Medicinrådet

Bilag til Medicinrådets anbefaling vedrørende entrectinib til førstelinje-behandling af uhelbredelig ROS1-positiv ikke-småcellet lungekræft

Vers. 1.0

Bilagsoversigt

1. Medicinrådets sundhedsøkonomiske afrapportering vedr. entrectinib, version 1.0
2. Forhandlingsnotat fra Amgros vedr. entrectinib
3. Høringssvar fra ansøger
4. Medicinrådets vurdering vedr. entrectinib til behandling af uhelbredelig ROS1-positiv ikke-småcellet lungekræft, version 1.0
5. Ansøgers endelige ansøgning
6. Ansøgers tekniske dokument til den sundhedsøkonomiske ansøgning
7. Medicinrådets protokol for vurdering af entrectinib til førstelinjebehandling af uhelbredelig ROS1-positiv ikke-småcellet lungekræft, version 1.0

Medicinrådet

Medicinrådets sundheds-økonomiske afrapportering

Entrectinib

Uhelbredelig ROS1-positiv ikke-småcellet lungekræft

Version 1.0

Om Medicinrådet

Medicinrådet er et uafhængigt råd, som udarbejder anbefalinger og vejledninger om lægemidler til de fem regioner. Medicinrådet vurderer, om nye lægemidler og nye indikationer kan anbefales som standardbehandling, og udarbejder fælles regionale behandlingsvejledninger. Nye lægemidler vurderes i forhold til effekt, eksisterende behandling og pris. Det skal give lavere priser og lægemidler, der er til størst mulig gavn for patienterne.

Dokumentets formål

Dette dokument indeholder en beskrivelse af den sundhedsøkonomiske analyse, som ligger til grund for ansøgningen for entrectinib til uhelbredelig ROS1-positiv ikke-småcellet lungekræft, samt en gennemgang af ansøgers modelantagelser til den sundhedsøkonomiske model. Sekretariatet vil kommentere på ansøgers modelantagelser under afsnittene "*Sekretariatets vurdering*". Her vil sekretariatets vurdering fremgå sammen med eventuelle ændrede modelantagelser og begrundelser herfor.
Afsnit 4.4 indeholder en tabel, der opsummerer både ansøgers og sekretariatets modelantagelser med det formål tydeligt at vise, hvordan sekretariatets sundhedsøkonomiske analyse afviger fra ansøgers sundhedsøkonomiske analyse. Resultatafsnittet baserer sig på sekretariatets modelantagelser og sundhedsøkonomiske analyse.

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Indholdsfortegnelse

1. Liste over forkortelser

AIP	Apotekernes indkøbspris
ALK	Anaplastisk lymfom kinase
DKK	Danske kroner
EGFR	*Epidermal growth factor receptor*
EKG	Elektrokardiografi
DRG	Diagnose Relaterede Grupper
KM	Kaplan-Meier
MAIC	*Matching Adjusted Indirect Comparison*
NSCLC	Ikke-småcellet lungekræft (*non small-cell lung cancer*)
OS	Overlevelse
PD	Progredieret overlevelse
PFS	Progressionsfri overlevelse
ToT	*Time on Treatment*
ROS1	*ROS proto-onkogene 1 receptor tyrosin kinase*
SAIP	Sygehusapotekernes indkøbspriser

2. Opsummering

Baggrund
Entrectinib som monoterapi er indiceret til behandling af voksne patienter med uhelbredelig ROS1-positiv, fremskreden ikke-småcellet lungekræft (NSCLC), der ikke tidligere er behandlet med ROS1-hæmmere. Ca. 10 nye patienter pr. år kandiderer til behandling af den ansøgte indikation i Danmark. Sekretariatets vurdering tager udgangspunkt i dokumentation indsendt af Roche.

Analyse
Den sundhedsøkonomiske analyse estimerer de inkrementelle omkostninger pr. patient ved behandling med entrectinib over en tidshorisont på 20 år. Entrectinib sammenlignes med crizotinib til patienter med uhelbredelig ROS1-positiv ikke-småcellet lungekræft.

Inkrementelle omkostninger og budgetkonsekvenser
I det scenarie, sekretariatet mener er mest sandsynligt, er de inkrementelle omkostninger for entrectinib ca. [redacted] DKK sammenlignet med crizotinib over en tidshorisont på 20 år. Hvis analysen udføres med AIP, bliver de inkrementelle omkostninger til sammenligning ca. 238.000 DKK pr. patient.

Sekretariatet vurderer, at budgetkonsekvenserne for regionerne ved anbefaling af entrectinib som standardbehandling vil være ca. [redacted] DKK i år 5. Hvis analysen udføres med AIP, er budgetkonsekvenserne ca. 2,4 mio. DKK i år 5.

Konklusion
Fagudvalget har i forbindelse med udarbejdelsen af den kliniske vurdering fundet, at den samlede værdi af entrectinib sammenlignet med crizotinib ikke kan kategoriseres. På baggrund af det foreliggende datagrundlag og fagudvalgets kliniske erfaring formoder fagudvalget, at der ikke er klinisk relevante forskelle på crizotinib og entrectinib på de undersøgte effektmål. Derfor vælger sekretariatet i sin hovedanalyse at sætte den kliniske effekt og bivirkninger til at være identiske for entrectinib og crizotinib. Det betyder derfor, at de inkrementelle omkostninger udelukkende er drevet af lægemiddelomkostningerne for entrectinib. Der er dog usikkerhed ved disse resultater, og der er derfor også udført en følsomhedsanalyse, hvor den relative effekt mellem entrectinib og crizotinib er udtrykt ved en hazard ratio, som er estimeret baseret på to forskellige MAIC-analyser. Dette har stor betydning på de inkrementelle omkostninger, men fagudvalget har dog vurderet, at de bagvedliggende data til estimering af disse hazard ratios er mangelfulde. MAIC-analysen indgik heller ikke i den kliniske vurdering af entrectinib. Derudover er der usikkerhed om ekstrapolering af både PFS- og OS-kurverne for entrectinib, da data ikke er modne.

3. Baggrund for den sundhedsøkonomiske analyse

Roche (herefter omtalt som ansøger) er markedsføringstilladelsesindehaver af entrectinib og har den 9. september 2020 indsendt en ansøgning til Medicinrådet om anbefaling af entrectinib som standardbehandling på danske hospitaler af den nævnte indikation. Som et led i denne ansøgning vurderer Medicinrådets sekretariat, på vegne af Medicinrådet, den sundhedsøkonomiske analyse, ansøger har indsendt. Denne rapport er sekretariatets vurdering af den fremsendte sundhedsøkonomiske analyse (herefter omtalt som analysen).

3.1 Patientpopulation

Omtrent 4.600 danskere diagnosticeres årligt med lungekræft, og dermed er lungekræft en af de hyppigst forekommende kræftsygdomme i Danmark [1,2]. Af de diagnosticerede har ca. 85-90 % ikke-småcellet lungekræft (NSCLC) [3]. Ikke-småcellet lungekræft inddeles i planocellulære og ikke-planocellulære tumorer. Fagudvalget estimerer, at ca. 25 % af patienterne har planocellulære tumorer, og ca. 75 % har ikke-planocellulære tumorer. Langt de fleste ikke-planocellulære tumorer er såkaldte adenokarcinomer.

I slutningen af 2016 levede knap 11.151 personer med lungekræft, mens ca. 3.700 personer årligt dør af lungekræft [2]. Den seneste årsrapport fra Dansk Lunge Cancer Register viser, at 1-årsoverlevelsesraten for patienter med lungekræft udredt i 2017 uanset stadie var 51,4 %, mens 5-årsoverlevelsen for patienter udredt i 2013 var 15,9 % [6]. Der er altså tale om en sygdom med en dårlig prognose og kort overlevelse efter diagnosetidspunkt for størstedelen af patienterne

Behandlingsmålet for patienter med uhelbredelig NSCLC er symptomlindring og levetidsforlængelse. Patienter med uhelbredelig NSCLC kan få forskellige typer behandling afhængig af tumorkarakteristika. Hvis en undersøgelse viser mutationer, som en behandling kan målrettes mod, vil en såkaldt targeteret behandling være første valg. I dansk klinisk praksis drejer det sig på nuværende tidspunkt om aktiverende epidermal growth factor receptor (EGFR)-mutationer samt anaplastisk lymfom kinase (ALK)-translokationer [3]. Targeteret behandling er kun relevant for patienter med uhelbredelig NSCLC og ikke for patienter med NSCLC i tidligere stadier.
En tredje mutation, som er fundet hos nogle patienter med lungekræft, er translokationer som involverer genet ROS proto-onkogene 1 receptor tyrosin kinase (ROS1). Hvis en tumor har en kromosomal translokation, som involverer ROS1 (ROS1-rearrangement), kaldes den ROS-1 positiv. ROS1-rearrangementer giver ophav til fusionproteiner, som aktiverer signaleringskaskader involveret i udvikling og spredning af kræft. ROS1-rearrangementer er sjældne i lungekræft og ses i omkring 0,9-2 % af alle undersøgte tilfælde af NSCLC [4].

Fagudvalget vurderer, at antallet af uhelbredelig ROS1-positive patienter med NSCLC i Danmark er ca. 10 om året.

3.1.1 Komparator

Medicinrådet har defineret crizotinib som komparator til entrectinib, se Tabel 1.

Tabel 1. Definerede populationer og komparatorer

Population	Komparator
Patienter med uhelbredelig NSCLC, som er ROS1-positiv og ikke tidligere er behandlet med ROS1-hæmmere	Crizotinib

3.2 Problemstilling

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

Klinisk spørgsmål 1:
Hvilken værdi har entrectinib sammenlignet med crizotinib som førstelinjebehandling af patienter med uhelbredelig ROS1-positiv NSCLC?

4. Vurdering af den sundhedsøkonomiske analyse

Ansøger har indsendt en sundhedsøkonomisk analyse, der estimerer de inkrementelle omkostninger pr. patient for entrectinib sammenlignet med crizotinib. I det nedenstående vil den sundhedsøkonomiske model, som ligger til grund for estimeringen af de inkrementelle omkostninger pr. patient, blive præsenteret.

