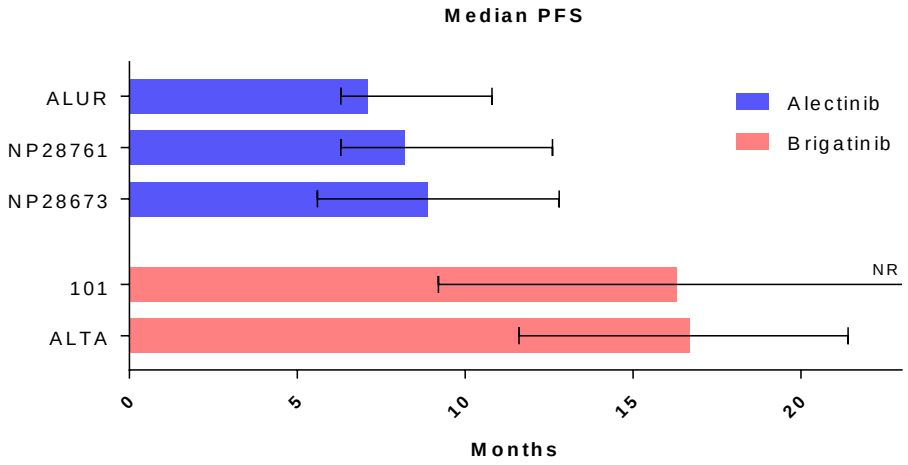


Figure 12. Naive median PFS from the trials presented in this application. Outcome Variables are 95% CI. Note that the upper CI of study 101 has not been reached (NR).

The meta-analysis based on MAICs using the latest data cut-off has demonstrated a PFS HR for ALTA vs. NP28761/NP28673/ALUR of 0,60 (95% CI: 0.48; 0.76), Takeda Data on File.

Table 16 summarizes the data from the published analysis [1].

	NP28761			NP28673		
	Alectinib (N=87)	Brigatinib Naive (N = 110)	Brigatinib MAIC (ESS = 78)	Alectinib (N=138)	Brigatinib Naive (N = 110)	Brigatinib MAIC (ESS = 71)
Median PFS, Months (95% CI)	8.2 (6.3, 12.6)	16.7 (11.6, NA)	17.6 (11.1, NA)	8.9 (5.6, 12.8)	16.7 (11.6, NA)	17.6 (11.1, NA)
PFS, HR (95% CI) Cox-regression	--	0.59 (0.40, 0.87)	0.56 (0.36, 0.86)	--	0.64 (0.45, 0.92)	0.61 (0.40, 0.93)
P-value	--	0.009	0.009	--	0.015	0.023

TABLE 16. NAIVE AND MAIC-ADJUSTED PFS FROM [1].

It is seen from table 16, that the naïve median PFS is 8.5 months and 7.8 months longer for brigatinib, while the MAIC adjusted PFS is 9.4 months and 8.8 months longer for brigatinib. Similarly, the HR consistently favors brigatinib and reaches statistical significance.

Figures 13-14 depicts the corresponding Kaplan-Meier plots.

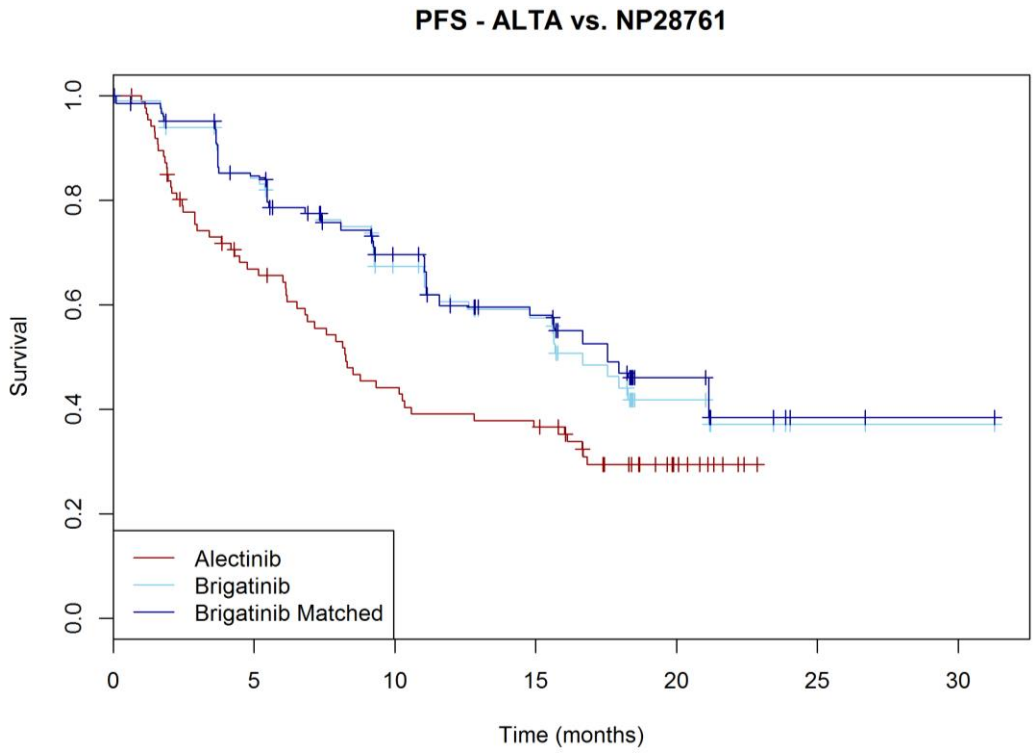


FIGURE 13. KAPLAN-MEIER CURVES OF PROGRESSION-FREE SURVIVAL FROM THE ALTA AND NP28761 TRIALS.

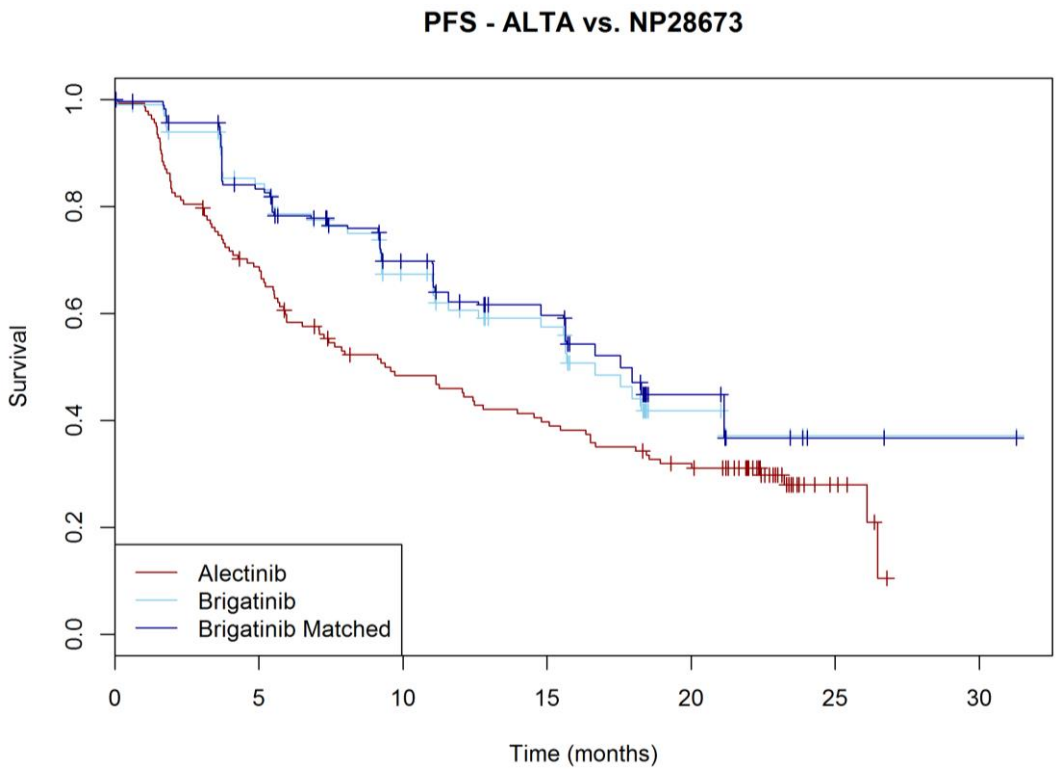


FIGURE 14. KAPLAN-MEIER CURVES OF PROGRESSION-FREE SURVIVAL FROM THE ALTA AND NP28673 TRIALS.

Overall, the above summary of naïve data (figure 12), a meta-analysis of MAIC adjusted data and MAIC readouts for individual comparisons (table 16, figures 13-14), consistently suggest that brigatinib has a favorable impact on PFS compared to alectinib.

Indeed, both the naïve comparisons and MAIC adjusted comparisons consistently result in a PFS-difference that is higher than the 3 months stipulated as the minimal clinically relevant differences by the Medicines Council as well as statistically significant (table 16, tables A3f-g).

GRADE 3-4 ADVERSE EVENTS

Summary Statistics

The safety populations and corresponding rates of discontinuations due to AEs from the trials relevant for this application is summarized naively below, table 17.

Study and Pharmaceutical	No. of Patients	Grade 3-4 Adverse Events, N (%)	Safety Follow-up, Months	Reference
101 - brigatinib	32	20 (63)	17	[10]
ALTA – brigatinib	110	78 (70.9)	24.3	[10]
Total – brigatinib	**142**	**98 (69.0)**	-	
NP28761- alectinib	87	36 (41.4)	17	[9]
NP28673 – alectinib	138	55 (39.9)	21	[9]
ALUR - alectinib	70	18 (25.7)	6.5	[6]

Total - alectinib	**295**	**109 (36.9)**	**-**	

TABLE 17. RELEVANT SAFETY POPULATIONS AND THE CORRESPONDING RATES OF GRADE 3-4 AES FROM THE TRIALS SUPPORTING THIS APPLICATION.

The delta in the total rate of grade 3-4 AEs is 32.1% points between the developmental programs of brigatinib and alectinib (grey rows).

Table 18, below, depicts the data with "neoplasm progression" removed from the brigatinib data set, in accordance with the rationale outlined in the "discontinuation due to AEs" section, above.

In this analysis, the grade 3-4 AE rate is 59% and 63% for the 101-study and ALTA-trial, respectively, table 18 & tables A3a-b. The delta between brigatinib and alectinib using a similar approach to sign and symptoms of the underlying disease is 25.1%, OR 2.83 (95% CI: 1.87; 4.29), $p < 0.0001$, table A4.

Study and Pharmaceutical	No. of Patients	Grade 3-4 Adverse Events, N (%)	Safety Follow-up, Months	Reference
101 - brigatinib	32	19 (59)	17	[10]
ALTA – brigatinib	110	69 (63)	24.3	[10]
Total – brigatinib	**142**	**88 (62.0)**	**-**	
NP28761- alectinib	87	36 (41.4)	17	[9]
NP28673 – alectinib	138	55 (39.9)	21	[9]
ALUR - alectinib	70	18 (25.7)	6.5	[6]
Total - alectinib	**295**	**109 (36.9)**	**-**	

TABLE 18: RELEVANT SAFETY POPULATIONS AND THE CORRESPONDING RATES OF GRADE 3-4 AES FROM THE TRIALS SUPPORTING THIS APPLICATION, WITH *AES CLEARLY CONSISTENT WITH THE EXPECTED PATTERN OF PROGRESSION OF THE UNDERLYING DISEASE* REMOVED FROM THE DATA SET OF BRIGATINIB IN ACCORDANCE WITH A CLINICAL TRIAL PROTOCOL FROM THE ALECTINIB DEVELOPMENTAL PROGRAM [27].

Qualitative comparison of Adverse Reactions

Adverse Reactions differ from Adverse Events by the assumed causality between the intake/administration of a drug and the development of the Adverse Reaction.
Please see table 5A for a complete comparison of the Adverse Reactions associated with brigatinib and alectinib as reported in their respective SPCs.

Grade 5 Adverse Reactions

Alectinib

The table of adverse reactions for alectinib published by EMA (SPC) includes 1.0% Acute Kidney Injury (common ADR), of which one included a grade 5 event, table A5.
Four patients (out of 138) died in the NP28673 trial. One of them died from *intestinal perforation*, which was considered possible related to alectinib [4].
In the NP28761 trial two patients died. One of them died from haemorrhage, which was considered related to alectinib [5].

Brigatinib
22 patients died in the ALTA and 101 study combined [10].

At the relevant dose of 90 mg → 180 mg QD, one study death is possible related to brigatinib [10].

This patient died on day seven after study drug initiation after experiencing dyspnea, cough, and pneumonia. The autopsy revealed lymphangitic carcinomatosis, widespread lung scarring, and diffuse alveolar damage. Pathologist reported causes of death were lung cancer, adhesive pericarditis, and respiratory failure [3].

Early Onset Pulmonary Events (EOPE)
The early development program of brigatinib identified a safety signal composed of severe, life-threatening, and fatal pulmonary adverse reactions, including those with features consistent with ILD/pneumonitis.

Most pulmonary adverse reactions were observed within the first 7 days of treatment; the majority were associated with high doses of brigatinib. Additionally, increased age and shorter interval (less than 7 days) between the last dose of crizotinib and the first dose of brigatinib were independently associated with an increased rate of these pulmonary adverse reactions.

Grade 1-2 pulmonary adverse reactions resolved with interruption of treatment or dose modification. Patients should be monitored for new or worsening respiratory symptoms (e.g., dyspnoea, cough, etc.), particularly in the first week of treatment.

In study 101, 11 cases (8.0%) were identified, all but one at starting doses > 90 mg QD [10]. The identified cases were characterized by a pneumonitis-like process during the first week of treatment which in most cases responded to dose interruption and steroids. Two thirds of the cases were severe and over half of cases required discontinuation. Four of the events were fatal – none of them occurred at the approved dose of 90 → 180 mg QD.

The finding that all EOPEs, but one, were identified at starting doses > 90 mg is the rationale behind the approved dose of 180 mg with a 7-day lead-in of 90 mg, tested in the ALTA trial.

In the ALTA-trial, there were 14 cases of at least possible EOPE (6.4%), all on the 90 mg QD dose [10]. One event was fatal, and considered possible related to brigatinib.

In an ongoing phase 3 trial (the 301 study), there were 2.9% (4/136) brigatinib patients with early onset ILD/pneumonitis, of which 3 cases were severe.

The CHMP considers it reassuring, that the rate of EOPE continues to be low, that all events have resolved or improved, and that no deaths from EOPE have so far been observed in the phase 3 trial [10]. Consequently, the CHMP assumes that this is most likely due to increased attention to, and better handling of, these early-onset serious events and conclude that this rate may reflect the future risk of EOPE better than the phase 1 and 2 results [10], due to a demonstrated learning curve of better handling and consequential diminished seriousness of this potentially fatal adverse event over time [10].
In support of this is the fact that, 3 patients died from EOPE in phase 1, 1 patient died in phase 2, and so far, no patients have died from this in phase 3 [10].

In summary,

- Brigatinib is associated with a statistically significant higher rate of Grade 3-4 AEs than alectinib, table A4.
- Three patients are considered to have died from adverse reactions to alectinib; at the approved dose, one patient is considered to have died from adverse reactions to brigatinib [3-6, 9, 10].
- The early development program of brigatinib identified a risk of EOPEs, which appear manageable by awareness and attention, as proven by the decrease in events trough-out the development program [10].

Quality of Life

The NP28761 trial reported "a change from baseline of ten or more points", that was "maintained for at least two consecutive visits…" on the Global Health Status scale from EORTC QLQ-C30 instrument [5]. QoL was in this trial reported for the first 10 months only.
QoL data from the ALTA trial, using the same EORTC QLQ-C30 instrument, demonstrated improvements between 5 and 10 points throughout 24 months on both the Global Health Status scale and the disease relevant Dyspnea single scale, figures 7-8, section 5.1.2.2.
No other trials reported QoL data.

Objective Response Rates

The meta-analysis based on MAICs using the latest data cut-off has demonstrated an ORR Odds Ratio for ALTA vs. NP28761/NP28673/ALUR of 1.82 (95% CI: 1.30; 5.57), Takeda Data on File.

The hallmark of a MAIC analysis is to ensure consistency in the input data for the analysis. In the published analysis, the data from ALTA is thus ORR rather than *confirmed* ORR, and all data from all three trials (NP28761, NP28673, and ALTA) are assessed by IRCs in the ITT population [25], see section 5.1.1.4 for further details.
Table 19 summarizes the data [1].

	NP28761			NP28673		
	Alectinib (N=87)	Brigatinib Naive (N = 110)	Brigatinib MAIC (ESS = 78)	Alectinib (N=138)	Brigatinib Naive (N = 110)	Brigatinib MAIC (ESS = 71)
ORR (95% CI)	40 (30; 51)	55 (45; 64)	53 (42; 64)	45 (37; 53)	55 (45; 64)	54 (42; 66)
ORR OR (95% CI)	--	1.78 (1.01; 3.17	1.69 (0.91 ; 3.15	--	1.47 (0.89 ; 2.44)	1.44 (0.81 ; 2.58
P-value	--	0.047	0.096	--	0.133	0.212

Table 19. Naive and MAIC-adjusted IRC-assessed ORR in the ITT-population, from [1].

It is seen from table 19, that the naïve numerical ORRs are 15% and 10% higher for brigatinib, while the MAIC adjusted ORRs are 13% and 9% higher than alectinib. Similarly, the Odds Ratios consistently favor brigatinib, although they do not reach statistical significance.

CONCLUDING REMARKS

In total all the efficacy outcome measures (OS, CNS PFS, PFS, and ORR) demonstrated numerical superiority of brigatinib compared to alectinib, discontinuation rates due to AEs were found to be similar, the rate of grade 3-4 AEs were higher for brigatinib, and Quality of Life were found to be similar.

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7 Appendices

Literature search

Table A1 Inclusion and exclusion criteria

Inclusion criteria	Population: ALK+ NSCLC adult patients who have progressed on crizotinib Intervention(s): brigatinib 90 mg → 180 mg QD Comparator(s): alectinib 600 mg BID Outcomes: minimum one of: OS, discontinuation due to AEs, CNS PFS, PFS, Grade 3-4 AEs, QoL graded by EORTC QLQC30, or ORR Settings (if applicable): Clinical Trials Study design: Phase I-III, single arm or controlled, comparative analysis Language restrictions: English Other search limits or restrictions applied:
Exclusion criteria	Population: All non-ALK+ NSCLC patients Intervention(s): No comparator of interest Comparator(s): other treatment modalities such as radiotherapy etc Outcomes: outcomes not included in the PICO. Settings (if applicable): NA Study design: NA Language restrictions: all non-English Other search limits or restrictions applied: conference abstracts, posters, editorials, comments.

Main characteristics of included studies

Study characteristics

Table A2a Main study characteristics

Trial name	**Study 101**: A Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Preliminary Anti-Tumor Activity of the Oral Anaplastic Lymphoma Kinase (ALK)/Epidermal Growth Factor Receptor (EGFR) Inhibitor Brigatinib (AP26113)
NCT number	NCT01449461
Objective	To Evaluate the Safety, Tolerability, Pharmacokinetics and Preliminary Anti-Tumor Activity of the Oral Anaplastic Lymphoma Kinase (ALK)/Epidermal Growth Factor Receptor (EGFR) Inhibitor Brigatinib (AP26113)
Publications – title, author, journal, year	1) *Activity and safety of brigatinib in ALK-rearranged non-small-cell lung cancer and other malignancies: a single-arm, open-label, phase 1/2 trial*. Gettinger, S. N., Bazhenova, L. A. Et al., *Lancet Oncol*, 2016 2) *Exploratory Analysis of Brigatinib Activity in Patients With Anaplastic Lymphoma Kinase-Positive Non-Small-Cell Lung Cancer and Brain Metastases in Two Clinical Trials*. Camidge, D. R., Kim, D. W., *et al*, Journal of Clinical Oncology, 2018
Study type and design	Phase 1/2 trial, first-in human, single-arm, nonrandomized, uncontrolled, multicentre, open-label study with two parts: a dose escalation phase using a 3+3 design to determine the recommended phase 2 dose (RP2D), followed by an expansion cohort.
Follow-up time	17.0 (11.4-22.1) months for the patients with ALK+ NSCLC.
Population (inclusion and exclusion criteria)	Inclusion Criteria: General Eligibility Criteria 1. All participants must have tumor tissue available for analysis. If sufficient tissue is not available, participants must undergo a biopsy to obtain adequate samples. For participants in expansion cohorts 2, 3 and 5, for whom failure of prior therapy is specified (crizotinib for cohorts 2 and 5, one epidermal growth factor receptor-tyrosine kinase inhibitor (EGFR-TKI) for cohort 3),tumor tissue must be available following failure of the prior therapy. 2. Must have measurable disease by Response Evaluation Criteria in Solid Tumors (RECIST). 3. Male or female participants ≥ 18 years old. 4. Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1. 5. Minimum life expectancy of 3 months or more. 6. Adequate renal and hepatic function. 7. Adequate bone marrow function. 8. Normal QT interval on screening electrocardiogram (ECG) evaluation. 9. For females of childbearing potential, a negative pregnancy test must be documented prior to enrollment. 10. Female participants who are of childbearing potential and fertile male participants must agree to use an effective form of contraception with their sexual partners throughout study participation. 11. Signed and dated informed consent indicating that the participant has been informed of all pertinent aspects of the study.

	12. Willingness and ability to comply with scheduled visits and study procedures. Exclusion Criteria: 1. Received an investigational agent ≤ 14 days prior to initiating brigatinib. 2. Received systemic anticancer therapy (including monoclonal antibodies and irreversible TKIs such as afatinib or dacomitinib) or radiation therapy ≤ 14 days prior to initiating brigatinib. a. Except for a reversable TKI (ie, erlotinib or gefitinib) or crizotinib, which are allowed up to 72 hours prior to initiating brigatinib, provided that the participant is free of treatment-related toxicity that might confound the safety evaluation of brigatinib. 3. Received any prior agents targeted against ALK, with the exception of crizotinib, or received more than 1 prior EGFR TKI. a. Re-challenge with the same TKI is allowed. 4. Major surgery within 28 days prior to initiating brigatinib. 5. Brain metastases that are neurologically unstable or require anticonvulsants or an increasing dose of corticosteroids. 1. Participants with previously treated brain metastases without evidence of disease or recurrence are allowed for cohorts 1-4. 2. Participants with evaluable but non-measurable, active brain lesions who otherwise meet the criteria for cohort 5 for CNS disease can be enrolled in other cohorts. 6. Significant uncontrolled or active cardiovascular disease. 7. Uncontrolled hypertension (diastolic blood pressure [BP] > 100 mm Hg; systolic > 150 mm Hg). 8. Prolonged QT interval, or being treated with medications known to cause Torsades de Pointes. 9. History or presence of pulmonary interstitial disease or drug-related pneumonitis. 10. Ongoing or active infection. The requirement for intravenous (IV) antibiotics is considered active infection. 11. Known history of human immunodeficiency virus (HIV). Testing is not required in the absence of history. 12. Pregnant or breastfeeding. 13. Malabsorption syndrome or other gastrointestinal illness that could affect oral absorption of brigatinib. 14. Any condition or illness that, in the opinion of the Investigator, would compromise participant safety or interfere with the evaluation of the safety of the drug. 15. Leptomeningeal carcinomatosis and spinal cord compression. In the case of suspected meningeal involvement, a negative lumbar puncture prior to study entry is required.
Intervention	Daily doses of brigatinib were escalated from 30 mg QD to 300 mg QD orally. The expansion phase included mainly patients with ALK+ advanced NSCLC. At the data cut-off of 31/05/2016, a total of 137 patients were enrolled and dosed. For the purpose of the analysis, dose groups were collapsed and data from dose escalation and expansion cohorts were combined. The complete study population included 79 patients with ALK+ NSCLC; the majority had been previously treated with crizotinib: The 90 →180 mg QD group, corresponding to the proposed dose for this application, included 25 ALK+NSCLC patients previously treated with crizotinib.

Baseline characteristics	Baseline characteristics of the 79 ALK+ NSCLC patients were: - median age: 54 (44-64) - gender distribution: 49% women, 51% men. - performance status: 39%, 59% & 1% for ECOG PS 0, 1, and 2, respectively - previous treatments: 90% had previously received crizotinib, 28%, 25%, 29%, and 18% had received 0, 1, 2, and ≥3 lines of prior chemotherapy, respectively. - average weight / body surface area: Not reported - organ function: Not reported
Primary and secondary endpoints	**Primary Endpoint** Objective Response Rate (ORR) ORR assessed by the investigator, is defined as the proportion of the participants with complete response (CR) or partial response (PR) according to Response Evaluation Criteria in Solid tumors (RECIST) v1.1 after the initiation of study treatment. **Secondary Endpoints** 1. Number of Participants Who Had at Least One Treatment-Emergent Adverse Event (TEAE) 2. Maximum Tolerated Dose (MTD) Assessed in Dose Escalation Phase of the Study 3. Number of Participants With Dose Limiting Toxicities (DLTs) Assessed in Dose Escalation Phase of the Study 4. Cmax: Maximum Observed Plasma Concentration for Brigatinib [Time Frame: Cycle 1 Day 1] 5. Cmax: Maximum Observed Plasma Concentration for Brigatinib [Time Frame: Cycle 2 Day 2] 6. Tmax: Time to Reach the Maximum Plasma Concentration (Cmax) for Brigatinib [Time Frame: Cycle 1 Day 1] 7. Tmax: Time to Reach the Maximum Plasma Concentration (Cmax) for Brigatinib [Time Frame: Cycle 2 Day 1] 8. AUC(0-24): Area Under the Plasma Concentration-Time Curve From Time 0 to 24 Hours Post-dose for Brigatinib Terminal Phase Elimination Half-life (T1/2) for Brigatinib [Time Frame: Cycle 2 Day 1] 9. Best Overall Response 10. Duration of Response 11. Progression Free Survival (PFS) 12. Overall Survival (OS) 13. Intracranial Objective Response 14. Duration of Intracranial Response 15. Intracranial Progression Free Survival (PFS)
Method of analysis	All efficacy analyses were done in the ITT-population. Response and progression was assessed by CT scans of the chest and abdomen (and MRI of the brain in patients with CNS metastasis) at 8 week intervals. RECIST-defined (V1.1) responses were confirmed with an imaging assessment 4 weeks after the responses. PFS and intracranial duration of response was calculated by Kaplan-Meier estimation. CIs for the proportions of patients with objective response, median duration of response,

	and median progression-free survival are post-hoc analyses No comparisons were made in this phase I/II study.
Subgroup analyses	Phase I was a dose-escalation phase in patients with histologically confirmed advanced malignancies and was followed by an expansion phase (phase II) in five histologically and molecularly defined cohorts. During phase II, three oral once-daily regimens were assessed in ALK+ NSCLC patients: 90mg, 180mg and 90mg→180mg. In total, 25 patients fell within the scope of this application: pre-treated with crizotinib and treated with 90mg→180mg brigatinib QD Baseline characteristics of this population is not available. This population is part of the baseline characteristics of the general ALK+ NSCLC population presented above. The efficacy analysis was done as post-hoc analysis. All analysis was performed as described for the general population.

Table A2b Main study characteristics

Trial name	**ALTA**
NCT number	NCT02094573
Objective	To Evaluate the Efficacy of Brigatinib (AP26113) in Participants With Anaplastic Lymphoma Kinase (ALK)-Positive, Non-small Cell Lung Cancer (NSCLC) Previously Treated With Crizotinib
Publications – title, author, journal, year	1) *Brigatinib in Patients with Crizotinib-Refractory Anaplastic Lymphoma Kinase-Positive Non-Small-Cell Lung Cancer: A Randomized, Multicenter Phase II Trial* Kim, D. W. Tiseo, M., *et al*., *Journal of Clinical Oncology*, 2017 2) *Exploratory Analysis of Brigatinib Activity in Patients With Anaplastic Lymphoma Kinase-Positive Non-Small-Cell Lung Cancer and Brain Metastases in Two Clinical Trials.* Camidge, D. R., Kim, D. W., *et al*, *Journal of Clinical Oncology*, 2018
Study type and design	Ongoing open-label, randomized, multicenter, international phase II study. Patients were stratified by baseline brain metastases (present v absent) and best investigator-assessed response to crizotinib (complete response [CR] or partial response [PR] v other or unknown) and were randomly assigned (1:1) to 90 mg once daily or 180 mg once daily with a 7-day lead-in at 90 mg (90 mg →180 mg). There was no placebo or active control arm. Treatment continued until disease progression requiring alternative systemic therapy, intolerable toxicity, or consent withdrawal. Treatment in either arm could be continued at the investigator's discretion after progression. Patients in arm A could receive brigatinib 180 mg once daily after objective progression at 90 mg once daily. Dose interruptions or reductions were allowed to manage treatment-related AEs, on the basis of the investigator's judgment. AEs were graded with National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0. In total 222 patients were treated; 110 patients were treated with the relevant regiment of 90 mg → 180 mg.
Follow-up time	Median follow-up time from the most recent data extraction (September 29th 2017) is 24.3 months.