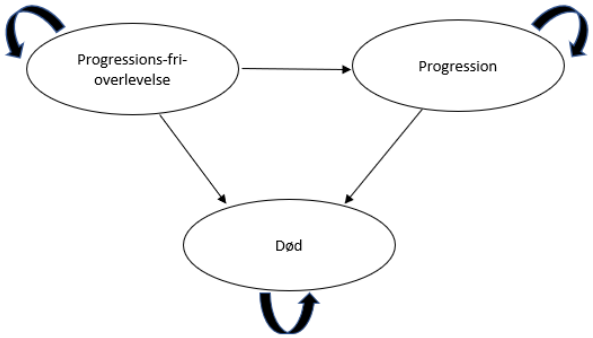
4.1 Antagelser og forudsætninger for model

Den sundhedsøkonomiske model har til formål at estimere de inkrementelle omkostninger ved behandling af patienter med entrectinib af ROS1-positiv ikke-småcellet lungekræft. Data for entrectinib består af et kombineret datasæt af patienter fra single-arm-studierne ALKA-372-001, STARTRK-1 og STARTRK-2 [5,6]. ALKA-372-001 og STARTRK-1 er begge fase I-studier, mens STARTRK-2 er et fase II-studie. Da ingen af disse studier direkte sammenligner entrectinib med crizotinib, udarbejder ansøger en matching adjusted indirect comparison (MAIC) for at belyse den relative effekt af entrectinib sammenlignet med crizotinib udtrykt ved en hazard ratio. Det 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 *unanchored* analyse). Denne analyse kan benyttes til at sammenligne to single-arm-studier, som er datagrundlaget i dette tilfælde. Grundet heterogenitet mellem single-arm-studier skal der i en MAIC-analyse være individuelle patientdata tilgængelige for én, men ikke nødvendigvis begge grupper af patienter, der sammenlignes, så det er muligt at isolere og estimere den relative effekt mellem crizotinib og entrectinib. I denne MAIC-analyse sammenlignes data fra studiet af entrectinib med data fra PROFILE 1001 af crizotinib. Der er individuelle patientdata tilgængelige for entrectinib og ikke crizotinib. Da antallet af patienter med CNS-metastaser ved studiets start ikke var kendt for PROFILE 1001, antages tre forskellige værdier, og resultaterne angives for de tre scenarier. I den sundhedsvidenskabelige vurdering har fagudvalget valgt at benytte en rent narrativ tilgang frem for MAIC-analysens kvantitative estimater.

4.1.1 Modelbeskrivelse

Ansøger har indleveret en *partitioned survival model*, der estimerer omkostninger baseret på den tid, patienten er i de tre stadier: progressionsfri overlevelse (PFS), progression (PD) og død. Patienterne er i PFS-stadiet, indtil de progredierer, hvorefter de er i PD-stadiet, indtil de dør, men der vil også være nogle patienter, der går direkte fra PFS-stadiet til død af naturlige årsager. I løbet af PFS-stadiet bliver patienterne behandlet med enten entrectinib eller crizotinib.

En cyklus i modellen er én uge. Figur 1 viser modellens struktur.



Figur 1. Beskrivelse af modelstrukturen i omkostningsanalysen

Ansøger modellerer tiden i de forskellige stadier ud fra estimerede og ekstrapolerede data baseret på Kaplan-Meier (KM)-data for PFS og OS. KM-data for entrectinib kommer fra et kombineret datasæt fra ALKA-372-001, STARTRK-1 og STARTRK-2. PFS- og OS-kurver for crizotinib er genereret ud fra disse KM-data for entrectinib og en konstant hazard ratio fra den omtalte MAIC-analyse. I MAIC-analysen anvender ansøger et andet datasæt end det, de har præsenteret i den kliniske ansøgning. Datasættet anvendt i den sundhedsøkonomiske analyse består af 161 patienter med 15,8 måneders opfølgning, mens datasættet præsenteret i den klinisk ansøgning består af 94 patienter med 20,3 måneders opfølgning. I modellen er det muligt at anvende den hazard ratio, som er estimeret på datasættet, præsenteret i den kliniske del af ansøgningen, samt øvrige hazard ratios estimeret på varierende datasæt, og hvor *real world data* er anvendt som input for crizotinib.

Tabel 2. Estimerede hazard ratios mellem entrectinib og crizotinib

	HR-værdi PFS	HR-værdi OS	Patientantal [Antal]	Opfølgning [Måneder]
Hazard ratio estimeret, baseret på data præsenteret i den sundhedsøkonomiske ansøgning	[redacted]	[redacted]	[redacted]	[redacted]
Hazard ratio estimeret, baseret på data præsenteret i den kliniske ansøgning	[redacted]	[redacted]	[redacted]	[redacted]

Ansøger har anvendt en [redacted] funktion til at ekstrapolere både PFS og OS for entrectinib. Dette er valgt baseret på det statistiske fit (AIC- og BIC-værdierne), se Figur 2 og Figur 3.

Figur 2. PFS for uhelbredelig ROS1-positiv NSCLC-behandlet med entrectinib

Figur 3. OS for uhelbredelig ROS1-positiv NSCLC behandlet med entrectinib

Crizotinib vil derfor pr. konstruktion også være ekstrapoleret med en [redacted] funktion. I Figur 4 og Figur 5 er de estimerede PFS- og OS-kurver for crizotinib baseret på de to HR-værdier, præsenteret sammen med de ekstrapolerede kurver for entrectinib. Den samlede tid i modellens stadier for entrectinib og crizotinib (estimeret med begge HR-værdier) er præsenteret i Tabel 3.

Figur 4. PFS for uhelbredelig ROS1-positiv NSCLC behandlet med crizotinib

Figur 5. OS for uhelbredelig ROS1-positiv NSCLC behandlet med crizotinib

Tabel 3. Estimeret tid i modellens stadier ved anvendelse af forskellige HR-værdier

	Entrectinib PFS [måneder]	Entrectinib OS [måneder]	Crizotinib PFS [måneder]	Crizotinib OS [måneder]
Hazard ratio estimeret, baseret på data præsenteret i den sundhedsøkonomiske ansøgning	[redacted]	[redacted]	[redacted]	[redacted]
Hazard ratio estimeret, baseret på data præsenteret i den kliniske ansøgning	[redacted]	[redacted]	[redacted]	[redacted]

Sekretariatets vurdering

Fagudvalget har i forbindelse med udarbejdelsen af den kliniske vurdering fundet, at den samlede værdi af entrectinib sammenlignet med crizotinib ikke kan kategoriseres, men på baggrund af det foreliggende datagrundlag og fagudvalgets kliniske erfaring formoder fagudvalget, at der ikke er klinisk relevante forskelle på crizotinib og entrectinib på de undersøgte effektmål. Derfor vælger sekretariatet i hovedanalysen at antage, at den kliniske effekt og bivirkninger er identiske for entrectinib og crizotinib. Sekretariatet vælger dog at præsentere resultaterne baseret på anvendelse af hazard ratios fra MAIC-analysen i en følsomhedsanalyse. I følsomhedsanalyserne præsenteres resultaterne både for ansøgers foretrukne hazard ratio, som er estimeret på baggrund af data med flere patienter og kortere opfølgning end data præsenteret i den kliniske vurdering, og baseret på den hazard ratio, som ansøger har estimeret på baggrund af det datasæt, som bliver præsenteret i den kliniske del af ansøgningen.

Sekretariatet accepterer ansøgers tilgang vedr. ekstrapolering og data, men vælger at præsentere de resultater, som er estimeret ud fra hazard ratios, i to følsomhedsanalyser. I hovedanalysen antager sekretariatet, at effekt og bivirkninger er identiske for entrectinib og crizotinib.

4.1.2 Analyseperspektiv

Ansøgers omkostningsanalyse har et begrænset samfundsperspektiv. Analysen har en tidshorisont på 20 år. Omkostninger, der ligger efter det første år, er diskonteret med en rate på 4 %.

Sekretariatets vurdering

Sekretariatet vurderer, at ansøger har demonstreret, at tidshorisonten er tilstrækkelig lang til at opfange samtlige forskelle i omkostningerne mellem entrectinib og crizotinib.

Sekretariatet accepterer ansøgers valg vedr. perspektiv, tidshorisont og diskontering.

4.2 Omkostninger

I det følgende præsenteres ansøgers antagelser for omkostningerne i den sundhedsøkonomiske analyse af entrectinib sammenlignet med crizotinib. De inkluderede omkostninger i ansøgers analyse er lægemiddelomkostninger, hospitalsomkostninger, bivirkningsomkostninger og patientomkostninger. Ansøgers estimering af lægemiddelomkostninger bygger på AIP, hvilket sekretariatet udskifter med SAIP.

4.2.1 Lægemiddelomkostninger

De anvendte doser er hentet i de respektive produkters produktresuméer (SPC'er), se Tabel 4. Ansøger antager en dosisintensitet på [redacted] baseret på STARTRK-2 for både entrectinib og crizotinib, men da ansøger antager, at entrectinib og crizotinib kun kan administreres i hele tabletter, vil en dosisintensitet på [redacted]. Der er i modellen inkluderet omkostninger til spild, og her antager ansøger, at patienter vil få udleveret én pakke af hhv. entrectinib og crizotinib, og hvis patienten dør, vil resten af pakken gå til spilde. Ansøger antager, at denne spildte pakke udgør et gennemsnit af de to pakningsstørrelser.

Entrectinib: 600 mg én gang dagligt.
Crizotinib: 250 mg to gange om dagen.

De anvendte pakninger og priser er præsenteret i Tabel 4. Den betingede pris anvendes i hovedanalysen, mens der udføres en følsomhedsanalyse, hvor den ikke-betingede pris anvendes.

Tabel 4. Anvendte lægemiddelpriser, SAIP (januar 2021)

Lægemiddel	Styrke	Mg/dosis	Pakningsstørrelse	Pris [DKK]	Betingede pris* [DKK]	Kilde
Entrectinib	200 mg	600 mg	90 stk.	[redacted]	[redacted]	Amgros
Entrectinib	100 mg	600 mg	30 stk.	[redacted]	[redacted]	Amgros
Crizotinib	250 mg	250 mg	60 stk.	[redacted]		Amgros

[redacted]

Sekretariatets vurdering

Fagudvalget vurderer, at der potentielt vil være større spild ved både crizotinib og entrectinib end antaget af ansøger. Det skyldes, at patienterne sandsynligvis vil få udleveret mere end én pakke medicin ad gangen.

[redacted], men størrelsesordenen er svær at kvantificere, da praksis er forskellig fra klinik til klinik. Der er ligeledes usikkerhed omkring, hvilken pakningstørrelse som udleveres ved entrectinib. Ansøger antager, at der udleveres en lille pakning (100 mg og 30 stk.) til patienterne halvdelen af tiden og en stor pakning (200 mg og 90 stk.) til patienterne den anden halvdel af tiden. Den lille pakning indeholder kun medicin til under én uge. Udlevering af den lille pakning vil derfor kræve ugentlig udlevering og forårsage ekstra ressourceomkostninger for entrectinib, som ikke er inkluderet i modellen. Usikkerheden vedr. lægemiddelspild for entrectinib er altså i to dimensioner og udgør både usikkerhed ved pakningsstørrelsen og mængden af udleverede pakninger. For crizotinib er der kun usikkerhed vedr. mængden af udleverede pakker.

[redacted]

Sekretariatet accepterer ansøgers antagelser vedr. lægemiddelomkostninger, [redacted]*, således at alle lægemiddelomkostningerne justeres med den gennemsnitlige dosisintensitet fra* STARTRK-2*.*

[redacted]

4.2.2 Hospitalsomkostninger

Entrectinib og crizotinib administreres begge oralt, og derfor har ansøger kun inkluderet omkostninger til administration af første dosis. Herefter antager ansøger, at patienterne selv kan administrere lægemidlerne. I Tabel 5 er omkostningerne til administration præsenteret.

Tabel 5. Omkostninger til lægemiddeladministration

	Enhedsomkostning [DKK]	Kode	Frekvens	Kilde
Oplæring i administration	1.799	04MA98	Én gang	DRG-takser 2020

Ansøger har inkluderet omkostninger til monitorering og opfølgning. Ansøgers antagelser er præsenteret i Tabel 6.

Tabel 6. Omkostninger til opfølgning og monitorering

	Andel patienter [%]	Månedlig frekvens	Tidsforbrug [min.]	Omkostning pr. time [DKK]	Kilde
PFS – Første cyklus					
Onkolog-besøg	100	1	90	1.316	Medicinrådets værdisætning af enhedsomkostninger
Sygeplejerske-besøg	100	1	90	554	Medicinrådets værdisætning af enhedsomkostninger
Blodprøver	100	1	30	352	Mikrobaseret tilgang
CT-scanning	100	1	60	2.470	DRG 2020: 36PR07
PFS – Efterfølgende cyklus					
Onkolog-besøg	100	0,33	30	1.316	Medicinrådets værdisætning af enhedsomkostninger
Sygeplejerske-besøg	100	0,33	60	554	Medicinrådets værdisætning af enhedsomkostninger
MR-scanning	5	0,33	60	2.470	DRG 2020: 36PR07
CT-scanning	100	0,33	60	2.470	DRG 2020: 36PR07
Efter progression					
Onkolog-besøg	100	0,33	30	1.316	Medicinrådets værdisætning af enhedsomkostninger
Sygeplejerske-besøg	100	0,33	60	554	Medicinrådets værdisætning af enhedsomkostninger
MR-scanning	5	0,33	60	2.470	DRG 2020: 36PR07
CT-scanning	100	0,33	60	2.470	DRG 2020: 36PR07

Ansøger har desuden inkluderet terminalomkostninger. Her anvender ansøger et britisk studie [7] fra 2014, som opgør gennemsnitlige omkostninger for terminal pleje i England for forskellige kræftsygdomme. I studiet er omkostningerne estimeret for patienter med bryst-, kolorektal-, lunge- og prostatakræft. I studiet er omkostningerne opdelt på *health care*, *social care*, *charity care* og *informal care*. Ansøger antager, at terminalomkostningerne for entrectinib udgør et gennemsnit af de fire kræfttyper, men inkluderer kun *health care, social care og charity care* (6.551 GBP). Disse omkostninger er opgivet i 2013-priser i britiske pund, hvilket ansøger omregner til 2020-priser i danske kroner. Dette gøres ved at anvende valutakursen mellem DKK og GBP fra d. 3. september

2020, den relative købekræftsparitet mellem England og Danmark fra 2013 samt nettoprisindekset fra 2013 til 2020.

Sekretariatets vurdering
Fagudvalget vurderer, at man i dansk klinisk praksis ikke vil monitorere patienter efter progression, og vurderer desuden, at der også vil udføres en EKG ved opstart af behandling og hver 3. måned under behandlingen i sekretariatets hovedanalyse. Desuden fremhæver sekretariatet igen, at ansøgers antagelse om, at entrectinib udleveres i en lille pakning (100 mg og 30 stk.) 50 % af tiden og i en stor pakning (200 mg og 90 stk.) de resterende 50 %, vil kræve udlevering af entrectinib ca. hver [redacted]. For crizotinib udleveres en pakning med 250 mg og 60 stk., hvilket vil resultere i udlevering ca. hver [redacted]. Der er dermed forskel i udleveringsfrekvensen, hvilket ikke er inkluderet i modellen, og dermed vil de inkrementelle hospitalsomkostninger være underestimeret, da entrectinib kræver hyppigere udleveringsbesøg. Sekretariatet vælger dog ikke at ændre på denne antagelse, da dette er vanskeligt at kvantificere, men fremhæver usikkerheden.

Sekretariatet vurderer, at estimatet for terminalomkostninger er meget usikkert, da det baseres på et britisk studie, og at ressourceforbruget er anderledes i England end i dansk klinisk praksis. I mangel på bedre estimater accepterer sekretariatet dog denne kilde. Sekretariatet vælger at erstatte ansøgers terminalomkostninger med terminalomkostninger specifikt for patienter med lungekræft (4.974 GBP). Sekretariatet vurderer dog, at ansøger ikke har omregnet det engelske estimat til en dansk kontekst korrekt. Derfor vælger sekretariatet at omregne terminalomkostninger fra GBP til DKK baseret på den gennemsnitlige valutakurs fra 2013 frem for valutakursen fra en specifik dag i 2020 for at undgå udsving i valutakursen.

Sekretariatet accepterer ansøgers tilgang vedr. hospitalsomkostninger. Dog vælger sekretariatet at tilføje omkostninger til EKG ved opstart og derefter hver 3. måned samt at ekskludere omkostninger til monitorering efter progression.
Sekretariatet vælger at anvende terminalomkostningerne specifikt for lungekræft frem for et gennemsnit af fire kræfttyper og vælger desuden at justere valutakursen anvendt til omregning af terminalomkostningerne fra GBP til DKK til den gennemsnitlige valutakurs i 2013.

4.2.3 Bivirkningsomkostninger

Ansøger har inkluderet bivirkningsomkostninger ved behandlingsstart, da det argumenteres, at bivirkninger forekommer oftere ved behandlingsstart, se Tabel 7. Ansøger inkluderer kun omkostninger til bivirkninger af grad 3 eller mere og benytter bivirkningsfrekvenserne fra entrectinib-studierne og bivirkningsfrekvenserne fra PROFILE 1001 for crizotinib.

Ansøger har baseret ressourcerne brugt i forbindelse med de forskellige bivirkninger på 2020 DRG-takster. I forbindelse med ressourceforbruget ved bivirkninger har ansøger antaget, at de lægemidler, der benyttes i forbindelse med bivirkninger, ikke udgør nogen stor omkostning og har derfor valgt at ekskludere dem.

Tabel 7. Rapporterede bivirkningsfrekvenser ved behandling med entrectinib og crizotinib

	Entrectinib [%]	Crizotinib [%]	Omkostning [DKK]	Kilde
Akut nyreinsufficiens	1,2	1,2	43.160	DRG 2020: 11MA01
Forhøjet alanin-aminotransferase	2,5	2,5	1.748	DRG 2020: 3MA98
Ledsmerter	1,9	1,9	1.796	DRG 2020: 08MA17
Forhøjet aspartat-aminotransferase	1,9	1,9	1.748	DRG 2020: 3MA98
Forhøjet creatin phosphokinase	1,2	1,2	2.734	DRG 2020: 23MA03
Forhøjet blodkreatinin	1,2	1,2	4.082	DRG 2020: 01MA06
Kognitiv svækkelse	1,2	1,2	30.628	DRG 2020: 10MA98
Dehydrering	1,2	1,2	1.540	DRG 2020: 06MA11
Diarré	2,5	2,5	5.297	DRG 2020: 05MA98
Forlænget QT	1,2	3,8	1.162	DRG 2020: 10MA98
Hyperglykæmi	2,5	2,5	1.540	DRG 2020: 10MA98
Hyperuricemia	5,6	5,6	4.082	DRG 2020: 05MA08
Hypotension	1,2	1,2	1.847	DRG 2020: 08MA15
Muskelsvaghed	1,2	1,2	1.676	DRG 2020: 08MA15
Myalgi	2,5	2,5	1.676	DRG 2020: 08MA15
Neutropeni	3,1	9,4	20.376	DRG 2020: 16MA98 + 16MA03
Fald i antal neutrofile leukocytter	5,0	15,1	20.376	DRG 2020: 16MA98 + 16MA03
Lungeemboli	11,3	11,3	31.882	DRG 2020: 04MA04
Feber	2,5	2,5	2.711	DRG 2020: 18MA98
Synkope	5,7	5,7	8.544	DRG 2020: 05MA98
Opkast	1,2	5,7	0	Antagelse
Vægtforøgelse	9,3	9,3	0	Antagelse

Sekretariatets vurdering

Som tidligere beskrevet har fagudvalget fundet, at den samlede værdi af entrectinib sammenlignet med crizotinib ikke kan kategoriseres, men på baggrund af det foreliggende datagrundlag og fagudvalgets kliniske erfaring formoder fagudvalget, at der ikke er klinisk relevante forskelle på crizotinib og entrectinib på de undersøgte effektmål. Derfor antager sekretariatet i hovedanalysen, at bivirkningsprofilerne er identisk for

entrectinib og crizotinib. Sekretariatet har præsenteret resultaterne med forskel i bivirkningsprofilerne i en følsomhedsanalyse.

Sekretariatet accepterer ansøgers tilgang vedr. bivirkningsomkostninger, men vælger at præsentere dette i en følsomhedsanalyse. I hovedanalysen vælger sekretariatet at antage, at bivirkningsprofilerne er identisk for entrectinib og crizotinib.

4.2.4 Patientomkostninger

Patientomkostninger er estimeret på baggrund af monitoreringsfrekvensen og inkluderer den effektive tid på hospitalet samt ventetid, se i Tabel 8. Ansøger anvender en patientomkostning på 179 DKK pr. time til at udregne patientomkostningerne. Desuden inkluderer ansøger transportomkostninger til hvert besøg på hospitalet. Ansøger antager, at den gennemsnitlige afstand til hospitalet er 28 km, og anvender en omkostning på 3,52 DKK/km.

Tabel 8. Ansøgers estimat af effektiv patienttid og transport pr. sygdomsstadie

	Andel patienter [%]	Månedlig frekvens	Patienttid [min.]
PFS			
Onkolog-besøg	100	0,33	30
Sygeplejerske-besøg	100	0,33	60
Blodprøver	100	0,33	60
CT-scanning	100	0,33	60
Efter progression			
Onkolog-besøg	100	0,33	30
Sygeplejerske-besøg	100	0,33	60
Blodprøver	100	0,33	60
CT-scanning	100	0,33	60

Sekretariatets vurdering
Som konsekvens af fagudvalgets vurdering i afsnit 4.2.2 vil patientomkostningerne inkludere omkostninger til EKG og ikke inkludere patientomkostninger efter progression i sekretariatets hovedanalyse.