Population (inclusion and exclusion criteria)	Inclusion Criteria:
	1. Have histologically or cytologically confirmed locally advanced or metastatic Non-small Cell Lung Cancer (NSCLC) that is anaplastic lymphoma kinase (ALK+).
	2. Must meet one of the following two criteria:
	  1. Have documented ALK rearrangement by a positive result from the Vysis® ALK Break-Apart fluorescence in situ hybridization (FISH) Probe Kit; or
	  2. Have documented ALK positivity by a different test and tissue available for the Vysis® FISH test. Tissue should be derived preferably from a biopsy taken after progression with crizotinib. If such a sample is not available, testing may be performed with archived tumor tissue.
	3. Had progressive disease while on crizotinib, as assessed by the investigator or treating physician.
	4. Have at least 1 measurable lesion per RECIST v1.1. Note: Previously irradiated lesions may not be used for target lesions, unless there is unambiguous

	radiological progression after radiotherapy. Brain lesions may not be used as target lesions if they were: 1) previously treated with whole brain radiation therapy (WBRT) within 3 months, or 2) previously treated by stereotactic radiosurgery (SRS) or surgical resection. 5. Recovered from toxicities related to prior anticancer therapy to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE, v4.0) grade ≤2. 6. Are a male or female participants ≥18 years old. 7. Have a life expectancy ≥3 months. 8. Have adequate organ and hematologic function, as determined by: 1. Alanine aminotransferase (ALT)/aspartate aminotransferase (AST) ≤2.5 x upper limit of normal (ULN; ≤5 x ULN is acceptable if liver metastases are present) 2. Total serum bilirubin ≤1.5 x ULN (<3.0 x ULN for participants with Gilbert syndrome) 3. Serum creatinine ≤1.5 x ULN 4. Serum lipase/amylase ≤1.5 x ULN 5. Absolute neutrophil count (ANC) ≥1500/µL 6. Platelets ≥75000/µL 7. Hemoglobin ≥10 g/dL 9. Have Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2. 10. Have normal QT interval on screening electrocardiogram (ECG) evaluation, defined as QT interval corrected (Fridericia) (QTcF) of ≤450 ms in males or ≤470 ms in females. 11. For female participants of childbearing potential, a negative pregnancy test must be documented prior to enrollment. 12. Female and male participants who are fertile must agree to use a highly effective form of contraception with their sexual partners throughout study participation. 13. Must provide a signed and dated informed consent indicating that the participant has been informed of all pertinent aspects of the study, including the potential risks, and is willingly participating. 14. Have the willingness and ability to comply with scheduled visits and study procedures. Exclusion Criteria: 1. Received any prior ALK-targeted TKI other than crizotinib. 2. Received crizotinib within 3 days of the first dose of brigatinib (Day 1, Cycle 1). 3. Received cytotoxic chemotherapy, investigational agents, or radiation within 14 days, except SRS or stereotactic body radiosurgery. 4. Received monoclonal antibodies or had major surgery within 30 days of the first dose of brigatinib (Day 1, Cycle 1). 5. Have been diagnosed with another primary malignancy within the past 3 years (except for adequately treated non-melanoma skin cancer, cervical cancer in situ, or prostate cancer, which are allowed within 3 years). 6. Have symptomatic CNS metastases that are neurologically unstable or require an increasing dose of corticosteroids. 7. Have current spinal cord compression. 8. Have significant, uncontrolled, or active cardiovascular disease, specifically including, but not restricted to: 1. Myocardial infarction (MI) within 6 months prior to the first dose of brigatinib 2. Unstable angina within 6 months prior to first dose 3. Congestive heart failure (CHF) within 6 months prior to first dose

4. History of clinically significant (as determined by the treating physician) atrial arrhythmia
5. Any history of ventricular arrhythmia
6. Cerebrovascular accident or transient ischemic attack within 6 months prior to first dose

9. Have a history or the presence of pulmonary interstitial disease or drug-related pneumonitis.
10. Have an ongoing or active infection. The requirement for intravenous (IV) antibiotics is considered active infection.
11. Have a known history of human immunodeficiency virus (HIV). Testing is not required in the absence of history.
12. Have a history of or active significant gastrointestinal (GI) bleeding within 3 months of the first dose of brigatinib.
13. Have a known or suspected hypersensitivity to brigatinib or its excipients.
14. Have malabsorption syndrome or other GI illness that could affect oral absorption of the study drug.
15. Have any condition or illness that, in the opinion of the investigator, would compromise participants safety or interfere with evaluation of the drug study.
16. Be pregnant or breastfeeding.

Intervention

Patients were randomized to one of either interventions:
a) 90 mg once daily, or
b) 180 mg once daily with a 7-day lead-in at 90 mg (90 mg →180 mg)
until disease progression or intolerable toxicity.
The current application is concerned with the b-arm (90 mg → 180 mg), which comprised 110 patients.

Baseline characteristics

Baseline Characteristics	**Total Population (N = 222)**	**90 mg → 180 mg Once Daily (n = 110)**
Age, median (range), years	54 (18-82)	56,5 (20-81)
Sex, n (%)		
Male	96 (43)	46 (42)
Female	126 (57)	64 (58)
Ethnicity, n (%)		
Asian	69 (31)	30 (27)
White	148 (67)	76 (69)
Other	5 (2)	4 (4)
Smoking history, n (%)		
No/unknown	135 (61)	63 (57)
Yes	87 (39)	47 (43)
ECOG PS, n (%)		
0/1	206 (93)	101 (92)
2	16 (7)	9 (8)
Prior chemotherapy, n (%)	164 (74)	81 (74)
Best response to prior crizotinib, n (%)		
PR or CR	144 (64)	73 (65)
Other response or unknown	78 (36)	37 (35)
Brain metastases, n (%)	154 (69)	74 (67)

CR, complete response; ECOG PS, Eastern Cooperative Oncology Group performance status; PR, partial response.

Primary and secondary endpoints	The **primary endpoint**, confirmed ORR assessed by the investigator, was defined as the proportion of patients who were confirmed to have achieved CR or PR, as determined per RECIST v1.1; confirmed responses were those that persisted on repeat imaging 4 weeks or more after initial response. **Secondary efficacy endpoints** were as follows: • Confirmed ORR assessed by IRC. • For randomized patients with active brain metastases at enrollment: o intracranial ORR as evaluated by IRC o intracranial PFS as evaluated by IRC • Time to response • Duration of response • Time on treatment • Disease control rate • PFS • OS • Patient-Reported Symptoms of Lung Cancer and HRQoL assessed by administering the EORTC QLQ-C30 (v3.0) questionnaire at screening and every 4 weeks thereafter.
Method of analysis	All efficacy analysis was done in the ITT-population. Patients with baseline brain metastases (by IRC assessment) were included in IRC analyses of intracranial efficacy. Patients who received any brigatinib were included in the safety population. The primary endpoint was ORR and the 95%/97.5% confidence intervals were calculated as exact 2-sided binomial confidence intervals. The study was considered to have achieved the primary endpoint, if the ORR was shown to be significantly higher than 20% at a two-sided alpha level of 0.025 at the final analysis for that regimen. Patients were stratified at randomization by brain metastases at baseline (present vs absent) and best prior response to crizotinib therapy (CR or PR vs any other response or status unknown). CIs were calculated using the exact binomial method; 97.5% CIs were estimated for confirmed ORR (primary end point), and 95% CIs were used for other end-points. For time-to-event efficacy analyses (duration of response, PFS, and OS), median values and two-sided 95% CIs were estimated using Kaplan-Meier methods. Response was assessed according to RECIST V1.1. Any response was confirmed four weeks following first response and independently verified by IRC. The trial was not designed for statistical comparisons between arms; however, post hoc hazard ratios were estimated for PFS to support dose selection. Statistical analyses were performed using SAS software (version 9.4).
Subgroup analyses	The two different arms in the study were analyzed independently of each other. All analysis were done according to above section

Table A2c Main study characteristics

Trial name	NP28761 A Study of Alectinib (CH5424802/RO5424802) in Participants With Anaplastic Lymphoma Kinase (ALK)-Rearranged Non-Small Cell Lung Cancer (NSCLC)
NCT number	NCT01871805
Objective	To assess efficacy and safety in a phase 2 study of alectinib in patients from the USA and Canada with crizotinib-resistant, ALK-positive NSCLC.
Publications – title, author, journal, year	1) *Alectinib in ALK-positive, crizotinib-resistant, non-small-cell lung cancer: a single-group, multicentre, phase 2 trial.* Shaw, A. T., Gandhi, L., *et al., Lancet Oncology,* 2015 *2) Pooled Analysis of CNS Response to Alectinib in Two Studies of Pretreated Patients With ALK-Positive Non-Small-Cell Lung Cancer*. Gadgeel, S. M., Shaw, A. T., *et al.*, *Journal of Clinical Oncology.* 2016
Study type and design	Phase 2, single-group, open-label, multicentre study to determine the safety, tolerability and activity of alectinib as a single agent in patients with either locally advanced (AJCC Stage IIIB) and not amenable to curative therapy or metastatic (AJCC Stage IV) ALK-positive NSCLC who had experienced disease progression on crizotinib with or without prior chemotherapy. Single arm study; no active comparator or placebo.
Follow-up time	17 months, as per data cut-off on January 22th, 2016 [9].
Population (inclusion and exclusion criteria)	**Inclusion Criteria**: Histologically confirmed, locally advanced, not amenable to curative therapy, or metastatic NSCLC ALK-rearrangement confirmed by the Food and Drug Administration (FDA) approved test NSCLC that has failed crizotinib treatment Measurable disease as defined by RECIST v1.1 Eastern Cooperative Oncology Group (ECOG) performance status less than or equal to (<=) 2 Adequate hematologic, hepatic and renal function **Exclusion Criteria**: Prior therapy with ALK inhibitor other than crizotinib Brain or leptomeningeal metastases that are symptomatic and/or requiring treatment History of serious cardiac dysfunction History of or current active infection with hepatitis B, hepatitis C or human immunodeficiency virus (HIV) Clinically significant gastrointestinal abnormality that would affect absorption of the drug Pregnant or lactating women
Intervention	600 mg alectinib was administered to the patient orally BID starting on Day 1 through Day 21 of each 21-day treatment cycle. Patients were treated continuously until disease progression, death, or withdrawal for any other reason. 87 patients were treated.
Baseline characteristics	- age: 54 (29-79) - gender distribution: Female 55% - performance status: 35%, 48% and 10% of the patients were PS 0, 1, and 2 respectively.

	- previous treatments: 74% had previously received chemotherapy. - 99% of the patients had stage IV disease, 1% had stage IIIB.
Primary and secondary endpoints	**Primary objective** To evaluate the efficacy of alectinib based on ORR (according to RECIST 1.1) as per independent review committee (IRC) in patients ALK-positive NSCLC who have failed crizotinib. **Secondary objectives** • ORR according to RECIST 1.1 based on investigator review of radiographs • DCR, DOR and PFS according to RECIST v1.1 by IRC and investigator review of radiographs • OS • safety of alectinib • to characterize the PK of alectinib and metabolite(s) • to assess QoL using the EORTC QLQ − C30 and − LC13 • CNS ORR (CORR) in patients with CNS metastases who have measurable disease in the CNS at baseline, based on IRC review of radiographs by RECIST 1.1 and Response Assessment in Neuro-Oncology (RANO) criteria • CNS duration of response (CDOR) in patients who have a CNS objective response based on IRC review of radiographs by RECIST 1.1 and RANO criteria • CNS progression rates (CPR) at 3, 6, 9 and 12 months based on cumulative incidence by IRC review of radiographs by RECIST v1.1 and RANO criteria. **Exploratory objectives** • To assess blood based methods to detect point mutations in plasma • To identify molecular determinants of clinical resistance to ALK inhibitors • To identify potential genetic determinants of PK variability and safety parameters (pharmacogenomics research) • To assess alectinib CNS penetration by measuring the cerebrospinal fluid (CSF): plasma concentration ratio
Method of analysis	Statistical methods The following null (H0) and alternative (Ha) hypotheses were tested at a two-sided 5% significance level to compare ORR according to RECIST per IRC review in the response evaluable (RE) population (i.e., the primary efficacy endpoint): H0: ORR = 35% versus Ha: ORR ≠ 35% A sample size of 85 was chosen such that the lower limit of the 2-sided 95% confidence interval (CI) (using a Clopper-Pearson CI) around the point estimate of the ORR allowed identification of a clinically relevant response in order to reject the null hypothesis (H0) that ORR = 35%. With 85 patients, an observed response rate of 46% (39/85 responses) would have a lower limit of the two-sided 95% CI of 35%. The primary analysis, reported in this CSR, was to occur once all patients enrolled in Phase II were followed for a minimum of 12 weeks, i.e., after two tumor assessments had been performed in order that any observed CR or PR could be confirmed, unless patients progressed, died or withdrew sooner. The ITT population corresponded to the safety population (87 patients). The response evaluable population for the IRC consisted of 69 patients out of 87 total. These patients were analyzed for ORR. PFS, safety, OS, and response by investigator were analyzed in the safety population consisting of 87 patients. The Kaplan–Meier method was used to estimate rates of progression-free survival and overall survival. Response was evaluated according to RESCIST 1.1
Subgroup analyses	Not applicable

Table A2d Main study characteristics

NP28761	NP28673 A Study of Alectinib (RO5424802) in Participants With Non-Small Cell Lung Cancer Who Have Anaplastic Lymphoma Kinase (ALK) Mutation and Failed Crizotinib Treatment.
NCT number	NCT01801111
Objective	To determine the safety, efficacy, and pharmacokinetics (PK) of alectinib in patients with advanced ALK-rearranged NSCLC who had experienced progression while receiving crizotinib.
Publications – title, author, journal, year	1) *Alectinib in Crizotinib-Refractory ALK-Rearranged Non-Small-Cell Lung Cancer: A Phase II Global Study.* Ou, S. H., Ahn, J. S. *et al*, *Journal of Clinical Oncology*. 2016 2) *Pooled Analysis of CNS Response to Alectinib in Two Studies of Pretreated Patients With ALK-Positive Non-Small-Cell Lung Cancer*. Gadgeel, S. M., Shaw, A. T., *et al.*, *Journal of Clinical Oncology.* 2016
Study type and design	Phase 2, global, single-arm, open-label, multicentre study to determine the safety, tolerability and activity of alectinib as a single agent in patients with either locally advanced (AJCC Stage IIIB) and not amenable to curative therapy or metastatic (AJCC Stage IV) ALK-positive NSCLC who had experienced disease progression on crizotinib with or without prior chemotherapy.
Follow-up time	21 months, as per data cut-off on February 1st, 2016 [9].
Population (inclusion and exclusion criteria)	**Inclusion Criteria**: • Locally advanced or metastatic non-small cell lung cancer (stage IIIB or IV by American Joint Committee on Cancer [AJCC]) • Eastern Cooperative Oncology Group (ECOG) performance status 0-2 • Documented ALK rearrangement based on Food and Drug Administration (FDA)-approved test • Prior treatment with crizotinib and progression according to response evaluation criteria in solid tumors version 1.1 (RECIST v1.1) criteria. Participants had to have a minimum 1-week wash-out period between the last dose of crizotinib and the first dose of study treatment. Participants can either be chemotherapy-naïve or have received at least one line of platinum-based chemotherapy • Adequate hematologic, hepatic, and renal function • Participants with brain or leptomeningeal metastases are allowed if protocol defined criteria are met • Measurable disease according to RECIST v1.1 prior to administration of first dose of study drug **Exclusion Criteria**: • Receipt of any other ALK inhibitors in addition to crizotinib • Receipt of any prior cytotoxic chemotherapy for ALK-positive NSCLC within 4 weeks prior to the first dose of study drug

	• Participants who received crizotinib or any other tyrosine kinase inhibitors need to have a minimum 1-week washout period before the first dose of study drug • Active or uncontrolled infectious diseases requiring treatment • National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03 (NCI CTCAE v4.03) Grade 3 or higher toxicities due to prior therapy that have not shown improvement and are 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 corrected Q-T interval (QTc) greater than (>) 470 milliseconds, or baseline symptomatic bradycardia (less than 45 heart beats per minute) • Pregnant or breastfeeding women • Known Human Immunodeficiency Virus (HIV) positivity or Acquired Immunodeficiency Syndrome (AIDS)-related illness • History of hypersensitivity to any of the additives in the alectinib formulation • Any clinically significant concomitant disease or condition that could interfere with, or for which treatment might interfere with, the conduct of the study, or absorption of oral medications, or that would, in the opinion of the principal investigator, pose an unacceptable risk to the participant in the study
Intervention	600 mg alectinib was administered to the patient orally BID starting on Day 1 through Day 21 of each 21-day treatment cycle. Patients were treated continuously until disease progression, death, or withdrawal for any other reason. 138 patients were treated.
Baseline characteristics	- age: Mean 51.5 (STD: 11.1), Median: 52, rang: 22-79 - gender distribution: Female 56% - performance status: 32%, 59% and 9% of the patients were PS 0, 1, and 2 respectively. - previous treatments: 80% had previously received chemotherapy. - 99% of the patients had stage IV disease, 1% had stage IIIB.
Primary and secondary endpoints	**Primary objective** To evaluate the efficacy of alectinib based on ORR (according to RECIST 1.1) as per independent review committee (IRC) in patients ALK-positive NSCLC who have failed crizotinib. **Secondary objectives** • ORR according to RECIST 1.1 based on investigator review of radiographs • DCR, DOR and PFS according to RECIST v1.1 by IRC and investigator review of radiographs • OS • safety of alectinib • to characterize the PK of alectinib and metabolite(s) • to assess QoL using the EORTC QLQ − C30 and − LC13 • CNS ORR (CORR) in patients with CNS metastases who have measurable disease in the CNS at baseline, based on IRC review of radiographs by RECIST 1.1 and Response Assessment in Neuro-Oncology (RANO) criteria • CNS duration of response (CDOR) in patients who have a CNS objective response based on IRC review of radiographs by RECIST 1.1 and RANO criteria • CNS progression rates (CPR) at 3, 6, 9 and 12 months based on cumulative incidence by IRC review of radiographs by RECIST v1.1 and RANO criteria. **Exploratory objectives** • To assess blood based methods to detect point mutations in plasma

	• To identify molecular determinants of clinical resistance to ALK inhibitors • To identify potential genetic determinants of PK variability and safety parameters (pharmacogenomics research) • To assess alectinib CNS penetration by measuring the cerebrospinal fluid (CSF): plasma concentration ratio
Method of analysis	***Statistical methods*** The ITT population corresponded to the safety population (138 patients). The response evaluable population for the IRC consisted of 122 patients out of 138 total. These patients were analyzed for ORR. PFS, safety, OS, and response by investigator were analyzed in the safety population consisting of 138 patients. The Kaplan–Meier method was used to estimate rates of progression-free survival and overall survival. Response was evaluated according to RESCIST 1.1
Subgroup analyses	Not applicable

Table A2e Main study characteristics
(Complete this table for each included study.)