Sekretariatets accepterer ansøgers tilgang vedr. patientomkostninger, men vælger at inkludere patientomkostninger ved EKG samt ekskludere patientomkostninger efter progression.

4.3 Følsomhedsanalyser

Formålet med følsomhedsanalyserne er at undersøge usikkerhederne i analysen. Ansøger har udarbejdet en række følsomhedsanalyser, hvor effekten af variation i forskellige parametre undersøges. Følgende følsomhedsanalyser er udført:

- Ekstrapolering af PFS og OS for entrectinib baseret på en række varierende parametriske funktioner
- Estimering af PFS og OS for crizotinib baseret på række varierende datasæt og metoder
- Varierende tidshorisont
- Antagelse om samme effekt og sikkerhedsprofil mellem crizotinib og entrectinib
- Inkludering af lægemiddelspild.

Sekretariatets vurdering
De præsenterede følsomhedsanalyser beskriver modellens usikkerheder, men sekretariatet vælger kun at præsentere et udsnit af følsomhedsanalyserne. Sekretariatet har desuden, som beskrevet i afsnit 4.1.1, baseret hovedanalysen på en af ansøgers følsomhedsanalyser, hvor det antages, at effekten og bivirkningerne er identiske for entrectinib og crizotinib. Derfor har sekretariatet foretaget to ekstra følsomhedsanalyse, hvor resultaterne er estimeret ud fra de to hazard ratios beskrevet i afsnit 4.1.1.
Desuden vælger sekretariatet at inkludere lægemiddelspild i hovedanalysen, og derfor foretages en følsomhedsanalyse, hvor lægemiddelspild er ekskluderet.
Slutteligt udføres en følsomhedsanalyse af sekretariatets hovedanalyse, hvor den ikke-betingede pris anvendes.

Sekretariatet accepterer ansøgers tilgang vedr. følsomhedsanalyser, men vælger at anvende ansøgers følsomhedsanalyse med antagelse om samme effekt og sikkerhedsprofil for entrectinib og crizotinib som hovedanalyse, og vælger derfor at udføre to ekstra følsomhedsanalyse, hvor de to estimerede hazard ratios mellem entrectinib og crizotinib anvendes. Desuden udføres en følsomhedsanalyse, hvor den ikke-betingede pris anvendes til at udregne sekretariatets hovedanalyse.

4.4 Opsummering af basisantagelser

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

Tabel 9. Basisantagelser for ansøgers og sekretariatets hovedanalyse

Basisantagelser	Ansøger	Sekretariatet
Tidshorisont	20 år	20 år
Diskonteringsrate	4 %	4 %
Inkluderede omkostninger	Lægemiddelomkostninger Administrationsomkostninger Bivirkningsomkostninger Patient- og transportomkostninger	Lægemiddelomkostninger Administrationsomkostninger Bivirkningsomkostninger Patient- og transportomkostninger
Dosering	Entrectinib: 600 mg dagligt Crizotinib: 250 mg to gange dagligt	Entrectinib: 600 mg dagligt Crizotinib: 250 mg to gange dagligt
Behandlingslinje	1. linjebehandling	1. linjebehandling
Behandlingslængder		
Intervention:	[redacted]	[redacted]
Komparator:	[redacted]	[redacted]
Parametriske overlevelses-funktioner for PFS		
Intervention:	[redacted]	[redacted]
Komparator:	PFS-kurven for entrectinib justeret med en hazard ratio	PFS-kurven for entrectinib
Parametriske overlevelses-funktioner for OS		
Intervention:	[redacted]	[redacted]
Komparator:	OS-kurven for entrectinib justeret med en hazard ratio	OS-kurven for entrectinib
Inkludering af spild	Ja	Ja
Andre væsentlige antagelser	Anvendelse af en hazard ratio mellem entrectinib og crizotinib som er estimeret i en MAIC-analyse med 161 patienter og 15,8 måneders opfølgning	Identisk effekt og sikkerhedsprofil for entrectinib og crizotinib

5. Resultater

5.1 Resultatet af sekretariatets hovedanalyse

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

- I den kliniske vurdering er det ikke muligt at vurdere, om der var klinisk betydende forskelle på PFS ved entrectinib og crizotinib, og derfor vurderer fagudvalget og sekretariatet, at det er mest rimeligt at antage, at effekt og sikkerhedsprofil er identiske for entrectinib og crizotinib.
- Ekskludering af monitoreringsomkostninger efter progression.
- Inkludering af omkostninger til EKG ved monitoreringsbesøg.

Den inkrementelle omkostning pr. patient bliver ca. [redacted] DKK over en tidshorisont på 20 år i sekretariatets hovedanalyse. Udføres analysen med AIP, bliver den inkrementelle omkostning pr. patient ca. 238.000 DKK

Resultaterne fra sekretariatets hovedanalyse præsenteres i Tabel 10.

Tabel 10. Resultatet af sekretariatets hovedanalyse ved sammenligning med crizotinib, DKK, diskonterede tal, betingede pris for entrectinib

	Entrectinib [DKK]	Crizotinib [DKK]	Inkrementelle omkostninger [DKK]
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Hospitalsomkostninger	81.685	81.685	0
Bivirkningsomkostninger	7.433	7.433	0
Patientomkostninger	7.447	7.447	0
Totale omkostninger	[redacted]	[redacted]	[redacted]

5.1.1 Resultatet af sekretariatets følsomhedsanalyser

Ved samme antagelser som i sekretariatets hovedanalyse for meromkostninger udfører sekretariatet følsomhedsanalyserne præsenteret i Tabel 11.

Tabel 11. Resultatet af sekretariatets følsomhedsanalyse sammenlignet med hovedanalysen, DKK, betingede pris for entrectinib

Scenarie	Inkrementelle omkostninger
Resultatet af hovedanalysen	[redacted]
Anvendelse af hazard ratio estimeret af ansøger, baseret på datasættet med 94 patienter og opfølgning på 20,3 måneder samt forskelle i bivirkningsprofilerne	[redacted]
Anvendelse af hazard ratio estimeret af ansøger, baseret på datasættet med 161 patienter og opfølgning på 15,8 måneder og anvendt i ansøgers analyse samt forskelle i bivirkningsprofilerne	[redacted]
Tidshorisont på 5 år	[redacted]
Tidshorisont på 17,5 år	[redacted]
Tidshorisont på 30 år	[redacted]
Ekskludering af spild	[redacted]
Resultat af hovedanalysen med den ikke-betingede pris	[redacted]

6. Budgetkonsekvenser

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

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

Budgetkonsekvenserne bliver differencen mellem budgetkonsekvenserne i de to scenarier.

I det tilfælde, hvor entrectinib bliver anbefalet som ligestillet med crizotinib, og det anbefales at benytte det lægemiddel, der er forbundet med færrest omkostninger, så vil de samlede budgetkonsekvenser ved en anbefaling af entrectinib maksimalt være lig med de nuværende omkostninger og budgetkonsekvenser for crizotinib, men sandsynligvis mindre.

6.1 Ansøgers estimat af patientantal og markedsandel

Ansøger antager, at der vil være 10 nye patienter om året, som kandiderer til behandling med entrectinib. Samtidig antager ansøger, at entrectinib, hvis anbefalet, vil opnå et markedsoptag på 100 % allerede fra år 1. Hvis entrectinib derimod ikke anbefales, vil markedsoptaget være 5 % i år 1 og 0 % de efterfølgende år.

Tabel 12 viser ansøgers estimat af patientantallet anvendt i budgetkonsekvenserne.

Tabel 12. Ansøgers estimat af antal nye patienter pr. år

	År 1	År 2	År 3	År 4	År 5
Anbefales					
Entrectinib	10	10	10	10	10
Crizotinib	0	0	0	0	0
Anbefales ikke					
Entrectinib	1	0	0	0	0
Crizotinib	9	10	10	10	10

Sekretariatets vurdering
Fagudvalget vurderer, at entrectinib vil have et markedsoptag på 0 % allerede fra år 1, hvis entrectinib ikke anbefales.

Sekretariatet accepterer ansøgers tilgang vedr. patientantal og markedsoptag, men vælger at justere markedsoptaget til 0 % allerede fra år 1, hvis entrectinib ikke anbefales, i sekretariatets budgetkonsekvensanalyse.

6.2 Sekretariatets budgetkonsekvensanalyse

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

- Markedsoptaget for entrectinib, hvis ikke anbefalet, justeres til 0 % allerede fra år 1.
- Inkludering af terminalomkostninger i budgetkonsekvenserne.

Sekretariatet estimerer, at anvendelse af entrectinib vil resultere i budgetkonsekvenser på ca. [redacted] DKK i år 5. Resultaterne er præsenteret i Tabel 13.

Hvis analysen udføres med AIP, bliver budgetkonsekvenserne ca. 2,4 mio. DKK i år 5.

Tabel 13. Sekretariatets analyse af totale budgetkonsekvenser ved et markedsoptag på 100 %, mio. DKK, ikke-diskonterede tal, betingede pris for entrectinib ved anbefaling

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

6.2.1 Resultat af følsomhedsanalyser for budgetkonsekvensanalysen

Ved samme antagelser som i sekretariatets hovedanalyse for budgetkonsekvenser, men med den ikke-betingede pris for entrectinib bliver budgetkonsekvenserne ca. [redacted] DKK i år 5, se Tabel 14.

Tabel 14. Sekretariatets analyse af totale budgetkonsekvenser med den ikke-betingede pris, mio. DKK, ikke-diskonterede tal, ikke-betingede pris for entrectinib

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

7. Diskussion

Behandling med entrectinib er forbundet med inkrementelle omkostninger sammenlignet med behandling med crizotinib. De inkrementelle omkostninger er udelukkende drevet af lægemiddelomkostningerne for entrectinib.