Trial name	**ALUR** Alectinib Versus Pemetrexed or Docetaxel in Anaplastic Lymphoma Kinase (ALK)-Positive Advanced Non-Small Cell Lung Cancer (NSCLC) Participants Previously Treated With Platinum-Based Chemotherapy and Crizotinib
NCT number	NCT02604342
Objective	ALUR examined alectinib efficacy and safety versus chemotherapy in advanced/metastatic ALK-positive NSCLC pretreated with platinum-based doublet chemotherapy (PDC) and crizotinib.
Publications – title, author, journal, year	*Alectinib versus chemotherapy in crizotinib-pretreated anaplastic lymphoma kinase (ALK)-positive non-small-cell lung cancer: results from the phase III ALUR study.* Novello, S., Mazieres, J., *et al.*, *Ann Oncol.* 2018
Study type and design	ALUR was a randomized, open-label, phase III trial. Patients were randomized 2 : 1 to receive alectinib 600 mg twice daily, or chemotherapy (pemetrexed 500 mg/m2 or docetaxel 75 mg/m2, every 3 weeks, at the investigators' discretion) until disease progression, death, or withdrawal. Randomization was carried out using the following stratification factors: ECOG PS (0/1 versus 2); baseline CNS metastases (yes/no); and, for patients with baseline CNS metastases, brain radiotherapy history (yes/no). Crossover from chemotherapy to alectinib was permitted following progression. At the investigators' discretion, alectinib could be continued beyond radiologic progression until loss of clinical benefit. 107 patients were randomized; 72 received alectinib and 35 received chemotherapy.
Follow-up time	6.5 Months
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. ALK positivity must have been determined by a validated fluorescence in situ hybridization (FISH) test (recommended probe, Vysis ALK Break-Apart Probe) or a validated immunohistochemistry (IHC) test (recommended antibody, clone D5F3) Participant had received two prior systemic lines of therapy, which must have included one line of platinum-based chemotherapy and one line of crizotinib Prior CNS or leptomeningeal metastases allowed if asymptomatic Participants with symptomatic CNS metastases for whom radiotherapy is not an option will be allowed to participate in this study Measurable disease by RECIST Version 1.1 prior to the administration of study treatment Eastern Cooperative Oncology Group (ECOG) performance status of 0-2 For all females of childbearing potential, a negative pregnancy test must be obtained within 3 days before starting study treatment

	Exclusion Criteria: Participants with a previous malignancy within the past 3 years are excluded (other than curatively treated basal cell carcinoma of the skin, early gastrointestinal [GI] cancer by endoscopic resection or in situ carcinoma of the cervix) Participants who have received any previous ALK inhibitor other than crizotinib Any GI disorder that may affect absorption of oral medications
Intervention	600 mg alectinib was administered to the patient orally BID starting on Day 1 through Day 21 of each 21-day treatment cycle. Patients were treated continuously until disease progression, death, or withdrawal for any other reason. 72 patients were treated.
Baseline characteristics	- age: Median: 55.5, range: 21-82 - gender distribution: Female 43.1% - performance status: 40.3%, 51.4% and 8.3% of the patients were PS 0, 1, and 2 respectively. - previous treatments: 100% had previously received crizotinib. - 94% of the patients had stage IV disease, 4% had stage IIIB.
Primary and secondary endpoints	**Primary Outcome** Progression-Free Survival (PFS) Using Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 as Assessed by Investigator **Secondary Outcomes** : • Percentage of Participants With CNS Objective Response Rate (ORR) With Measurable CNS Metastases at Baseline Using RECIST Version 1.1 as Assessed By IRC • PFS Using RECIST Version 1.1 as Assessed by IRC • Percentage of Participants With Objective Response of CR or PR Using RECIST Version 1.1 as Assessed by Investigator and IRC • Percentage of Participants With Disease Control Using RECIST Version 1.1 as Assessed by Investigator and IRC • Duration of Response (DOR) Using RECIST Version 1.1 as Assessed by Investigator and IRC • PFS in C-ITT Population Using RECIST Version 1.1 as Assessed by Investigator and IRC • Time to CNS Progression in C-ITT Population Using RECIST Version 1.1 as Assessed by IRC • Percentage of Participants With Disease Control in C-ITT Population Using RECIST Version 1.1 as Assessed by IRC • Percentage of Participants With ORR in C-ITT Population Using RECIST Version 1.1 as Assessed by IRC • Duration of Response for Lesions in the CNS (C-DOR) Using RECIST Version 1.1 as Assessed by IRC

	• Overall Survival (OS) • Plasma Concentration of Alectinib • Plasma Concentration of Alectinib Metabolite • Compliance of European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core-30 (EORTC QLQ-C30) Over Time • Compliance of European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Lung Cancer-13 (EORTC QLQ-LC13) Over Time • Compliance of European Quality of Life (EuroQoL) 5 Dimension 5 Levels (EQ-5D-5L) Questionnaire Over Time • Time to Deterioration (TTD) in Lung Cancer Symptoms Using EORTC QLQ-LC13 Score for ITT Population • Time to Deterioration (TTD) in Lung Cancer Symptoms Using EORTC QLQ-LC13 Score for C-ITT Population • Time to Deterioration (TTD) in Lung Cancer Symptoms Using EORTC QLQ-LC30 Score for ITT Population • Time to Deterioration (TTD) in Lung Cancer Symptoms Using EORTC QLQ-LC30 Score for C-ITT Population • TTD in Composite of Three Symptoms (Cough, Dyspnea, and Chest Pain) Using EORTC QLQ-LC13 Score for C-ITT Population • TTD in Composite of Three Symptoms (Cough, Dyspnea, and Chest Pain) Using EORTC QLQ-LC13 Score for ITT Population • Percentage of Participants With Adverse Events (AEs) [Time Frame: Approximately 15 months]
Method of analysis	The ITT population comprised all patients randomized. The safety population comprised all patients who received _1 dose of assigned study medication. ITT patients with measurable and/or nonmeasurable baseline CNS disease comprised the CNS ITT (C-ITT) population; C-ITT patients were further classified into those with measurable (mC-ITT) or nonmeasurable baseline CNS disease. Primary analysis of investigator-assessed PFS (ITT) was carried out using a stratified Cox model including treatment arm variable and stratification factors. Estimates for PFS were obtained using a Kaplan–Meier approach, the P-value of log-rank test was calculated with estimated HRs (stratified Cox model) and corresponding 95% CIs (Brookmeyer and Crowley method). Hypothesis testing for the primary end point was carried out (two-sided a at 0.05). If superiority for the primary end point was concluded, subsequent hierarchical testing for the key secondary end point, CNS ORR in patients with measurable baseline CNS metastases, was carried out (70% power at one-sided 5% alpha)
Subgroup analyses	*Not Applicable*

Results per study

Table A3a

Trial name:	**Study AP26113-11-101: 25 crizotinib exposed patients with ALK+ NSCLC treated with 90 mg → 180 mg**									
NCT number:	*NA*									
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Hazard/Odds/Risk ratio	95% CI	*P* value	
Median overall survival	90 mg → 180 mg	25	Not Reached							Assessed by Kaplan-Maier methodology. Data is from [10]
Discontinuation due to AEs	90 mg → 180 mg	32	9.4%							Data is from [10]
CNS PFS	90 mg → 180 mg	18	Not Reached							CNS PFS was determined by Investigator. Assessed by Kaplan-Maier methodology. Data is from [10]
PFS	90 mg → 180 mg	25	16,3 (9,2; NR)							Assessed by IRC. Assessed by Kaplan-Maier methodology. Data is from [10]
Raten af grad 3-4 utilsigtede hændelser	90 mg → 180 mg	32	59%							"Neoplasm progression" were removed from the data set, according to

						[27], see section 5.1.3 for details. From [2, 10]
Quality of Life EORTC QLQ30		25	Not Reported			
Objective Response Rate (ORR)	90 mg → 180 mg	25	80 % (59.3; 93.2)			Assessed by Investigator in the ITT population. Data is from [10]

Table A3b

Trial name:	Study AP26113-13-201, ALTA – Arm B: 90 mg → 180 mg									
NCT number:	*NA*									
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Hazard/Odds/Risk ratio	95% CI	*P* value	
Median overall survival	90 mg → 180 mg	110	34,1 (27,7; NR)							Assessed by Kaplan-Maier methodology. Assessed by IRC. Data is from [10]
Discontinuation due to AEs	90 mg → 180 mg	110	9.2 %							"Neoplasm progression" were removed from the data set, according to [27], see section 5.1.3 for details. Data is from [10]
CNS PFS	90 mg → 180 mg	110	18,4 (12,8; NR)							Assessed by IRC. Data is from [7].
PFS	90 mg → 180 mg	110	16,7 (11,6;21,4)							Assessed by IRC. Data is from [10].
Raten af grad 3-4 utilsigtede hændelser	90 mg → 180 mg	110	63.0%							"Neoplasm progression" were removed from the data set, according to [27], see section 5.1.3 for details. Data is from [10].

Quality of Life EORTC QLQ30	90 mg → 180 mg	110	5-12 points			**Takeda Data File.**
Confirmed Objective Response Rate (ORR)	90 mg → 180 mg	110	56,4 % (46,6; 65,8)			Assessed by IRC in the ITT population. Data is from [10].

Table A3c

Trial name:	NP28761									
NCT number:	**NCT01871805**									
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Hazard/Odds/Risk ratio	95% CI	*P* value	
Median overall survival - Months	600 mg BID	87	22,7 (17,2; NE)							Data is from [9]
Discontinuation due to AEs (%)		87	2,0%							Data is extracted from published article [5].
CNS PFS		136	8,3 (5,9; 11,2)							CNS PFS is only available from Alectinib as pooled data from two trials (NP28673 & NP28761). Reference: [8]
Median PFS - Months		87	8,2 (6.3; 12.6)							Assessed by IRC. Data is from EPAR [9].
Raten af grad 3-4 utilsigtede hændelser		87	41,4							Data is from EPAR [9]
Quality of Life EORTC QLQ-C30		87	≥ 10% change in Global Health Status compared to baseline							Details are not reported. Data is from [9].

Objective Response Rate (ORR)	67	52,2 (39,7;64,6)			IRC-Assessed in the response evaluable population, see ORR paragraph in section 5.1.3 for details. Data is from [9]

Table A3d

Trial name:	NP28673									
NCT number:	*NA*									
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Hazard/Odds/Risk ratio	95% CI	*P* value	
Median overall survival	600 mg BID	138	26,0 (21,5; NE)							Data is from EPAR [9]
Discontinuation due to AEs %	600 mg BID	138	8%							Data is based on published article [4]
CNS PFS, Months		136	8,3 (5,9; 11,2)							CNS PFS is only available from Alectinib as pooled data from two trials (NP28673 & NP28761). Reference: [8]
PFS	600 mg BID	138	8,9 (5,6; 12,8)							Assessed by IRC**.** Data is from Updated data cut-off presented in EPAR [9]
Raten af grad 3-4 utilsigtede hændelser (%)		138	39,9							Data is from EPAR [9]
Quality of Life EORTC QLQ30										Not reported
Objective Response Rate (ORR) (%)		122	50,8 (41,6; 59,9)							IRC assessed, in the Response Evaluable population. IRC-Assessed in the response evaluable population, see ORR

			paragraph in section 5.1.3 for details. Data is from EPAR [9]

Table 3e

Trial name:	ALUR									
NCT number:	*NA*									
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Hazard/Odds/Risk ratio	95% CI	*P* value	
Median overall survival	600 mg BID	72	12,6 (9,7; NE)							Data is immature and from published article [6]
Discontinuation due to AEs %	600 mg BID	70	5,7							Data is based on published article [6]
CNS PFS, Months	600 mg BID	50	Not reported							Not reported.
PFS	600 mg BID	72	7,1 (6,3; 10,8)							Assessed by IRC**.** Data is from published article [6]
Raten af grad 3-4 utilsigtede hændelser (%)		72	27,1%							Data is based on published article [6]
Quality of Life EORTC QLQ30			Not Reported							Not reported
Objective Response Rate (ORR) (%)		72	37,5 (26; 50)							IRC assessed in the ITT population. Data is from [6]

Table A3f

Trial name:	Virtual study ALTA vs. NP28761 Based on a published MAIC analysis [1]								
NCT number:	*NA*								
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Hazard/Odds/Risk ratio	95% CI	*P* value	
Median overall survival	Brigatinib	77,5[§]	27,6 (27,6; NE)	4,9			HR: 0,70	0,42-1,16	0,163	Data is based on MAIC [1]. The OS data for brigatinib from this publication is immature and short at 27.6 months as opposed to 34.1 months in the mature dataset [10].
	Alectinib	87	22,7 (17,2; NE)							
Discontinuation due to AEs										Not included in this analysis.
CNS PFS	Brigatinib									Not included in this analysis.
	Alectinib									
PFS	Brigatinib	77,5[§]	17,6 (11,1;NR)	9.4			HR: 0.56	0.36-0.86	0,009	Data is based on MAIC [1].
	Alectinib	87	8,2 (6,3;12,6)							
Raten af grad 3-4 utilsigtede hændelser										Not included in this analysis.
Quality of Life EORTC QLQ30		NR		NA	NA	NA	NA	NA	NA	Not included in this analysis.

Objective Response Rate (ORR)	Brigatinib	77,5[§]	53 (42-64)	13 %	ORR: 1,69	0,91- 3,15	0,096	Data is based on MAIC [1]. ORR are IRC-assessed in the ITT-population [1] and references therein.
	Alectinib	87	40 (30-51)					

TABLE A3F: [§:] EES: EFFECTIVE SAMPLE SIZE

Table A3g

Trial name:	Virtual study (MAIC based): ALTA vs. NP28673 [1]								
NCT number:	*NA*								
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Hazard/Odds/Risk ratio	95% CI	*P* value	
Median overall survival	Brigatinib	70,7[§]	27,6 (27,6; NE)	1,7			HR: 0,66	0,39-1,09	0,104	Data is based on MAIC [1]. The OS data from this publication [1] is immature and short at 27.6 months as opposed to 34.1 months in the mature dataset [10]
	Alectinib	138	26,0 (21,5; NE)							
Discontinuation due to AEs	Brigatinib									Not included in this analysis.
	Alectinib									
CNS PFS	Brigatinib									Not included in this analysis.
	Alectinib									
PFS	Brigatinib	70,7[§]	17,6 (11,1 - NR)	8,7			HR: 0,61	0,40 – 0,93	0,023	Data is based on MAIC [1].
	Alectinib	138	8,9 (5,6; 12,8)							
Raten af grad 3-4 utilsigtede hændelser	Brigatinib									Not included in this analysis.
	Alectinib									
Quality of Life EORTC QLQ30		NR								Not included in this analysis.

Objective Response Rate (ORR)	Brigatinib	70,7[§]	54 (42; 66)	9 %	OR: 1,44	0,81; 2,58	0,212	Data is based on MAIC [1]. ORR are IRC-assessed in the ITT-population [1] and references therein.
	Alectinib	138	45 (37;53)					

Results per PICO (clinical question)

Table A4 Results referring to *what is the added clinical value of brigatinib as monotherapy for the treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC) previously treated with crizotinib*?

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	
Rate of Discontinuation Due to Aes, %	101, ALTA vs. NP28761, NP28673, and ALUR	3.1	NA	NA	OR: 1.55	0.74-3.26	0.25	Indirect comparison. AEs of the Neoplasm progression type has been removed from the data set of brigatinib, see section 5.1.3 – Discontinuation due to AEs. Data are summaries of EPARs [9, 10] supplemented with the ALUR trial [6]. OR and CI are calculated according to [28]; P-value according to [29].
CNS PFS	ALTA vs. NP28761 and NP28673	10.1						Study 101, was not included in the summary analysis as the median CNS PFS was not reached for the relevant patient population [10]. ALUR was not included I the summary analysis as CNS PFS was not reported [6].
Rate of grade 3-4 AEs	101, ALTA vs. NP28761, NP28673, and ALUR	25.1			OR: 2.83	1.87-4.29	< 0.0001	Indirect comparison. AEs of the Neoplasm progression type has been removed from the data set of brigatinib, see section 5.1.3 – Discontinuation due to AEs. Date are summaries of EPARs [9, 10] supplemented with the ALUR trial [6]. OR and CI are calculated according to [28]; P-value according to [29].

Table A5 – Overview of Adverse Reactions reported for brigatinib and alectinib, combined from relevant 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 Decreased platelet count	Lymphocyte count decreased	Very common	Anemia[1)] – 17%	Anemia[1)] - 3.0%
	Common		APTT increased Anaemia Neutrophil count decreased	Common		
Metabolism and nutrition disorders	Very common	Hyperglycaemia Hyperinsulinaemia[b] Hypophosphataemia Decreased appetite Hypokalaemia Hypomagnesaemia Hyponatraemia Hypercalcaemia		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[e]		Very common		
	Common		Visual disturbance[e]	Common	Vision Disorder[3)] – 8.6%	
Cardiac disorders	Common	Tachycardia[f] Electrocardiogram QT prolonged Bradycardia[g] Palpitations		Common	Bradycardia[4)] – 8.9 %	
	Uncommon		Electrocardiogram QT prolonged	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] Dry mouth 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	Amylase increased Abdominal pain[k]	Common	Stomatitis[5)] – 3.0%	
	Uncommon	Pancreatitis	Nausea Dyspepsia Pancreatitis	Uncommon		
Hepatobiliary disorders	Very common	AST increased ALT increased Alkaline phosphatase increased		Very common	Bilirubin increase[6)] – 18% AST increased – 15%	Bilirubin increase[6)], 3.2% AST increased, 3.7%
	Common	Blood LDH increased Hyperbilirubinaemia	ALT increased AST increased Alkaline phosphatase increased Hyperbilirubinaemia	Common	Alkaline phosphatase increased**, 6.2% Drug-induced liver injury[7)], 0.7%	Alkaline phosphatase increased**, 0.2% Drug-induced liver injury[7)], 0.7%
	Very Common	Rash[m] Pruritus		Very Common	Rash[8)], 18%	Rash[8)], 0.5%

Skin and subcutaneous tissue disorders	Common	Dry skin Photosensitivity reaction	Rash[m] Photosensitivity reaction	Common	Photosensitivity, 9.1%	0.2%
	Uncommon		Dry skin	Uncommon		
Musculoskeletal and connective tissue disorders	Very common	Blood CPK increased Myalgia[n] Arthralgia Musculoskeletal chest pain	Blood CPK increased	Very common	Myalgia[9)], 28% Blood CPK increased, 10%	Blood CPK increased, 3.2% Myalgia[9)], 0.7%
	Common	Pain in extremity Musculoskeletal stiffness	Pain in extremity	Common		
	Uncommon		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	Uncommon		
Investigations	Very			Very	Weight increased,	Weight increased,
	Common	Weight decreased		Common		
	Uncommon		Weight decreased	Uncommon		

[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.

Appendix A6:

Reckamp K, Lin HM, Huang J, Proskorovsky I, Reichmann W, Krotneva S, et al. Comparative efficacy of brigatinib versus ceritinib and alectinib in patients with crizotinib-refractory anaplastic lymphoma kinase-positive non-small cell lung cancer. Current Medical Research and Opinion. 2018:1-8.

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ORIGINAL ARTICLE

Comparative efficacy of brigatinib versus ceritinib and alectinib in patients with crizotinib-refractory anaplastic lymphoma kinase-positive non-small cell lung cancer

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ABSTRACT

Objective: Brigatinib, ceritinib, and alectinib are approved to treat crizotinib-refractory anaplastic lymphoma kinase-positive (ALK+) non-small cell lung cancer (NSCLC), but no trial has compared them head-to-head. A matching-adjusted indirect comparison (MAIC) was conducted to estimate the relative efficacy of these agents in the crizotinib-refractory setting.

Methods: MAIC is a propensity score-type method that adjusts for differences in baseline characteristics between trials to estimate relative efficacy. Analyses were based on patient-level data from the ALTA trial for brigatinib and published summary-level trial data from ASCEND-1 and ASCEND-2 for ceritinib and NP28761 and NP28673 for alectinib. Objective response rate (ORR), progression-free survival (PFS), and overall survival (OS) were compared.

Results: After matching, all key baseline characteristics were balanced between trials. Compared with ceritinib, brigatinib was associated with longer PFS (ASCEND-1: median 15.7 vs 6.9 months, hazard ratio (HR) [95% confidence interval] = 0.38 [0.26–0.57]; ASCEND-2: median = 18.3 vs 7.2 months, HR = 0.33 [0.20–0.56]) and OS (ASCEND-1: not available; ASCEND-2: median 27.6 vs 14.9 months, HR = 0.33 [0.17–0.63]). Versus alectinib, brigatinib was associated with longer PFS (NP28761: median = 17.6 vs 8.2 months, HR = 0.56 [0.36–0.86]; NP28673: median = 17.6 vs 8.9 months, HR = 0.61 [0.40–0.93]); results for OS were inconclusive (NP28761: median = 27.6 vs 22.7 months, HR = 0.70 [0.42–1.16]; NP28673: median = 27.6 vs 26.0 months, HR = 0.66 [0.39–1.09]). ORR was similar.

Conclusion: In crizotinib-refractory ALK + NSCLC patients, relative efficacy estimates suggest brigatinib may have prolonged PFS and OS vs ceritinib and prolonged PFS vs alectinib.

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ALK + NSCLC; Brigatinib; Ceritinib; Alectinib; Indirect comparison

Introduction

Lung cancer is the leading cause of cancer death worldwide[1]. Non-small cell lung cancer (NSCLC) makes up ~85% of lung cancer cases[1], of which 2–8% of cases are associated with anaplastic lymphoma kinase-positive (*ALK*) gene rearrangement[2]. ALK-positive (ALK+) patients are a genetically distinct sub-set of NSCLC patients who tend to be younger than other NSCLC patients and have little or no history of smoking[3,4].

In the US, approved targeted therapies for *ALK*+ NSCLC include the *ALK* inhibitors crizotinib, ceritinib, alectinib, and brigatinib. Crizotinib[5] was the first ALK tyrosine kinase inhibitor (TKI) approved for first-line therapy for *ALK*+ NSCLC, followed more recently by ceritinib[6] and alectinib[7]. Crizotinib demonstrated prolonged progression-free survival (PFS) vs chemotherapy (median PFS = 10.9 months vs 7.0 months)[5]. However, most patients on crizotinib develop progressive disease within 1 year[8].

Ceritinib, alectinib, and brigatinib are approved for treatment of patients with metastatic *ALK*+ NSCLC who have progressed on or are intolerant to crizotinib. In the crizotinib-refractory setting, the efficacy of ceritinib[9] was supported by two trials, Phase 1 ASCEND-1[10] (ALK inhibitor pre-treated patients: investigator [INV]-assessed objective response rate [ORR] was 56% and median PFS was 6.9 months) and Phase 2 ASCEND-2[11] (independent review committee [IRC]-assessed ORR was 35.7%, median PFS was 7.2 months, and median overall survival [OS] was 14.9 months). Alectinib[12] was supported by two trials, Phase 2 NP28761[13] (IRC-assessed intention-to-treat [ITT] ORR 40.2%, median PFS 8.2 months, and median OS 22.7 months) and Phase 2 NP28673[14] (IRC-assessed ITT ORR 44.9%, median PFS 8.9 months, and median OS 26.0 months). Brigatinib[15] was supported by one Phase 2 trial, ALTA (arm B, recommended dose: IRC-assessed ORR 54.5%, median PFS 16.7 months, median OS 27.6 months). No randomized trial has directly compared these second-line ALK inhibitor treatments.

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In the absence of a head-to-head study, an indirect treatment comparison (ITC) can be conducted to estimate the relative efficacy of ceritinib, alectinib, and brigatinib in the post-crizotinib setting. However, standard ITC methods such as Bucher indirect comparisons[16] and network meta-analyses[17] are not feasible because ASCEND-1, ASCEND-2, NP28761, NP28673, and ALTA are single-arm trials that lack a common comparator. In such cases, a matching adjusted indirect comparison (MAIC) can be used instead.

MAIC is a form of propensity score weighting that is applicable when individual patient data are available in one population (the index trial) and summary patient data are available in another (the comparator trial). An MAIC weights subjects in the index trial such that their weighted average characteristics match those of subjects in the comparator trial[18]. After matching, relative efficacy is estimated across balanced trial populations. The MAIC technique has been used to compare a number of compounds in oncology[19,20], including ceritinib and crizotinib as initial ALK-targeted therapies for *ALK*+ NSCLC[21].

The objective of this analysis was to conduct MAICs to estimate the relative efficacy of brigatinib vs ceritinib and alectinib in patients with crizotinib-refractory ALK + NSCLC. ALTA served as the index trial, while ASCEND-1, ASCEND-2, NP28761, and NP28673 served as the comparator trials. Relative efficacy estimates were generated for ORR, PFS, and OS.

Methods

Data sources

Analyses were based on individual patient-level data from arm B (recommended dose: 180 mg daily with a 7-day lead-in at 90 mg, $n = 110$) of the ALTA trial (ClinicalTrials.gov identifier: NCT02094573) for brigatinib (February 21, 2017 database extraction date, median follow-up = 18.6 months), published summary data from the ASCEND-1[10] (NCT01283516) ALK inhibitor pre-treated sub-group: median follow-up = 11.1 months) and ASCEND-2[11] (NCT01685060; median follow-up = 11.3 months) for ceritinib, and NP28761[13] (NCT01871805; median follow-up = 17 months) and NP28673[14] (NCT01801111; median follow-up = 21 months) for alectinib.

Individual patient-level data from the ALTA trial were obtained from data on file (ARIAD Pharmaceuticals, Inc., a wholly owned subsidiary of Takeda Pharmaceutical Company Limited, Cambridge, MA). Virtual patient-level (VPL) data for each comparator trial were generated by digitizing the published PFS and OS Kaplan-Meier (KM) curves and applying the method described by Hoyle and Henley[22]. VPL data estimate the underlying individual patient data (i.e. time of events or censorships) from the digitized survival curve and the number of patients at risk at multiple time points. The VPL data were checked for accuracy by plotting the VPL KM curves against the published graphs. Published proportions for ORR were used to derive the number of objective responses in comparator trials.

ALTA, ASCEND-1, ASCEND-2, NP28761, and NP28673 were similar in terms of trial design (Supplementary Table 1). Patients had locally advanced or metastatic crizotinib-refractory ALK + NSCLC. MAIC analyses prioritized IRC-assessed outcomes when available. ASCEND-1 outcomes were INV-assessed using RECIST 1.0 criteria; the ALTA/ASCEND-1 MAIC was, therefore, based on INV-assessed outcomes from ALTA. ASCEND-2, NP28761, and NP28673 outcomes were IRC-assessed using RECIST 1.1 criteria; the MAICs for these trials were, therefore, based on ALTA IRC-assessed outcomes. All trials were Phase 2 trials, except for Phase 1 ASCEND-1. ALTA, ASCEND-1, ASCEND-2, and NP28673 were global trials, while NP28761 was conducted in the US and Canada only. ASCEND-2, NP28761, and NP28673 were single-arm studies. ALTA was designed to have two parallel single arms that were analyzed separately; the relevant ALTA arm B and ASCEND-1 *ALK* inhibitor pre-treated sub-group were single-arm for the purposes of these analyses. The primary trial end-point was INV-assessed ORR for ALTA and ASCEND-2, IRC-assessed ORR for NP28761 and NP28673, and the maximum tolerated dose for ASCEND-1.

Statistical methods

MAIC is an ITC method used to estimate relative treatment effects when standard indirect comparisons are either inappropriate or infeasible. We implemented an unanchored MAIC because all trials were single-arm and lacked a common comparator. An unanchored MAIC makes the strong assumption that all effect modifiers and prognostic factors are accounted for in the matching process[23].

The baseline characteristics to be matched on included prognostic factors previously identified in the literature (Asian ethnicity[24–26], ECOG performance status[27–29], smoking status[28,30], and crizotinib as last prior therapy[31]) and variables with clinical relevance (age, sex, best response to prior crizotinib, previous chemotherapy, prior radiotherapy, number of metastatic sites, and brain metastases)[32]. Each MAIC matched on as many of these variables as were available in the comparator trial to limit the potential bias of the unanchored MAIC assumption.

The MAIC analyses followed the general methodology described by Signorovitch *et al.*[33], which has previously been used to support health technology assessment submissions[34,35]. An MAIC involves three key steps: (1) deriving balancing weights for the matching variables; (2) applying the balancing weights to obtain adjusted outcome estimates with the index trial data; and (3) deriving comparative efficacy estimates.

In the first step, weights were derived from a propensity score-type logistic regression equation that adjusted for differences in baseline characteristics between the trials. Weights were applied to patients in the ALTA trial such that their average baseline characteristics matched those of the comparator trial. The weights were used to calculate the effective sample size (ESS) of the matched population. The ESS and distribution of the weights were evaluated to

ensure that the estimated treatment effect was not driven by a small fraction of the patients.

In the second step, the weights were applied to ALTA patients to derive adjusted ORR, PFS, and OS estimates. Adjusted PFS and OS curves were obtained using the KM approach. The adjusted outcomes represent the expected outcomes for brigatinib in a population matching those from the ASCEND-1, ASCEND-2, NP28761, and NP28673 trials.

In the third step, relative treatment effects for brigatinib vs ceritinib and alectinib were estimated for ORR, PFS, and OS. The relative effect for ORR was quantified as an odds ratio (OR) with a 95% confidence interval (CI). Unadjusted and adjusted ORs were obtained using logistic regression based on unweighted and weighted ALTA patient-level data for brigatinib and the published number of subjects with response for the comparators. Relative effects for PFS and OS were quantified as hazard ratios (HRs) with a 95% CI and were obtained using a Cox regression based on unweighted and weighted ALTA patient-level data for brigatinib and VPL data for the comparators.