7.1 Usikkerheder

Der er usikkerhed omkring den relative effekt mellem entrectinib og crizotinib. Fagudvalget har i forbindelse med udarbejdelsen af den kliniske vurdering fundet, at den samlede værdi af entrectinib sammenlignet med crizotinib ikke kan kategoriseres, men på baggrund af det foreliggende datagrundlag og fagudvalgets kliniske erfaring formoder fagudvalget, at der ikke er klinisk relevante forskelle på crizotinib og entrectinib på de undersøgte effektmål. For eksempel er data for overlevelse umodne, og fagudvalget kunne derfor ikke vurdere, om der var forskelle på det kritiske effektmål. På baggrund af dette har sekretariatet antaget, at effekten af entrectinib og crizotinib er identisk.
Ansøger har i sin analyse estimeret de inkrementelle omkostninger baseret på en hazard ratio estimeret i en MAIC-analyse. I denne MAIC-analyse er der anvendt et andet datasæt end det, der er præsenteret i den kliniske del af ansøgningen, hvor patientantallet er større, men med kortere opfølgning. Estimeres de inkrementelle omkostninger ligesom ansøger, [redacted]de inkrementelle omkostninger med ca. [redacted] DKK i forhold til sekretariatets hovedanalyse. Det er dog også muligt at anvende en hazard ratio estimeret, baseret på samme datasæt, som er præsenteret i den kliniske del af ansøgningen, og her [redacted]de inkrementelle omkostninger med ca. [redacted] DKK.
I alle scenarier er omkostningerne afhængige af de ekstrapolerede kurver for entrectinib, og her fremhæver sekretariatet, at der er betydelig usikkerhed, da data ikke er modne.

Slutteligt er der usikkerhed omkring omfanget af lægemiddelspild for både entrectinib og crizotinib, hvor lægemiddelspildet potentielt er større end antaget i modellen. Dette skyldes både usikkerhed vedr. den udleverede pakningsstørrelse, og at patienterne sandsynligvis vil få udleveret mere end én pakke ad gangen.
[redacted] Denne usikkerhed er dog svær at kvantificere og vil variere på tværs af klinikker.

8. Referencer

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9. Bilag

9.1 Resultatet af ansøgers hovedanalyse

I ansøgers hovedanalyse bliver den inkrementelle omkostning pr. patient ca. [redacted] DKK over en tidshorisont på 20 år. Resultaterne fra ansøgers hovedanalyse er præsenteret i Tabel 15.

Tabel 15. Resultatet af ansøgers hovedanalyse, DKK, diskonterede tal, betingede priser

	Entrectinib [DKK]	Crizotinib [DKK]	Inkrementelle omkostninger [DKK]
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Hospitalsomkostninger	132.186	123.483	8.702
Bivirkningsomkostninger	7.433	10.815	-3.382
Patientomkostninger	14.743	13.118	1.625
Totale omkostninger	[redacted]	[redacted]	[redacted]

9.2 Ansøgers budgetkonsekvensanalyse

Ansøger har inkluderet de samme omkostninger i budgetkonsekvensanalysen, som er inkluderet i omkostningsanalysen.
Med de ovenstående antagelser om patientantal og markedsandel estimerer ansøger, at anvendelse af entrectinib vil resultere i budgetkonsekvenser på ca. [redacted] DKK i år 5. Ansøgers estimat af budgetkonsekvenserne fremgår af Tabel 16.

Tabel 16. Ansøgers hovedanalyse for totale budgetkonsekvenser, mio. DKK, ikke-diskonterede tal, betingede pris for entrectinib ved anbefaling

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

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Forhandlingsnotat

Dato for behandling i Medicinrådet	24.03.2021
Leverandør	Roche
Lægemiddel	Entrectinib (Rozlytrek)
Ansøgt indikation	1. Til behandling af NTRK-fusion-positiv kræft 2. Til behandling af uhelbredelig ROS1-positiv ikke-småcellet lungekræft

Forhandlingsresultat

OBS. Følgende forhandlingsnotat indeholder Amgros' resultat og vurdering af forhandling på entrectinib til **begge** indikationer.

Aftale betinget af en anbefaling til begge indikationer:

Roche og Amgros har indgået en aftalen med en rabat, der er betinget af en godkendelse af begge indikationer.

Aftalen løber over en periode på 24 måneder startende d. 25.03.2021 til d. 31.03.2023.

Amgros har opnået følgende pris på entrectinib:

Lægemiddel	Styrke/dosis	Pakningsstørrelse	AIP (DKK)	Forhandlet SAIP (DKK)*	Rabatprocent ift. AIP
Entrectinib	200 mg	90 stk.	48.042,69	[redacted]	[redacted]
Entrectinib	100 mg	30 stk.	8.076,68	[redacted]	[redacted]

Betinget pris af godkendelse til begge indikationer (ROS-1 samt NTRK-fusion gen). Godkendes entrectinib ikke, er AIP-prisen gældende.

[redacted]

Vurdering af forhandlingsresultatet

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

- Den kliniske vurdering af entrectinib "kan ikke kategoriseres" til begge indikationer.

[redacted]

Konklusion

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

[redacted]

Status fra andre lande

Entrectinib og Larotrectinib er på vej gennem processen Nye metoder i Norge[1].

Laroretctinib er blevet godkendt i Sverige til patienter under 18 år. 22.okt 2020[2].

[1] Entrectinib (Rozlytrek) - Indikasjon II (nyemetoder.no)
2. Underlag för beslut om subvention för Vitrakvi (tlv.se)

Til Medicinrådet 03-03-2021

Høringssvar fra Roche Danmark vedrørende vurdering af den kliniske værdi for Rozlytrek (entrectinib) til behandling af patienter med ROS1-positiv NSCLC

Roche takker for Medicinrådets vurdering af entrectinib til behandling af ROS1-positiv ikke-småcellet lungekræft og har ingen yderligere kommentarer til kategoriseringen. Roche ønsker dog at kommentere på enkelte dele i Medicinrådets tilgang i både den kliniske og sundhedsøkonomiske vurdering.

I nedenstående afsnit forholder Roche sig til følgende emner enkeltvis:

- Anvendelsen af indirekte analyser
- Vurderingen af CNS-progression
- Vurderingen af behandlingsophør grundet uønskede hændelser
- Omkostninger for spild og udleveringsbesøg

Anvendelsen af indirekte analyser i Medicinrådets vurdering

Roche har i sin ansøgning til sammenligningen mellem entrectinib og crizotinib anvendt to indirekte analyser:

- En Matching-Adjusted Indirect Comparison (MAIC) som sammenligner data fra den integrerede analyse af entrectinib med data fra det pivotale studie for crizotinib, PROFILE 1001 [1].
- Propensity Score Matching analyse som sammenligner data fra den integrerede analyse af entrectinib med RWE-data på crizotinib-behandlede patienter opsamlet via den amerikanske Flatiron database [2,3].

Disse analyser anvendes for at mindske usikkerhederne i sammenligningen mellem to eller flere single-arm studier, hvor det er nødvendigt at tage højde for forskellene i studiepopulationerne, da disse kan have en indflydelse på resultaterne. Begge analyser tillader at populationernes baseline-karakteristika "matches", hvilket kan bidrage til, at studiernes resultater kan sammenlignes ud fra et mere sammenligneligt grundlag.

I Medicinrådets vurderingsrapport fravælges begge analyser, da det vurderes, at de ikke bidrager med information, som kan ændre konklusionen på fagudvalgets vurdering. Vurderingen baseres i stedet på en narrativ sammenligning mellem den integrerede analyse for entrectinib og 4 forskellige studier på crizotinib i ROS1.

Roche stiller sig uforstående overfor Medicinrådets fravalg af de indirekte analyser, da det generelt må tilstræbes, at Medicinrådets vurderinger foretages ud fra det bedst mulige grundlag. Som nævnt i Medicinrådets vurderingsrapport for entrectinib, står narrative analyser lavere i evidenshierarkiet end både direkte og indirekte analyser [4]. Det fremstår derfor uvist, hvorfor disse analyser ikke kan indgå som en del af vurderingen, enten direkte eller som et supplement til den narrative analyse.

Vurderingen af effektmålet "CNS-progression"
Fagudvalget har i vurderingsrapporten vurderet, at effekten af entrectinib sammenlignet med crizotinib på effektmålet "CNS-progression" ikke kan kategoriseres.

Roche er enig i, at det på baggrund af det tilgængelige datagrundlag for komparatoren ikke er muligt at kategorisere effekten på nuværende tidspunkt. På trods af den manglende mulighed for sammenligning, mener vi, at der for dette vigtige effektmål skal tages følgende i betragtning ud fra et alvorlighedsprincip:

- ROS1-positive patienter har ofte spredning til hjernen [5,6].
- Der er i studierne målt 24,8 måneders median tid til CNS-progression for entrectinib, mens der ikke findes publiceret prospektiv data for crizotinib i ROS1 [2].
- Fagudvalget beskriver selv, at der opleves begrænset effekt af crizotinib på CNS-progression for patienter med ALK-translokationer [4].
- Real-world data viser, at crizotinib til ROS1 patienter giver en estimeret 4,6 måneders median PFS for patienter med CNS-metastaser, hvilket underbygger fagudvalgets erfaring [2,3].

Ud fra et alvorlighedsprincip bør det derfor tages i betragtning i den samlede afgørelse, at entrectinib har vist 24,8 måneders median tid til CNS-progression, selvom forskellen til crizotinib ikke kan kategoriseres jf. Medicinrådets metoder. Det skyldes, at resultatet er vist i en population, som er påvist ofte at have CNS-metastaser.

Vurdering af effektmål "Behandlingsophør grundet uønskede hændelser"
Fagudvalget har i vurderingsrapporten vurderet, at effekten af entrectinib sammenlignet med crizotinib på effektmålet "behandlingsophør grundet uønskede hændelser" ikke kan kategoriseres.

Fagudvalget skriver på s. 15, at sammenligning af entrectinib og crizotinib ikke er mulig fordi behandlingsophøret er rapporteret for den samlede studiepopulation. Senere referer fagudvalget selv til et tidligere datacut for ROS1-populationen (n=134), hvor behandlingsophør grundet uønskede hændelser er rapporteret til 9% (se s. 19) [2,4]. Som supplement kan det oplyses, at behandlingsophør grundet uønskede hændelser for den samlede population på daværende tidspunkt var 8,5%, hvilket er tæt på andelen ved det seneste datacut på 9,1% [2].

Roche mener, som beskrevet i den endelige ansøgning, de 18%, som er rapporteret for den største studiepopulation for crizotinib (n=1722) [7] bør tages i betragtning i den samlede vurdering af de to lægemidler. Selvom denne population inkluderer både ALK-positive og ROS1-positive patienter, mener vi ikke, at der er grund til at formode, at der skulle være en betydningsfuld forskel på behandlingsophøret mellem disse to grupper i behandling med crizotinib. Desuden er denne population den største, der er rapporteret fra crizotinib.

Omkostning for spild og udleveringsbesøg ved behandling med entrectinib
I den sundhedsøkonomiske afrapportering angives en usikkerhed omkring spild på grund af de to pakningsstørrelser, samt hvor mange pakninger patienter får udleveret på hospitalet. Det påpeges også,

at entrectinib potentielt kan medføre flere hospitalsbesøg for patienten, grundet brugen af mindre pakker, hvilket kan kræve hyppigere udlevering. Usikkerhederne beskrives som en bekymring, der relaterer sig til entrectinib og ikke komparatoren, crizotinib.