Results

Unadjusted trial results

Unadjusted PFS and OS results from the brigatinib ALTA trial and VPL data from the ceritinib (ASCEND-1 and ASCEND-2) and alectinib (NP28761 and NP28673) trials are shown in Figure 1. Before matching, patients receiving brigatinib in ALTA appeared to achieve better outcomes than patients in the ceritinib and alectinib trials, especially for PFS (OS data for ASCEND-1 were not available).

Adjusted comparison with ceritinib in ASCEND-1

ALTA and ASCEND-1 had similar baseline characteristics before matching. After matching, all baseline characteristics were balanced with an ESS of 75.8, indicating a reduction of 31% from the original ALTA sample size (Table 1).

ORR in ALTA (pre-matching 55%, post-matching 53%) was similar to ASCEND-1 (56%) (Table 2). The ORs for ORR were similar and not statistically significantly different (Table 3).

Median PFS was higher for ALTA (pre-matching 15.6 months, post-matching 15.7 months) than ASCEND-1 (6.9 months) (Table 2; Figure 2(A)). The HR for PFS (pre-matching = 0.40, post-matching = 0.38) was statistically significant in favor of brigatinib (Table 3).

Adjusted comparison with ceritinib in ASCEND-2

ALTA had fewer Asian subjects and fewer patients with previous chemotherapy than ASCEND-2 (Table 1). After matching, all baseline characteristics were balanced with an ESS of 50.8, indicating a reduction of 54% from the original ALTA sample size.

ORR in ALTA (pre-matching 55%, post-matching 55%) was higher than ASCEND-2 (36%) (Table 2). The ORs for ORR (pre-matching = 2.16, post-matching = 2.17) were statistically significant in favor of brigatinib (Table 3).

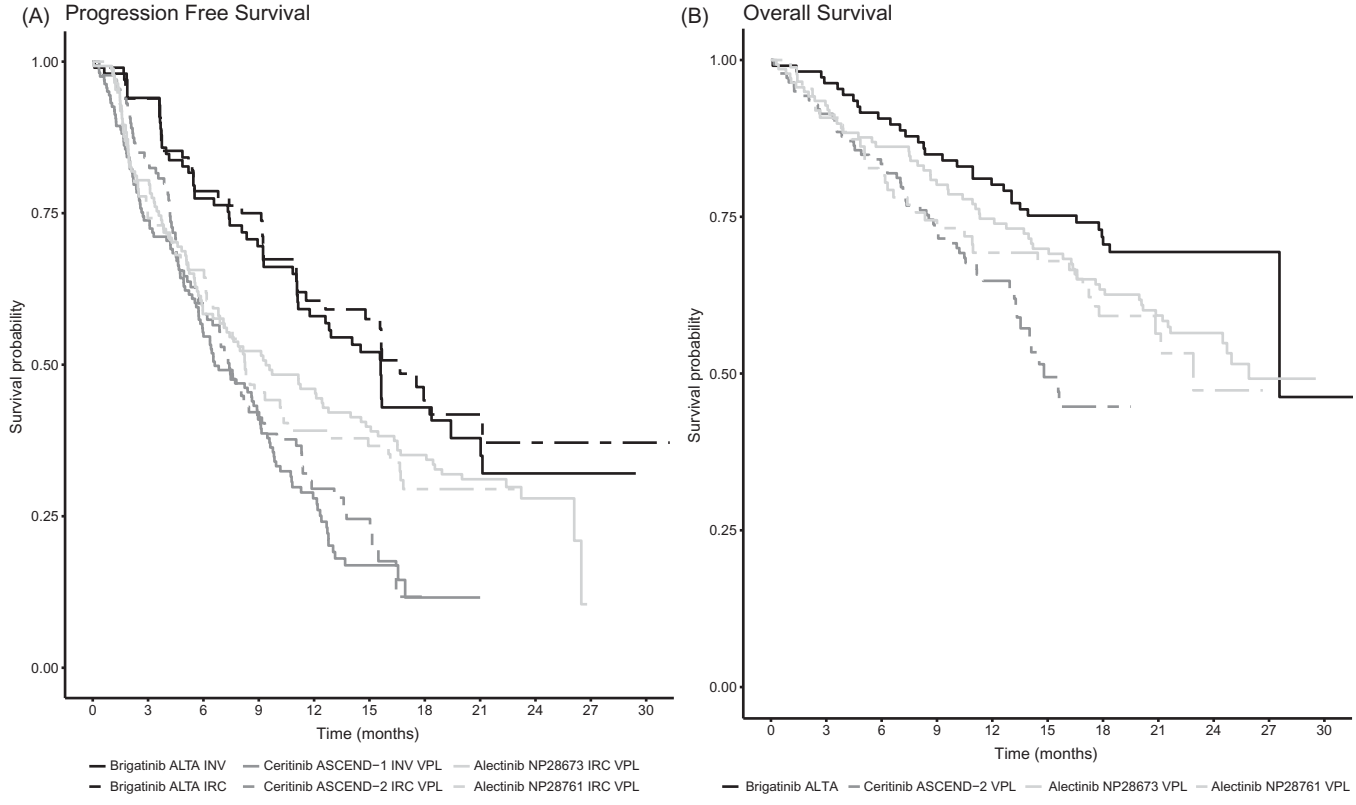

Figure 1. Unadjusted PFS and OS comparison of brigatinib ALTA trial and ceritinib and alectinib trial VPL data. Before matching, Kaplan-Meier estimates show brigatinib ALTA trial had higher (A) PFS and (B) OS. Abbreviations. INV, investigator; IRC, independent review committee; VPL, virtual patient-level.

Table 1. Baseline characteristics of brigatinib ALTA trial patients compared with the ASCEND-1, ASCEND-2, NP28761, and NP28673 trial populations, before and after matching.

	ALTA Arm B	ASCEND-1[a]		ASCEND-2		NP28761		NP28673	
	Brigatinib Pre-Match ($n = 110$)	Ceritinib ($n = 163$)	Brigatinib Post-Match (ESS =75.8)	Ceritinib ($n = 140$)	Brigatinib Post-Match (ESS =50.8)	Alectinib ($n = 87$)	Brigatinib Post-Match (ESS =77.5)	Alectinib ($n = 138$)	Brigatinib Post-Match (ESS =70.7)
Median age (years)	57	52	51	51	50	54	53	52	51
Male (%)	42	46	46	50	50	45	45	44	44
Asian (%)	27	29	29	38	38	8	8	26	26
White (%)	69	66	66	60	60	84	84	67	67
ECOG PS 0 (%)	41	23	23	30	30	35	35	32	32
ECOG PS 1 (%)	51	64	64	56	56	55	55	59	59
Brain metastases (%)	67	60	60	71	71	60	60	61	61
Previous chemotherapy (%)	74	84	84	100	100	74	74	80	80
Smoker – current (%)	4	3	3	NA	NA	NA	NA	NA	NA
Smoker – former (%)	39	NA	NA	NA	NA	38	38	NA	NA
Smoker – never (%)	57	NA	NA	NA	NA	62	62	70	70
Last treatment crizotinib (%)	96	NA	NA	100	100	NA	NA	NA	NA
Best prior response to crizotinib – CR/PR (%)	66	NA	NA	NA	NA	NA	NA	54	54

[a]ALK TKI-pre-treated cohort.

Abbreviations. CR, complete response; ECOG, Eastern Cooperative Oncology Group; NA, not available; PR, partial response; PS, performance status.

Table 2. Comparison of ORR, PFS, and OS outcomes before and after matching.

	ASCEND-1[a]			ASCEND-2			NP28761			NP28673		
	Ceritinib ASCEND-1 ($n = 163$)	Brigatinib Pre-Match ($n = 110$)	Brigatinib Post-Match (ESS =75.8)	Ceritinib ASCEND-2 ($n = 140$)	Brigatinib Pre-Match ($n = 110$)	Brigatinib Post-Match (ESS =50.8)	Alectinib NP28761 ($n = 87$)	Brigatinib Pre-Match ($n = 110$)	Brigatinib Post-Match (ESS =77.5)	Alectinib NP28673 ($n = 138$)	Brigatinib Pre-Match ($n = 110$)	Brigatinib Post-Match (ESS =70.7)
ORR												
Response rate, % (95% CI)	56 (49–64)	55 (45–64)	53 (42–65)	36 (28–44)	55 (45–64)	55 (41–68)	40 (30–51)	55 (45–64)	53 (42–64)	45 (37–53)	55 (45–64)	54 (42–66)
PFS												
Median survival, months (95% CI)	6.9 (5.6–8.7)	15.6 (11.1–19.4)	15.7 (11.1–21.0)	7.2 (5.4–9.0)	16.7 (11.6–NA)	18.3 (0.1–NA)	8.2 (6.3–12.6)	16.7 (11.6–NA)	17.6 (11.1–NA)	8.9 (5.6–12.8)	16.7 (11.6–NA)	17.6 (11.1–NA)
12-month survival, % (95% CI)	28.0[b] (20.6–35.7)	58.0 (47.2–67.4)	60.5 (46.9–71.6)	29.5[b] (21.1–38.5)	60.6 (49.2–70.1)	62.7 (45.3–75.9)	39.1[b] (28.5–49.5)	60.6 (49.2–70.1)	59.8 (45.9–71.2)	46.0[b] (37.4–54.2)	60.6 (49.2–70.1)	62.1 (47.9–73.5)
24-month survival, % (95% CI)	NR	32.1 (20.4–44.3)	30.0 (16.0–45.4)	NR	37.1 (23.6–50.7)	43.3 (24.0–61.1)	NR	37.1 (23.6–50.7)	38.4 (22.2–54.5)	27.9[b] (20.0–36.4)	37.1 (23.6–50.7)	36.7 (19.7–53.9)
OS												
Median survival, months (95% CI)	NA	NA	NA	14.9 (13.5–NA)	27.6 (27.6–NA)	27.6 (0.1–NA)	22.7 (17.2–NA)	27.6 (27.6–NA)	27.6 (27.6–NA)	26.0 (21.5–NA)	27.6 (27.6–NA)	27.6 (27.6–NA)
12-month survival, % (95% CI)	NA	NA	NA	64.8[b] (55.9–72.3)	80.1 (71.1–86.6)	83.0 (69.3–90.9)	69.3[b] (58.2–78.0)	80.1 (71.1–86.6)	75.3 (64–83.5)	74.7[b] (66.4–81.2)	80.1 (71.1–86.6)	79.5 (67.7–87.3)
24-month survival, % (95% CI)	NA	NA	NA	NR	69.4 (59.3–77.5)	77.7 (63.2–87.1)	47.3[b] (31.2–61.8)	69.4 (59.3–77.5)	66 (53.6–75.8)	56.5[b] (47.3–64.6)	69.4 (59.3–77.5)	71.5 (58.7–81.0)

[a]ALK TKI-pretreated cohort.

[b]Estimated from VPL data.

Abbreviations. CI, confidence interval; ESS, effective sample size; NA, not available; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; VPL, virtual patient-level.

Table 3. Relative efficacy comparison of ALTA vs comparator trials for ORR, PFS, and OS before and after matching.

		ASCEND-1[a]		ASCEND-2		NP28761		NP28673	
		Brigatinib Pre-Match ($n = 110$)	Brigatinib Post-Match (ESS = 75.8)	Brigatinib Pre-Match ($n = 110$)	Brigatinib Post-Match (ESS = 50.8)	Brigatinib Pre-Match ($n = 110$)	Brigatinib Post-Match (ESS = 77.5)	Brigatinib Pre-Match ($n = 110$)	Brigatinib Post-Match (ESS = 70.7)
ORR	OR	0.96	0.88	2.16*	2.17*	1.78	1.69	1.47	1.44
	95% CI	(0.59–1.57)	(0.51–1.53)	(1.30–3.61)	(1.13–4.20)	(1.01–3.17)	(0.91–3.15)	(0.89–2.44)	(0.81–2.58)
	p-value	.872	.659	.003	.020	.047	.096	.133	.212
PFS	HR	0.40*	0.38*	0.40*	0.33*	0.59*	0.56*	0.64*	0.61*
	95% CI	(0.28–0.55)	(0.26–0.57)	(0.27–0.58)	(0.20–0.56)	(0.40–0.87)	(0.36–0.86)	(0.45–0.92)	(0.40–0.93)
	p-value	<.001	<.001	<.001	<.001	.009	.009	.015	.023
OS	HR	NA	NA	0.45*	0.33*	0.60*	0.70	0.69	0.66
	95% CI			(0.28–0.70)	(0.17–0.63)	(0.37–0.97)	(0.42–1.16)	(0.45–1.06)	(0.39–1.09)
	p-value			<.001	<.001	.037	.163	.091	.104

*$p < .05$.
HR <1 and OR >1 suggest better outcome from brigatinib trial.
ORR odds ratios for alectinib are based on the ITT populations of NP28761 and NP28673.
[a]ALK TKI-pre-treated cohort.
Abbreviations. CI, confidence interval; ESS, effective sample size; HR, hazard ratio; NA, not available; OR, odds ratio; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.

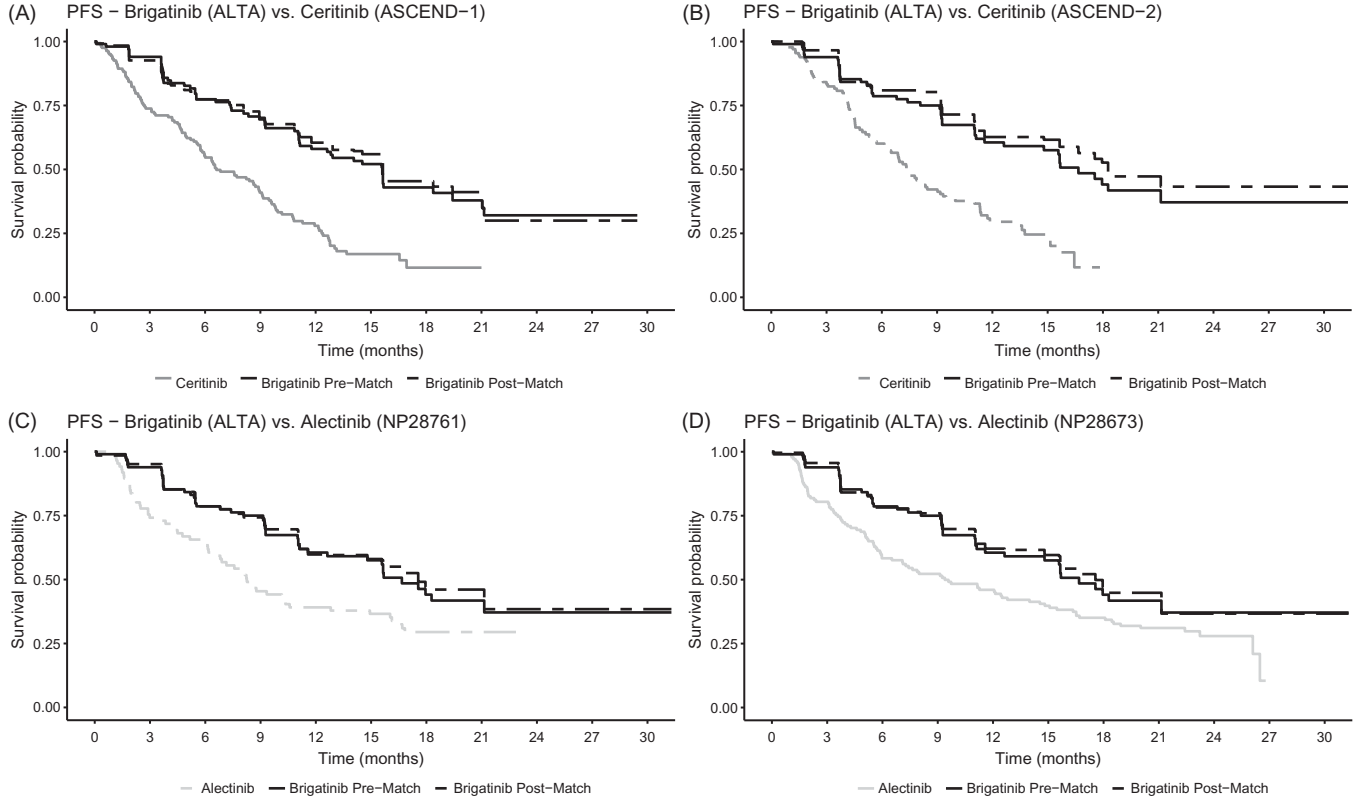

Figure 2. Pre-match and post-match adjusted PFS comparison. (A) Kaplan-Meier estimates of brigatinib ALTA vs ceritinib ASCEND-1 PFS. Median PFS for brigatinib was 15.6 months both before and after matching vs 6.6 months for ceritinib. (B) Kaplan-Meier estimates of brigatinib ALTA vs ceritinib ASCEND-2 PFS. Median PFS for brigatinib was 16.7 months before matching and 18.3 months after matching vs 7.4 months for ceritinib. (C) Kaplan-Meier estimates of brigatinib ALTA vs alectinib NP28761. Median PFS for brigatinib was 16.7 months before matching and 17.6 months after matching vs 8.3 months for alectinib. (D) Kaplan-Meier estimates of brigatinib ALTA vs alectinib NP28673. Median PFS for brigatinib was 16.7 months before matching and 17.6 months after matching vs 9.4 months for alectinib. Abbreviation. PFS, progression-free survival.

Median PFS was higher for ALTA (pre-matching = 16.7 months, post-matching = 18.3 months) than ASCEND-2 (7.2 months) (Table 2; Figure 2(B)). The HRs for PFS (pre-matching = 0.40, post-matching = 0.33) were statistically significant in favor of brigatinib (Table 3).

Median OS was higher for ALTA (pre-matching = 27.6 months, post-matching = 27.6 months) than ASCEND-2 (14.9 months) (Table 2; Figure 3(A)). The HRs for OS (pre-matching = 0.45, post-matching = 0.33) were statistically significant in favor of brigatinib (Table 3).

Adjusted comparison with alectinib in NP28761

ALTA had more Asian subjects than NP28761 (Table 1). After matching, all baseline characteristics were balanced with an

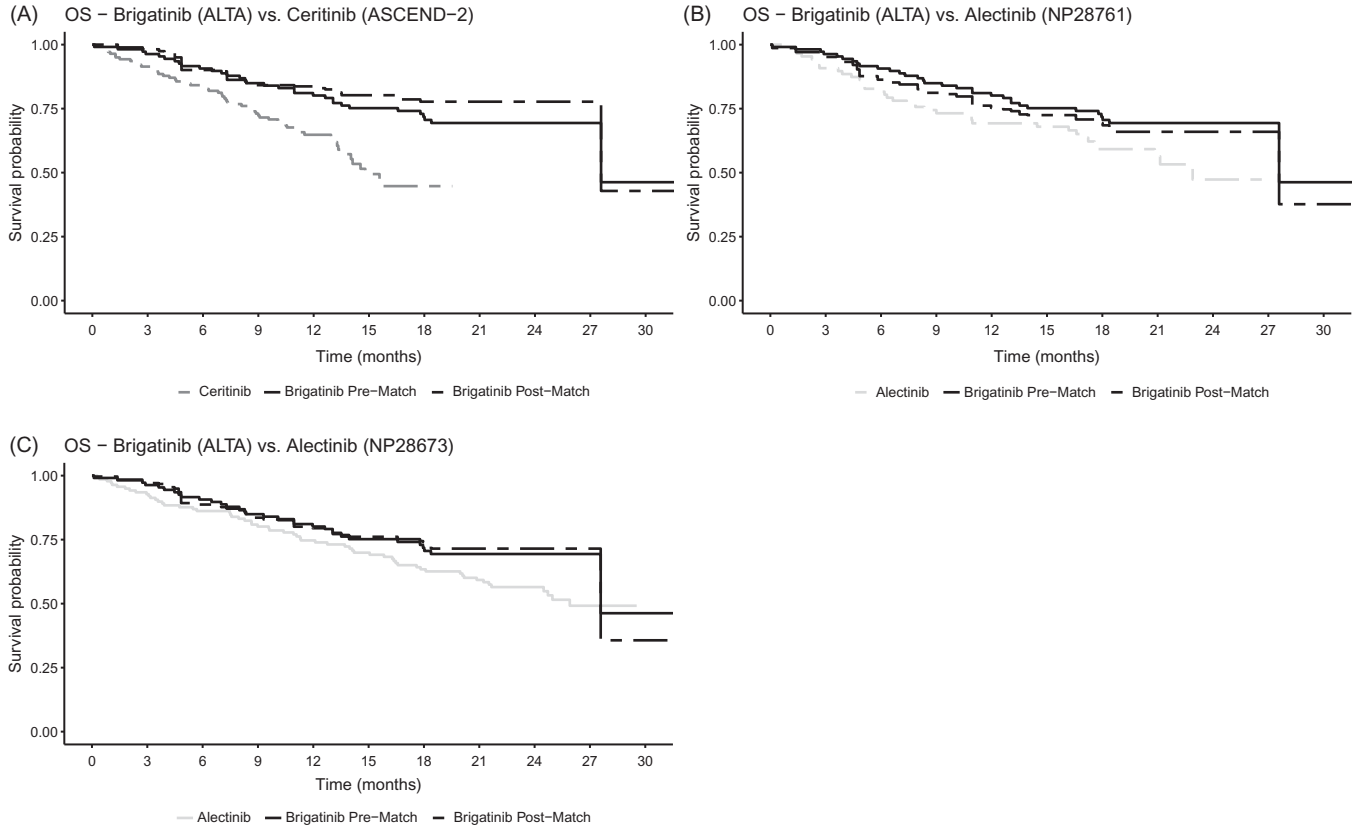

Figure 3. Pre-match and post-match adjusted OS comparison. OS results for ASCEND-1 were not available. (A) Kaplan-Meier estimates of brigatinib ALTA vs ceritinib ASCEND-2 OS. Median OS for brigatinib was 27.6 months both before and after matching vs 14.8 months for ceritinib. (B) Kaplan-Meier estimates of brigatinib ALTA vs alectinib NP28761 OS. Median OS for brigatinib was 27.6 months both before and after matching vs 22.9 months for alectinib. (C) Kaplan-Meier estimates of brigatinib ALTA vs alectinib NP28673 OS. Median OS for brigatinib was 27.6 months both before and after matching vs 25.9 months for alectinib. Abbreviation. OS, overall survival.

ESS of 77.5, indicating a reduction of 30% from the original ALTA sample size.

ORR in ALTA (pre-matching = 55%, post-matching = 53%) was numerically higher than in NP28761 (40%) (Table 2). The ORs for ORR were not statistically significantly different post-match (Table 3).

Median PFS was higher for ALTA (pre-matching = 16.7 months, post-matching = 17.6 months) than NP28761 (8.2 months) (Table 2; Figure 2(C)). The HRs for PFS (pre-matching = 0.59, post-matching = 0.56) were statistically significant in favor of brigatinib (Table 3).

Median OS was higher for ALTA (pre-matching = 27.6 months, post-matching = 27.6 months) than NP28761 (22.7 months) (Table 2; Figure 3(B)). Pre-matching, the 0.60 HR was statistically significant in favor of brigatinib. Post-matching, the 0.70 HR point estimate was in favor of brigatinib, but did not reach statistical significance (Table 3).

Adjusted comparison with alectinib in NP28673

Compared to NP28673, ALTA had fewer patients who were never smokers and more patients with best prior response of complete response (CR)/partial response (PR) (Table 1). After matching, all baseline characteristics were balanced with an ESS of 70.7, indicating a reduction of 36% from the original ALTA sample size.

ORR in ALTA (pre-matching = 55%, post-matching = 54%) was numerically higher than in NP28673 (45%) (Table 2). The ORs were not statistically significantly different (Table 3).

Median PFS was higher for ALTA (pre-matching = 16.7 months, post-matching = 17.6 months) than NP28673 (8.9 months) (Table 2; Figure 2(D)). The HRs for PFS (pre-matching = 0.64, post-matching = 0.61) were statistically significant in favor of brigatinib (Table 3).

Median OS for ALTA (pre-matching = 27.6 months, post-matching = 27.6 months) was similar to NP28673 (26.0 months) (Table 2; Figure 3(C)). The HR point estimates for OS (pre-matching = 0.69, post-matching = 0.66) were in favor of brigatinib, but they did not reach statistical significance (Table 3).

Discussion

This analysis estimated the comparative efficacy of brigatinib vs ceritinib and alectinib in crizotinib-refractory ALK + NSCLC populations. For the analysis from this data follow-up (February 21, 2017 database extraction date), patients treated with brigatinib in ALTA had similar ORR and statistically significantly better PFS and OS compared to ceritinib in ASCEND-1 and ASCEND-2. Additionally, patients treated with brigatinib in ALTA had similar ORR and statistically significantly better PFS compared to alectinib in NP28761 and

NP28673; results for OS were inconclusive. These relative efficacy estimates were consistent both pre- and post-matching.

The magnitude of PFS benefit is substantial from a clinical perspective. The median PFS for brigatinib in the ALTA trial is 9–10 months longer than that observed in trials for ceritinib (an increase of 125%) and 7–8 months longer than that observed in trials for alectinib (an increase of 90%). Similarly, the median OS for the ALTA trial is 12–13 months longer than that of trials for ceritinib (an increase of 80%). Median OS for brigatinib in the ALTA trial appeared numerically longer than median OS in trials for alectinib (1–5 months, an increase of 5–20%), although the clinical significance is inconclusive. In a sensitivity analysis, median duration of response with brigatinib in ALTA was significantly longer than with ceritinib in ASCEND-1 and ASCEND-2 and similar to alectinib in NP28673 (Supplementary Table 2; Supplementary Figure). However, analyses of duration of response (DOR) were limited to the sub-set of responders from each trial who may have had different distributions in their prognostic factors, despite matching for baseline characteristics of all patients in the trials. In addition, patients who had stable disease were not included in the DOR analysis.

We conducted an MAIC due to the absence of head-to-head randomized trials, which is an increasingly common methodological challenge when comparing new oncology treatments. The MAIC method is subject to several limitations. First, adjusting for trial differences incurs a loss of precision, indicated by the smaller ESS and the increase in the range of the CIs of the relative efficacy estimates compared to the unadjusted comparisons. Despite this loss of precision, brigatinib still demonstrated significantly better PFS than ceritinib or alectinib. Second, all studies used in these analyses were single-arm trials with no common comparator arm, limiting the ability to assess the presence of residual confounding (i.e. distortion in comparisons due to differences between studies beyond population characteristics). These analyses were also limited by data availability in terms of commonly reported baseline characteristics between the trials, which could have resulted in confounding due to unobserved or unadjusted differences. We mitigated these potential biases by matching on as many effect modifiers and prognostic factors as could be identified via literature searches. Additional limitations may include (1) difference in the length of median follow-up across the trials may have impacted results, and (2) trials included in the analyses were phase 1 and 2, and PFS and OS were not primary end-points. The OS results should be interpreted with caution because OS data were immature for ALTA, and subsequent treatments were allowed post-progression for all trials, which can confound OS. It is worth noting that, with longer follow-up, OS in the ALTA trial has been updated to 34.1 months[36], further confirming the efficacy of brigatinib in this population. Besides efficacy, it is also important to consider the safety profile of each ALK inhibitor when selecting treatment after progression on crizotinib[37].

Future work could implement an ITC based on ceritinib, alectinib, and brigatinib trials in which a common comparator arm is available. For instance, the ASCEND-5[38] and ALUR[39] trials (published after the completion of our analyses) compare ceritinib and alectinib vs chemotherapy in ALK + NSCLC patients previously treated with platinum-based doublet chemotherapy and crizotinib. Since median PFS estimates from these two trials are so far consistent with their single-arm counterparts, a common chemotherapy arm would enable a network meta-analysis or anchored MAIC analysis that could validate these unanchored MAIC results. Additional studies, including head-to-head randomized controlled trials, would provide confirmatory evidence on the comparative efficacy of ALK inhibitors. Future studies may also investigate the effectiveness of ALK inhibitors in the post-alectinib setting, as the preferred first-line standard of care has become alectinib rather than crizotinib[40].

Conclusions

These MAIC results may suggest longer PFS and OS for brigatinib vs ceritinib and longer PFS for brigatinib vs alectinib in the crizotinib-refractory setting. Newer and more potent treatment options for patients with *ALK*-translocated NSCLC have led to significant advances in the management of this sub-set of lung cancer. Clinicians currently have alectinib, brigatinib, and ceritinib as options for patient who progressed on crizotinib. In the absence of a direct comparison trial, this analysis provides additional data which may help inform treatment decisions for patients.

Transparency

Declaration of funding

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Declaration of financial/other relationships

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Medicinrådet

Medicinrådets protokol for vurdering af klinisk merværdi for brigatinib til behandling af ALK-positiv ikke-småcellet lungekræft

Versionsnr.: 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.

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

Om protokollen

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

Se Medicinrådets metodehåndbog for yderligere information.

Dokumentoplysninger	
Godkendelsesdato	04.02.2019
Ikrafttrædelsesdato	04.02.2019
Dokumentnummer	39685
Versionsnummer	1.0

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

Medicinrådet, Dampfærgevej 27-29, 3. th., 2100 København Ø
www.medicinraadet.dk
Sprog: dansk
Format: pdf
Udgivet af Medicinrådet, 04.02.2019

Indhold

1 Lægemiddelinformationer

Lægemidlets oplysninger	
Handelsnavn	Alunbrig
Generisk navn	Brigatinib
Firma	Takeda Pharma
ATC-kode	L01XE43
Virkningsmekanisme	Anaplastisk Lymfom Kinase (ALK)-hæmmer
Administration/dosis	Tablet 90 mg én gang dagligt i de første syv dage og derefter 180 mg én gang dagligt.
EMA-indikation	*Alunbrig er indiceret som monoterapi til behandling af voksne patienter med fremskreden anaplastisk lymfom-kinase(ALK)-positiv, ikke-småcellet lungecancer (NSCLC), som tidligere har fået behandling med crizotinib.*

2 Forkortelser

ALK:	Anaplastisk lymfom kinase (*anaplastic lymphoma kinase)*
ARR:	Absolut risikoreduktion
CI:	Konfidensinterval
CNS:	Centralnervesystem
EMA:	Det Europæiske Lægemiddelagentur (*European Medicines Agency)*
EORTC QLQ-C30:	*European Organisation for Research and Treatment of Cancer Quality-of-life Questionnaire-Core 30*
EORTC QLQ-L13:	*European Organisation for Research and Treatment of Cancer Quality-of-life Questionnaire-Lung Cancer 13*
EPAR:	*European public assessment report*
GRADE:	System til vurdering af evidens (*Grading of Recommendations Assessment, Development and Evaluation*)
HR:	*Hazard ratio*
ITT:	*Intention to treat*
NSCLC:	Ikke-småcellet lungekræft (*Non Small Cell Lung Cancer)*
OR:	*Odds ratio*
OS:	Overlevelse (*overall survival)*
PFS:	Progressionsfri overlevelse (*progression-free survival)*
RR:	Relativ risiko
SAE:	Alvorlig uønsket hændelse (*serious adverse event)*
SMD:	*Standardized Mean Difference*

3 Formål

Protokollen har til formål at definere de kliniske spørgsmål, der ønskes belyst i vurderingen af brigatinib som mulig standardbehandling af patienter med Anaplastisk Lymfom Kinase (ALK)-positiv ikke-småcellet lungekræft (NSCLC). I protokollen angives en definition af populationer, komparator og effektmål, der skal præsenteres i den endelige ansøgning, samt de metoder der ønskes anvendt til den komparative analyse. Arbejdet med protokollen er igangsat på baggrund af den foreløbige ansøgning vedrørende brigatinib modtaget den 15. oktober 2018.