I Rozlytrek SmPC er 600 mg entrectinib, én gang dagligt til voksne eller følgende dosering til pædiatriske patienter godkendt [8].

Kropsoverfladeareal	Dosis én gang dagligt
1,11 m^2 til 1,50 m^2	400 mg
≥ 1,51m^2	600 mg

I Roches sundhedsøkonomiske analyse antages det, at patienterne vil blive fordelt ligeligt mellem de to grupper, hvilket er en pragmatisk tilgang til at tage højde for spild.
I praksis er den lille pakningsstørrelse primært tiltænkt patienter med en overfladevolumen under 1,51 m^2, men begge grupper vil med fordel kunne benytte den større pakning indeholdende 90 kapsler med 200 mg, som vil passe til hhv. 45 og 30 dages behandling. Derved skal patienterne kun møde op med én til halvanden måneds mellemrum.

I praksis forventes det, at de fleste patienter vil modtage den større pakningsstørrelse, men i lighed med mange andre orale behandlinger, vil det være op til den enkelte afdeling, hvor meget der udleveres til patienten. I nogle afdelinger er det f.eks. praksis kun at give en enkelt blisterpakning med hjem af gangen. Det forventes dermed ikke, at der med de to pakningsstørrelser skulle være større eller anderledes spild ved entrectinib, end hvad der ses ved andre targeterede behandlinger såsom crizotinib.

Flere pakningsstørrelser giver desuden en ekstra fleksibilitet i forhold til udlevering af medicinen. Frekvensen for udlevering vil være op til den enkelte afdeling på baggrund af en vurdering af, hvad der er mest praktisk for patienten og personalet. Der er derfor ikke umiddelbart grund til at tro, at patienterne skal hyppigere ind til udlevering af deres behandling, og at der således kan forekomme ekstra hospitalsbesøg.

Muligheden for at anvende flere pakningsstørrelser burde således udelukkende bidrage til øget fleksibilitet på afdelingerne og ikke være årsag til øget spild eller flere hospitalsbesøg.

Med venlig hilsen

Niels Juul Brogaard
Strategic Market Access Partner
Roche a/s

Andreas Fanø
Scientific Partner
Roche a/s

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Medicinrådet

Medicinrådets vurdering vedrørende entrectinib til behandling af uhelbredelig ROS1-positiv ikke-småcellet lungekræft

Version 1.0

Om Medicinrådet

Medicinrådet er et uafhængigt råd etableret af Danske Regioner.

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

Om vurderingsrapporten

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

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

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

Dokumentoplysninger	
Godkendelsesdato	24. februar 2021
Dokumentnummer	103318
Versionsnummer	1.0

Indholdsfortegnelse

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

1. Medicinrådets konklusion

Medicinrådet finder, at data ikke er tilstrækkelige til at den samlede værdi af entrectinib kan kategoriseres sammenlignet med crizotinib til ROS1-positiv ikke-småcellet lungekræft. Vurderingen er baseret på en narrativ sammenligning af mindre single-arm-studier. For overlevelse er observationstiden for kort til at vurdere om der er forskelle. For sygdomsprogression i centralnervesystemet og livskvalitet er data for mangelfulde til at gennemføre en sammenligning. Progressionsfri overlevelse fremgår af alle studier, men på grund af forskelle i opfølgningstid og patientpopulationer, er det ikke muligt at drage konklusioner om en eventuel klinisk relevant forskel mellem entrectinib og crizotinib.

Medicinrådet vurderer, at sikkerhedsprofilerne for de to lægemidler er forskellige, men at det eksisterende datagrundlag og den foreliggende kliniske erfaring ikke tillader en vurdering af, om den ene bivirkningsprofil er mere fordelagtig for patienterne end den anden.

MEDICINRÅDET KATEGORISERER LÆGEMIDLERS VÆRDI I EN AF FØLGENDE KATEGORIER:

- **Stor merværdi:** Der er påvist en stor forbedring i effektforhold i forhold til gældende standardbehandling, eksempelvis markant forbedret overlevelse, markant reduktion i forekomsten af alvorlige symptomer og/eller alvorlige bivirkninger.
- **Moderat merværdi:** Der er påvist en moderat forbedring i forhold til gældende standardbehandling, eksempelvis moderat forbedret overlevelse, moderat reduktion i forekomsten af symptomer og/eller bivirkninger.
- **Lille merværdi:** Der er påvist en lille forbedring i forhold til gældende standardbehandling, eksempelvis en dokumenteret forbedret overlevelse, en reduktion i forekomsten af symptomer og/eller bivirkninger.
- **Merværdi af ukendt størrelse:** Der er påvist en forbedring i forhold til gældende standardbehandling, men størrelsen af forbedring kan ikke bestemmes. Lægemidlets merværdi er som minimum lille, men kunne også være moderat eller stor.
- **Ingen dokumenteret merværdi:** Der er ikke påvist en merværdi i forhold til gældende standardbehandling. Omvendt tyder den tilgængelige evidens heller ikke på, at der er en negativ værdi.
- **Negativ værdi:** Der er påvist en negativ værdi i forhold til gældende standardbehandling.

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

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

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

2. Begreber og forkortelser

ALK:	*Anaplastic Lymphoma Kinase*
CI:	Konfidensinterval
CNS:	Centralnervesystem *(Central nerveous system)*
EGFR:	*Epidermal Growth Factor Receptor*
EMA:	Det Europæiske Lægemiddelagentur (*European Medicines Agency)*
EORTC-QLQ-C30:	*European Organisation for Research and Treatment of Cancer Quality-of-life Questionnaire-Core 30*
EPAR:	*European Public Assessment Report*
FISH:	*Fluorescence in situ hybridization*
GRADE:	System til at vurdere evidens (*Grading of Recommendations, Assessment, Development and Evaluation*)
HR:	*Hazard ratio*
ITT:	*Intention-to-treat*
MKRF:	Mindste klinisk relevante forskel
NSCLC:	Ikke-småcellet lungekræft (*Non-Small-Cell Lung Cancer*)
NTRK:	*Neurotrophin receptor tyrosin kinase*
OR:	*Odds ratio*
ORR:	Objektiv responsrate (*Overall response rate*)
OS:	Samlet overlevelse (*Overall survival*)
PFS:	Progressionsfri overlevelse (*Progression Free Survival*)
PICO:	Population, intervention, komparator og effektmål (*Population, Intervention, Comparator and Outcome)*
PP:	*Per Protocol*
PS:	Performancestatus
RCT:	Randomiseret kontrolleret studie *(Randomised Controlled Trial)*
RECIST:	*Response Evaluation Criteria In Solid Tumors*
ROS1:	*ROS proto-oncogene 1 receptor tyrosine kinase*

RWD:	Real World Data
RR:	Relativ risiko
SMD:	*Standardized Mean Difference*
TKI:	Tyrosin kinase inhibitor
TNM:	System til at klassificere tumorer (*Tumor, Node, Metastasis)*

3. Introduktion

Formålet med Medicinrådets vurdering af entrectinib til uhelbredelig ROS1-positiv ikke-småcellet lungekræft er at vurdere den værdi, lægemidlet har sammenlignet med dansk standardbehandling.

Vurderingen er udarbejdet, fordi Medicinrådet har modtaget en endelig ansøgning fra Roche. Medicinrådet modtog ansøgningen den 9. september 2020.

Det kliniske spørgsmål er:

Hvilken værdi har entrectinib sammenlignet med crizotinib som førstelinjebehandling af patienter med uhelbredelig ROS1-positiv ikke-småcellet lungekræft?

3.1 Ikke-småcellet lungekræft

Omtrent 4.600 danskere diagnosticeres årligt med lungekræft, og dermed er lungekræft en af de hyppigst forekommende kræftsygdomme i Danmark [1,2]. Af de diagnosticerede har ca. 85-90 % ikke-småcellet lungekræft (NSCLC) [3]. Ikke-småcellet lungekræft inddeles i planocellulære og ikke-planocellulære tumorer. Fagudvalget estimerer, at ca. 25 % af patienterne har planocellulære tumorer, og ca. 75 % har ikke-planocellulære tumorer. Langt de fleste ikke-planocellulære tumorer er såkaldte adenokarcinomer. Symptomer på lungekræft kan være hoste, åndenød og smerter i brystkassen. Hvis kræften spreder sig til andre organer (fx andre strukturer i brystkassen, knogler eller hjerne), kan patienterne få symptomer fra disse i form af kvalme, opkast, smerter, forvirring og kognitive problemer.
Lungekræft er inddelt i stadier afhængigt af udbredelsesgrad, jf. International Association for the Study of Lung Cancer's (IASLC) Tumor, Node, Metastasis (TNM)-klassifikation for lungekræft. De epidemiologiske data er relateret til TNM-version 7[4], mens man i dansk klinisk praksis i dag anvender version 8 [5]. I henhold til version 7 har patienter med spredning til lymfeknuder svarende til N3-sygdom i stadium IIIB, mens stadium IV betegner metastatisk sygdom. Disse stadier betragtes som udgangspunkt som uhelbredelig NSCLC.
I slutningen af 2016 levede knap 11.151 personer med lungekræft, mens ca. 3.700 personer årligt dør af lungekræft [2]. Den seneste årsrapport fra Dansk Lunge Cancer Register viser, at 1-årsoverlevelsesraten for patienter med lungekræft udredt i 2017 uanset stadie var 51,4 %, mens 5-årsoverlevelsen for patienter udredt i 2013 var 15,9 % [6]. Der er altså tale om en sygdom med en dårlig prognose og kort overlevelse efter diagnosetidspunkt for størstedelen af patienterne.
Behandlingsmålet for patienter med uhelbredelig NSCLC er symptomlindring og livsforlængelse. Patienter med uhelbredelig NSCLC kan få forskellige typer behandling afhængig af tumorkarakteristika. Hvis en undersøgelse viser mutationer, som en behandling kan målrettes mod, vil en såkaldt targeteret behandling være første valg. I dansk klinisk praksis drejer det sig på nuværende tidspunkt om aktiverende epidermal growth factor receptor (EGFR)-mutationer og anaplastisk lymfom kinase (ALK)-