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

4 Baggrund

ALK-positiv lungekræft

I 2017 blev 4.856 danskere diagnosticeret med lungekræft [1], og dermed er lungekræft en af de hyppigst forekommende kræftsygdomme i Danmark [2]. Af de diagnosticerede har ca. 85 % NSCLC [3]. I slutningen af 2015 levede knap 10.450 personer med lungekræft, mens cirka 3.700 personer årligt dør af lungekræft [4]. Lungekræft har således en høj dødelighed med den senest opgjorte etårs overlevelse i Danmark på 50,8 % for samtlige nydiagnosticerede patienter [1].

Lungekræft inddeles i fire stadier (I-IV) afhængigt af udbredelsesgrad [5]. Stadie III betyder, at tumor enten har en vis størrelse, indvækst i nærliggende struktur eller spredning til regionale lymfeknuder. Metastatisk lungekræft betegnes som stadie IV, der som udgangspunkt betragtes som uhelbredelig. Nogle patienter med NSCLC i stadie III betragtes også som havende uhelbredelig lungekræft og behandles som patienter i stadie IV.

Man kender mange biomarkører, hvoraf enkelte har betydning for behandlingen. En af dem er anaplastisk lymfom kinase (ALK)-translokation [6]. I 2016 var andelen af patienter med ALK-translokation 1,7 % (svarende til 35 patienter) hos patienter med adenokarcinom m.fl. [1]. Dette skal ses i lyset af, at ALK-status ikke blev registreret hos omkring hver femte patient diagnosticeret med adenokarcinom m.fl.

Mange patienter med ALK-positiv NSCLC vil med tiden ofte få progression i centralnervesystemet (CNS) [7]. Generelt beskrives incidensen af hjernemetastaser blandt patienter med ALK-positiv NSCLC som værende høj og studier har vist, at 35-50 % af de inkluderede patienter havde hjernemetastaser. Lungekræft patienter med hjernemetastaser oplever betydelig morbiditet og reduceret livskvalitet, ofte med neurologiske dysfunktioner og kognitive ændringer og med en median overlevelse på 3-6 måneder [7,8].

4.1 Nuværende behandling

Crizotinib har tidligere været anbefalet som førstelinjebehandling til uhelbredelig ALK-positiv NSCLC. Den 30. maj 2018 anbefalede Medicinrådet imidlertid alectinib som mulig standardbehandling i første linje [9], og tilsvarende beskriver Dansk Lunge Cancer Gruppe (DLCG)s kliniske retningslinjer alectinib som førstelinjebehandling til patienter med uhelbredelig ALK-positiv NSCLC [10].

Brigatinib kan ifølge EMA indikationen kun anvendes til patienter, der har fået behandling i første linje med crizotinib. Størstedelen af danske patienter behandles nu i første linje med alectinib. Fagudvalget vurderer, at gruppen af danske patienter, der er kandidater til brigatinib i anden linje efter crizotinib, omfatter 0-5

patienter årligt. Dette kan eksempelvis dreje sig om patienter, der enten indledte behandling med crizotinib før alectinib blev anbefalet af Medicinrådet som mulig standardbehandling i første linje, eller patienter som ikke tåler alectinib.

4.2 Brigatinib

Brigatinib er en tyrosinkinasehæmmer med specifik aktivitet mod blandt andet ALK. Ved at hæmme ALK reduceres aktiviteten af centralt placerede molekyler i signaleringskaskader af betydning for cellulær overlevelse, vækst og proliferation [11].

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

Brigatinib administreres oralt som en enkelt tablet dagligt indtil sygdomsprogression. Efter en syv-dages indkøringsperiode med 90 mg én gang dagligt, øges dosis til 180 mg én gang dagligt.

5 Kliniske spørgsmål

De kliniske spørgsmål skal indeholde specifikation af patientgruppen, interventionen, alternativet/-erne til interventionen og effektmål.

5.1 Klinisk spørgsmål 1

Hvad er den kliniske merværdi af brigatinib til patienter med uhelbredelig ALK-positiv NSCLC, som tidligere har fået behandling med crizotinib?

Population
Patienter med uhelbredelig ALK-positiv NSCLC, som har fået behandling med crizotinib i første linje.

Intervention
Brigatinib jf. afsnit 4.2. Tablet 90 mg én gang dagligt i de første syv dage og derefter 180 mg én gang dagligt.

Komparator
Alectinib 600 mg to gange dagligt.

Effektmål
Se tabel 1.

5.2 Valg af effektmål

Tabel 1 summerer de valgte effektmål, deres vigtighed, mindste klinisk relevante forskel og kategori.

For alle effektmål ønskes både absolutte og relative værdier, jf. ansøgningsskemaet. For de relative værdier vurderes den kliniske relevans (merværdi), jf. væsentlighedskriterierne beskrevet i Medicinrådets metodehåndbog for vurdering af nye lægemidler. De relative effektestimater kan angives i relativ risiko (RR), odds ratio (OR) eller hazard ratio (HR). Det skal begrundes i ansøgningen, hvis der afviges fra de ønskede effektmål.

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

Effektmål*	**Vigtighed**	**Kategori**	**Måleenhed**	**Mindste klinisk relevante forskelle (absolutte værdier)**
Overlevelse (OS)	Kritisk	Overlevelse	Median forskel *eller* Andel patienter	3 måneder *eller* 5 % absolut risikoreduktion (ARR) efter 12 og 18 måneder
Behandlingsophør grundet uønskede hændelser	Kritisk	Alvorlige symptomer og bivirkninger	Andel patienter	5 % ARR
CNS-progression	Kritisk	Alvorlige symptomer og bivirkninger	Median forskel	3 måneder
Progressionsfri overlevelse (PFS)	Vigtig	Alvorlige symptomer og bivirkninger	Median forskel *eller* Andel patienter	3 måneder *eller* 5 % ARR efter 12 og 18 måneder
Alvorlige uønskede hændelser (grad 3-4)	Vigtig	Alvorlige symptomer og bivirkninger	Andel patienter *og* Kvalitativ sammenligning af bivirkningsprofiler	5 % ARR *og* Narrativ vurdering
Livskvalitet	Vigtig	Helbredsrelateret livskvalitet	Gennemsnitlig ændring over tid i EORTC-QLQ-C30	≥ 10 point
Objektiv responsrate (ORR)	Vigtig	Alvorlige symptomer og bivirkninger	Andel patienter	5 % ARR

* For alle effektmål ønskes data med længst mulig opfølgningstid.

Den samlede kliniske merværdi af brigatinib ønskes baseret på en så lang tidshorisont som muligt.

Kritiske effektmål

Overlevelse (OS)

Forbedret samlet overlevelse (OS) med mindst mulig toksicitet er det optimale mål for behandling af NSCLC. OS er derfor et kritisk effektmål. Fagudvalget vurderer, at et lægemiddel, der medfører en median forlængelse af levetiden med mindst 3 måneder, har en positiv klinisk merværdi vedrørende dette effektmål. Dette er fordi, restlevetiden hos lungecancer patienter generelt er forholdsvis kort trods kurativ intenderet behandling. Hvis data for median overlevelse ikke er modne, kan ansøger i stedet indsende data for absolut risiko reduktion (ARR) efter 12 og 18 måneder. Når overlevelse således opgøres som andel af patienter i live efter et år og halvandet år, anser fagudvalget en forskel på 5 % som klinisk relevant.

Behandlingsophør grundet uønskede hændelser

Fagudvalget finder, at ophør med en effektiv behandling er kritisk for patienterne. Derfor sættes behandlingsophør grundet bivirkninger som et kritisk effektmål. Fagudvalget vurderer, at lægemidlet har en negativ klinisk merværdi vedrørende dette effektmål, hvis det medfører behandlingsophør på grund af bivirkninger hos mere end 5 % sammenlignet med komparator.

CNS-progression
Da ALK-positiv NSCLC ofte metastaserer til centralnervesystemet med betydelig morbiditet og reduceret livskvalitet, anser fagudvalget *CNS progression* som et vigtigt effektmål. Fagudvalget vurderer, at en forskel i median på 3 måneder er klinisk relevant.

Vigtige effektmål

Progressionsfri overlevelse (PFS)
Progressionsfri overlevelse (PFS) anvendes til vurdering af sygdomsprogression og er et relevant og ofte benyttet effektmål i onkologiske studier. Fagudvalget vurderer, at et lægemiddel, der medfører en median forlængelse af PFS med mindst 3 måneder, har en positiv klinisk merværdi vedrørende PFS. Hvis data for median PFS ikke er modne, kan ansøger i stedet indsende data for absolut risiko reduktion (ARR) efter 12 og 18 måneder. Hvis effektmålet således opgøres som andel af patienter med PFS efter et år og halvandet år, anser fagudvalget en forskel på 5 % som klinisk relevant.

Alvorlige uønskede hændelser (grad 3-4)
Forekomst af alvorlige uønskede hændelser grad 3-4 er et udtryk for bl.a. alvorlig toksicitet af lægemidlet [12]. Fagudvalget anser grad 3-4 alvorlige uønskede hændelser som et vigtigt effektmål og vurderer, at lægemidlet har en negativ klinisk merværdi vedrørende effektmålet, hvis det medfører alvorlige uønskede hændelser hos mere end 5 % af patienterne i forhold til placebo.

Fagudvalget ønsker derudover en liste med relevante/alle bivirkninger og deres frekvens i både komparator- og interventionsgruppen. Der skal specielt fokuseres på de bivirkninger, som adskiller sig mellem de to grupper. Her ønsker fagudvalget også data på bivirkning grad 5, der afspejler dødelig toksicitet.

Livskvalitet
Livskvalitet kan for NSCLC patienter måles med flere forskellige instrumenter. De to mest velegnede instrumenter er her nævnt i prioriteret rækkefølge: European Organisation for Research and Treatment of Cancer Quality-of-life Questionnaire-Core 30 (EORTC QLQ-C30) eller det sygdomsspecifikke EORTC QLQ-Lung Cancer 13 (EORTC QLQ-LC13) [13–15]. Hvis der er data på livskvalitet baseret på flere af disse instrumenter, vil vurderingen blive baseret på det højest prioriterede instrument.

EORTC QLQ-C30 består af fem funktionsskalaer, tre symptomskalaer og en ”global” livskvalitetsskala. Der anvendes en scoringsskala fra 0-100. En høj score på de fem funktionsskalaer repræsenterer et højt/positivt funktionsniveau. En høj score for global helbredsstatus repræsenterer høj livskvalitet, mens en høj score på de tre symptomskalaer repræsenterer høj forekomst af symptomer/problemer [14]. Den mindste klinisk relevante forskel baserer sig på en lille ændring defineret som 5-10 point på den globale skala. En moderat ændring er 10-20 point, og en stor ændring er > 20 point [16]. Fagudvalget har defineret den mindste klinisk relevante forskel som 10 point, da dette vil overstige grænsen for en lille ændring.

Objektiv responsrate (ORR)
Objektiv responsrate (ORR) (defineret som partielt eller komplet respons) anvendes til belysning af behandlingsrespons. Fagudvalget vurderer, at tumorreduktion medfører en periode med forbedring eller ingen forværring af symptomer. Fagudvalget vurderer derfor, at responsraten er et vigtigt effektmål. Fagudvalget finder, at den mindste klinisk relevante forskel er en ARR på 5 %.

Mindre vigtige effektmål

Der indgik inden mindre vigtige effektmål i fagudvalgets drøftelser.

6 Litteratursøgning

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

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

Søgetermer
Søgningen skal inkludere det generiske navn og handelsnavnet for både det aktuelle lægemiddel og dets komparator(er), som kombineres med termer for indikationen.

Søgningen skal som minimum indeholde termer, som er beskrivende for de områder, der angivet i tabellen herunder. Både indekseret (f.eks. Medical Subject Headings, MeSH) og fritekstsøgning skal anvendes.

Lægemiddel		**Indikation**
[brigatinib, Alunbrig] *Termer for det generiske navn, handelsnavn og alternative stavemåder og eventuelle MeSH/Supplementary Concepts kombineres med OR. AND kan bruges, hvor flere termer skal forekomme samtidigt for at beskrive lægemidlet korrekt, fx ved coformuleringer.*	*Blokken til venstre og højre kombineres med* **AND**	[non-small cell lung cancer] *Termer for indikationen, alternative stavemåder og eventuelle MeSH kombineres med OR. AND kan bruges, hvor flere termer skal forekomme samtidigt for at beskrive indikationen korrekt.*
[alectinib, Alecensa] *Termer for det generiske navn, handelsnavn og alternative stavemåder og eventuelle MeSH/Supplementary Concepts kombineres med OR. AND kan bruges, hvor flere termer skal forekomme samtidigt for at beskrive lægemidlet korrekt, fx ved coformuleringer.*		

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

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

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

Inklusions- og eksklusionskriterier: Da det fremgår af ansøgers foreløbige ansøgning, at der ikke findes et randomiseret, kontrolleret studie af brigatinib, vil fagudvalget acceptere data fra andre typer studier af brigatinib. Studier med andre populationer og studier, som ikke rapporterer mindst et af de kritiske eller vigtige effektmål, skal ekskluderes.

Vurderingen af klinisk merværdi baseres som udgangspunkt på data fra peer-reviewed publicerede fuldtekstartikler og data fra EMAs EPAR – public assessment report. Data skal derudover stemme overens med protokollens beskrivelser.

7 Databehandling og analyse

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

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

Hvis ekstraherede data afviger fra de forhåndsdefinerede PICO-beskrivelser, specielt i forhold til præspecificeret population og effektmål, begrundes dette.

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

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

Hvis der er mere end ét sammenlignende studie, foretages en metaanalyse for de effektmål, hvor det er metodemæssigt forsvarligt. Hvis der ikke foreligger sammenlignende studier, kan data eventuelt syntetiseres indirekte (evt. i form af formelle netværksmetaanalyser eller ved brug af Buchers metode), hvis intervention og komparator er sammenlignet med samme alternative komparator i separate studier. Medicinrådet forbeholder sig retten til at foretage sensitivitets- og subgruppeanalyser på baggrund af studiernes validitet og relevans.

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

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

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

8 Andre overvejelser

Fagudvalget gør opmærksom på, patientpopulationen er yderst begrænset, og sandsynligvis kun er eksisterende i en kort tidsperiode, da patienter nu modtager alectinib som førstelinjebehandling og ikke crizotinib.

9 Referencer

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10 Sammensætning af fagudvalg og kontaktinformation til Medicinrådet

Medicinrådets fagudvalg vedrørende lungekræft

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11 Versionslog

Version	Dato	Ændring
1.0	04.02.2019	Godkendt af Medicinrådet.