translokationer [7]. Targeteret behandling er aktuelt kun relevant for patienter med uhelbredelig NSCLC og ikke for patienter med NSCLC i tidligere stadier.
En tredje genetisk ændring, som er fundet hos nogle patienter med lungekræft, er translokationer, som involverer genet ROS proto-onkogene 1 receptor tyrosin kinase (ROS1). Hvis en tumor har en kromosomal translokation, som involverer ROS1 (ROS1-rearrangement), kaldes den ROS1-positiv. Den terminologi bruger vi i vurdering af entrectinib. ROS1-rearrangementer giver ophav til fusionproteiner, som aktiverer signaleringskaskader involveret i udvikling og spredning af kræft. ROS1-rearrangementer er sjældne i lungekræft og ses i omkring 0,9-2 % af alle undersøgte tilfælde af NSCLC [8]. Patienter med ROS1-rearrangement ligner patienter med ALK-translokation ved at være yngre end gennemsnitlige patienter med lungekræft, og der er flere ikke-rygere. Med de targeterede behandlinger forventes ROS1-positive patienter ligesom patienter med ALK-translokation eller aktiverende EGFR-mutation at have en bedre prognose end patienter uden mutationer.
Rearrangementer i ROS1-genet kan detekteres ved hjælp af forskellige teknikker, enten *fluorescence in situ hybridization* (FISH), immunhistokemi eller gensekventering. I de danske regioner benyttes forskellige teknikker, men opgørelser for test for ROS1-rearrangement indgår endnu ikke i Dansk Lunge Cancer Gruppes årsrapporter. Det gør estimatet af antal patienter usikkert og betyder, at man ikke kan kontrollere, om test for ROS1-rearrangement er fuldt implementeret. Fagudvalget understreger, at alle patienter med ikke-planocellulær NSCLC i Danmark bør testes for ROS1-rearrangement. Undersøgelsen er en forudsætning for, at relevante patienter kan tilbydes targeteret behandling.
Medicinrådet har endnu ikke anbefalet nye lægemidler til ROS1-positive patienter, og indikationen indgik ikke i Medicinrådets behandlingsvejledning for førstelinjebehandling af uhelbredelig NSCLC [7].
Fagudvalget vurderer, at antallet af ROS1-positive patienter med uhelbredelig NSCLC i Danmark er ca. 10 om året. Dette tal er ikke fremkommet gennem udregninger, men er fagudvalgets bedste skøn ud fra det antal ROS1-positive patienter, de har mødt i dansk klinisk praksis.

3.2 Entrectinib

Entrectinib er en tyrosin kinase hæmmer (TKI), der virker gennem hæmning af neurotrophin receptor tyrosin kinaser (NTRK), ALK og ROS1. Molekylerne ALK og ROS1 spiller en afgørende rolle for cellevækst og differentiering. Ved at hæmme ROS1 reduceres aktiviteten af de signaleringskaskader, der har betydning for cellernes overlevelse og proliferation [9]. På den måde mindsker entrectinib tumors vækst og spredning.
Entrectinib har følgende indikation til NSCLC hos *European Medicines Agency* (EMA): *Entrectinib* er som enkeltstofbehandling *indiceret til behandling af voksne patienter med ROS1-positiv, fremskreden ikke-småcellet lungecancer (NSCLC), der ikke tidligere er behandlet med ROS1-hæmmere.*
Der er desuden givet markedsføringstilladelse til en tumoragnostisk indikation, nemlig 'sidstelinjebehandling' af patienter med solide tumorer med NTRK-fusion.

Denne indikation behandles sideløbende i Medicinrådet af fagudvalget vedr. tværgående kræftlægemidler.
Entrectinib administreres oralt. Standarddosis er 600 mg én gang dagligt. Entrectinib findes som kapsler på 100 og 200 mg. Behandlingen gives indtil sygdomsprogression eller intolerable bivirkninger.
Entrectinib fik betinget markedsføringstilladelse af Europa-Kommissionen d. 31. juli 2020. Ansøger er forpligtet til at indlevere data fra et randomiseret studie af patienter med CNS-metastaser senest i 2027.

3.3 Nuværende behandling

For patienter med uhelbredelig NSCLC med en genetisk ændring, hvortil der er en målrettet (targeteret) behandling, vil den targeterede behandling være førstevalg for hovedparten af patienterne i nuværende dansk klinisk praksis. Medicinrådets behandlingsvejledning for førstelinjebehandling af uhelbredelig NSCLC beskriver behandlingen af patienter med ALK-translokation og aktiverende EGFR-mutation [7]. Hverken Medicinrådet eller RADS har taget stilling til en targeteret standardbehandling i Danmark for patienter med uhelbredelig ROS1-positiv NSCLC. I Medicinrådets behandlingsvejledning for førstelinjebehandling af uhelbredelig NSCLC har fagudvalget anført, at "For patienter, som aldrig har røget, kan sjældnere markører (eksempelvis ROS proto-onkogen 1) i nogle tilfælde selektere patienter til targeteret behandling med en tyrosinkinasehæmmer." I nuværende dansk klinisk praksis er behandling af patienter med uhelbredelig NSCLC, som er ROS1-positive, dermed baseret på en individuel klinisk vurdering.
Nogle TKI'er med effekt på ALK-translokationer kan også have effekt på ROS1-positive tumorer. ALK-TKI'en crizotinib har som det hidtil eneste lægemiddel EMA-indikation til uhelbredelig ROS1-positiv NSCLC. Fagudvalget vurderer, at størstedelen af patienter, der er diagnosticeret som ROS1-positive i dansk klinisk praksis, behandles med crizotinib. Derfor kan crizotinib betragtes som dansk standardbehandling og blev valgt som komparator i protokollen.

4. Metode

Medicinrådets protokol for vurdering vedrørende entrectinib til uhelbredelig ROS1-positiv ikke-småcellet lungekræft [10] beskriver sammen med *Håndbog for Medicinrådets proces og metode vedr. nye lægemidler og indikationsudvidelser*, hvordan Medicinrådet vil vurdere lægemidlets værdi for patienterne.

5. Resultater

5.1 Klinisk spørgsmål 1

5.1.1 Litteratur

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

Ansøger har søgt litteratur med søgestrengen fra protokollen og har udvalgt syv fuldtekstartikler og et abstract. Heraf beskriver én artikel tre fase 1-2-studier af entrectinib, fem artikler beskriver fem single-arm kliniske studier af crizotinib, og én artikel og et abstract beskriver sammenlignende analyser af entrectinib og crizotinib.

Fagudvalget vælger at se bort fra abstractet, der indeholder en sammenlignende analyse af kliniske data for entrectinib og real world data (RWD) for crizotinib, da det ikke bidrager yderligere til evidensen fra de inkluderede artikler.
Desuden har fagudvalget valgt at se bort fra et crizotinib-studie [11] (OX-ONC-studiet), der udelukkende inkluderede østasiatiske patienter. Fagudvalget vurderer, at patientpopulationen kunne adskille sig fra en dansk patientpopulation, og studiet bidrager ikke med yderligere information end de inkluderede artikler.

Tabel 1 viser de kliniske studier, der indgår i Medicinrådets vurdering af entrectinib til ROS1-positiv ikke-småcellet lungekræft.

Tabel 1. Oversigt over studier

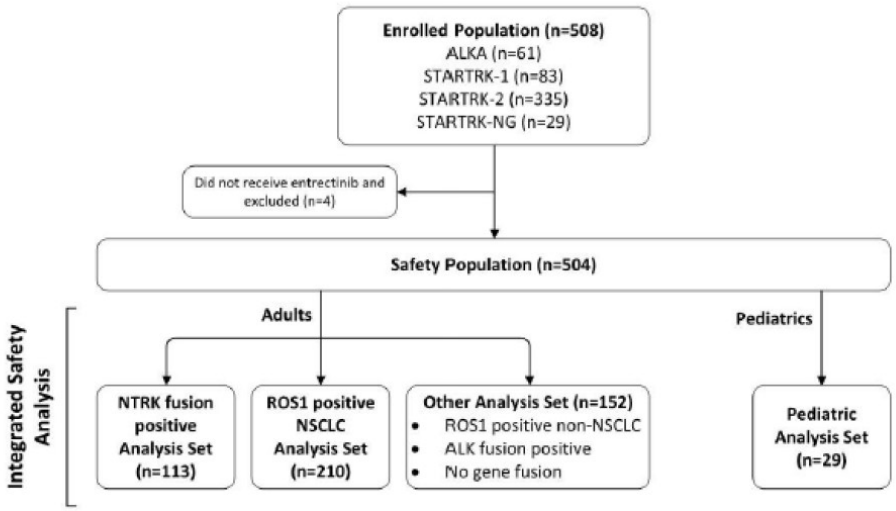
Reference	Titel	Studiedesign	Intervention	Indgår direkte i datagrundlag for denne vurdering
Drilon et al. [12]	Entrectinib in ROS1 fusion-positive non-small-cell lung cancer: integrated analysis of three phase 1-2 trials	Integreret analyse af tre fase 1-2-studier med forskellige patientpopulationer (basket trial)	Entrectinib	Ja, for alle effektmål
Profile 1001 [13]	Crizotinib in ROS1-rearranged advanced non-small-cell lung cancer (NSCLC): updated results, including overall survival, from PROFILE 1001	Single-arm-studie	Crizotinib	Ja, for alle effektmål undtagen CNS-progression og uønskede hændelser grad 3-4

Reference	Titel	Studiedesign	Intervention	Indgår direkte i datagrundlag for denne vurdering
AcSé trial [14]	Crizotinib in c-MET or ROS1-positive NSCLC: results of the AcSé phase II trial;	Single-arm-studie	Crizotinib	Ja, for alle effektmål undtagen CNS-progression og uønskede hændelser grad 3-4
EUCROSS [15]	Safety and Efficacy of Crizotinib in patients With Advanced or Metastatic ROS1-Rearranged Lung Cancer (EUCROSS): A European Phase II Clinical Trial;	Single-arm-studie	Crizotinib	Ja, for PFS og behandlingsophør grundet uønskede hændelser
METROS [16]	Crizotinib in MET-Deregulated or ROS1-Rearranged Pretreated Non-Small Cell Lung Cancer (METROS): A Phase II, Prospective, Multicenter, Two-Arms Trial;	Single-arm-studie	Crizotinib	Ja, for PFS og behandlingsophør grundet uønskede hændelser

De inkluderede studier beskrives nedenfor, og tabel 2 viser en oversigt over studiekarakteristika.

Entrectinib:

Entrectinib er undersøgt til forskellige indikationer i de fire kliniske studier ALKA, STARTRK-1, STARTRK-2 og STARTRK-NG. Ansøger har indleveret en integreret analyse af de fire studier, der sammen udgør en såkaldt ”basket trial”. Designet ses på figur 1 nedenfor (fra ansøgers endelige ansøgning).



ALK; anaplastic lymphoma kinase; NSCLC; non-small cell lung cancer; NTRK; Neurotrophic tyrosine receptor kinase; ROS1; ROS proto-oncogene 1 receptor tyrosine kinase.

Figur 1. Entrectinibs studiedesign (fra ansøgers endelige ansøgning). Tallene for ROS1-positive patienter stemmer ikke overens med analysernes tal (der indgår færre patienter i de datasæt, som indgår).

Den integrerede analyse udgør datagrundlaget for ROS1-positive NSCLC-patienter og er at betragte som et single-arm-studie. I den publicerede artikel for entrectinib indgår 53 ROS1-positive NSCLC-patienter [12]. I EMAs EPAR indgår et større datasæt med 94 ROS1-positive NSCLC-patienter fra 2017 (median opfølgning 20,3 måneder), der senere blev udvidet til at rumme 161 patienter (median opfølgning 15,8 måneder) [17]. Fagudvalget har bedt om data med længst mulig opfølgningstid, men da ansøger i sin endelige ansøgning har rapporteret data fra begge sæt, vil fagudvalget for hvert enkelt effektmål benytte det mest relevante (eksempelvis den største patientpopulation for ORR og længst opfølgningstid for OS). Fagudvalget benytter ikke data fra den publicerede artikel [12] i sin vurdering, men udelukkende fra EMAs EPAR, da der her er data med længst opfølgningstid.
Det primære endepunkt i entrectinibs kliniske studieprogram var objektiv responsrate (ORR), mens sekundære endepunkter, som er relevante for Medicinrådets vurdering, var PFS, OS, intrakranielt respons og uønskede hændelser.

For sikkerhedseffektmål er der i ansøgers endelige ansøgning taget udgangspunkt i den samlede studiepopulation på 504 patienter eller den samlede ROS1-positive NSCLC-population på 210 patienter (se figur 1). I den samlede patientpopulation indgår også pædiatriske patienter og patienter med andre typer kræft end lungekræft.

Crizotinib:
Profile 1000 1er et single-arm-studie af crizotinib, som inkluderede 53 patienter med ROS1-positiv NSCLC [13]. I en artikel publiceret i 2019 er der en median opfølgningstid på 62,6 måneder [13]. I artiklen er ORR, OS, PFS og uønskede hændelser beskrevet.

AcSé er et single-arm-studie af crizotinib, som inkluderede 37 patienter med ROS1-positiv NSCLC [14], og en artikel blev publiceret i 2019 [14]. Det primære endepunkt var ORR, og sekundære endepunkter relevante for Medicinrådets vurdering var PFS og OS.

EUCROSS er et single-arm-studie af crizotinib, som inkluderede 34 patienter med ROS1-positiv NSCLC, men kun 30 indgik i analyse af effekt [15]. I en artikel publiceret i 2019 er der data med en median opfølgningstid på 20,6 måneder [15]. Studiets primære endepunkt var ORR, og sekundære endepunkter relevante for Medicinrådets vurdering var PFS, OS, sikkerhed og livskvalitet.

METROS er et single-arm-studie af crizotinib, som inkluderede 26 patienter med ROS1-positiv NSCLC [16]. Et af inklusionskriterierne i studiet var, at patienterne havde fået mindst en kemoterapilinje. I en artikel publiceret i 2019 var der data med en median opfølgningstid på 21 måneder [16]. Det primære endepunkt i studiet var ORR, og sekundære endepunkter relevante for Medicinrådets vurdering var PFS, OS og sikkerhed.

Tabel 2. Studiekarakteristika

	Integreret analyse	Profile 1001	AcSé	EUCROSS	METROS
Studiedesign	Del af basket trial, kan opfattes som single-arm-studie af entrectinib	Single-arm-studie	Single-arm-studie	Single-arm-studie	Single-arm-studie
Data	I EMAs EPAR er der data for 161 patienter med 15,8 måneders opfølgning og 94 patienter med 20,3 måneders opfølgning	I en artikel fra 2019 er der data for 53 patienter med 62,6 måneders opfølgning	I en artikel fra 2019 er der data for 37 patienter	I en artikel fra 2019 er der data for 30 patienter med 20,6 måneders opfølgning	I en artikel fra 2019 er der data for 26 patienter med 21 måneders opfølgning
Lægemiddel	Entrectinib	Crizotinib	Crizotinib	Crizotinib	Crizotinib

Af tabel 3 fremgår baselinekarakteristika for patienter i de inkluderede studier, som er anvendt til at besvare det kliniske spørgsmål.

Tabel 3. Baselinekarakteristika

Studie	Behandling	N	Median-alder (range)	Kvinder n (%)	Antal patienter i PS2 (%)	Antal patienter med CNS-metastaser (%)	Antal patienter, som ikke tidligere har fået systemisk behandling (%)
Integreret analyse	Entrectinib	94 161	53 (33-86) 54 (20-86)	60 (63,8) 104 (64,5)	11 (11.7) 16 (9,9)	40 (42,6) 53 (32,9)	34 (36,2) 60 (37)
PROFILE 1001	Crizotinib	53	55 (25-81)	30 (57)	1 (2)	Ikke tilgængeligt	7 (13)
AcSé	Crizotinib	37	62 (33-81)	26 (70,3)	9 (24,3)	23 (18,1)	Ikke tilgængeligt
EUCROSS	Crizotinib	30	56 (33-84)	19 (56)	2 (6)	8 (21)	7 (21)
METROS	Crizotinib	26	68 (28-62)	16 (62)	1 (4)	6 (23)	0

PS: Performance status, CNS: Centralnervesystem.

Studiernes sammenlignelighed på tværs og i forhold til tilsvarende dansk population

Fagudvalget vurderer, at det generelt er vanskeligt at sammenligne resultater fra single-arm-studier med forskellig opfølgningstid og forskellige patientpopulationer. Fagudvalget bemærker, at der er flere patienter i studiet af entrectinib, som ikke tidligere har fået systemiske behandlinger, hvilket kan medføre, at effekten af entrectinib overestimeres i forhold til effekten af komparator. I studiet af entrectinib var antallet af patienter med centralnervesystem (CNS)-metastaser ved studiets begyndelse angivet. Dette var ikke tilfældet i det største studie af crizotinib (PROFILE 1001), men i de andre studier af crizotinib var der færre patienter med CNS-metastaser end i studiet af entrectinib. Dette kan medføre, at effekten af crizotinib overestimeres, da patienter med CNS-metastaser har en dårligere prognose. Desuden vanskeliggør det vurderingen af effektmålet "CNS-progression".

Fagudvalget gør opmærksom på, at ROS1-mutationer er sjældne, og at man ikke kan forvente store studier med ensartede populationer eller direkte sammenligninger. Baseret på fagudvalgets begrænsede kliniske erfaring med ROS1-positive patienter har fagudvalget ikke anledning til at tro, at studiepopulationerne er væsentlig forskellige fra de danske ROS1-positive patienter.

5.1.2 Databehandling og analyse

Vurderingen er baseret på en narrativ analyse. Medicinrådet understreger, at en narrativ analyse er lavere i evidenshierarkiet end en direkte eller indirekte analyse.
I den endelige ansøgning er medtaget en publiceret matching adjusted indirect comparison (MAIC)-analyse [18]. Det 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 *unanchored* analyse). Denne analyse kan benyttes til at sammenligne to single-arm-studier, som er datagrundlaget i dette tilfælde. Grundet heterogenitet mellem single-arm-studier skal der i en MAIC-analyse være individuelle patientdata tilgængelige for én, men ikke nødvendigvis begge grupper af patienter, der sammenlignes, så det er muligt at isolere og estimere den relative effekt mellem crizotinib og entrectinib. I den publicerede MAIC-analyse sammenlignes data fra studiet af entrectinib med data fra PROFILE 1001 af crizotinib. Der er individuelle patientdata tilgængelige for entrectinib og ikke crizotinib. Da antallet af patienter med CNS-metastaser ved studiets start ikke var kendt for PROFILE 1001, antages tre forskellige værdier, og resultaterne angives for de tre scenarier. Datagrundlaget for MAIC-analysen er altså mindre end datagrundlaget for den narrative analyse, da der kun indgår ét studie for crizotinib i MAIC-analysen sammenlignet med fire crizotinib-studier i den narrative analyse. Fagudvalget vurderer, at MAIC-analysen har et mindre datagrundlag og ikke bidrager med information, som kan ændre konklusionen baseret på den narrative analyse. Medicinrådet understreger desuden, at i sådan en MAIC-analyse er det væsentligt at kunne vurdere, om der er taget højde for alle prognostiske og effektmodificerende faktorer (faktorer, der påvirker effektestimaterne), når der matches, da der ellers kan indføres bias i resultaterne.
På baggrund af ovenstående er MAIC-analysens resultater ikke angivet for de enkelte effektmål i den sundhedsvidenskabelige vurdering. MAIC-analysens resultater benyttes i den sundhedsøkonomiske model, hvor kvantitative input er nødvendige, men er naturligvis forbundet med væsentlig usikkerhed.

Vurdering af datagrundlag

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

Fagudvalget har følgende bemærkninger til datagrundlaget, der vanskeliggør sammenligning af data:

- Datagrundlaget består af en række mindre single-arm-studier med forskellig opfølgningstid og forskelle i patientpopulationer.
- For studiet af entrectinib og flere af studierne af crizotinib er data ikke modne til at vurdere det kritiske effektmål OS.
- For det kritiske effektmål *behandlingsophør grundet uønskede hændelser* er data for entrectinib rapporteret for den samlede studiepopulation, der også inkluderer patienter med andre kræftsygdomme end ikke-småcellet lungekræft.
- Generelt er der stor usikkerhed på effektmål relateret til sikkerhed, da rapporteringen af uønskede hændelser og behandlingsophør varierer mellem studierne, og opfølgningstiden er forskellig.
- For effektmålet *CNS-progression* er der kun sparsom information om antal patienter med CNS-metastaser ved studiernes begyndelse for studierne af crizotinib.
- For effektmålet *livskvalitet* er der kun rapporteret sparsomme data for mindre patientgrupper behandlet med entrectinib og crizotinib.

5.1.3 Evidensens kvalitet

Der er tale om en narrativ analyse uden kvantitative sammenligninger på baggrund af ukontrollerede studier. Der findes ikke velvaliderede værktøjer til at vurdere evidensens kvalitet for non-komparative studier. Der er derfor hverken udarbejdet en Risk of Bias-profil eller en GRADE-profil.

Risk of Bias
Hverken Cochranes RoB 2.0-værktøj eller deres tilsvarende værktøj for non-randomiserede studier (ROBINS-I) er egnede til at vurdere risk of bias for studier med non-komparative design.

GRADE
Da alle studier er non-komparative, har det hverken været muligt at lave direkte eller indirekte sammenligninger, og der er ingen komparative, relative effektestimater at basere vurderingerne på.

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

5.1.4 Effektestimater og kategorier

Datagrundlaget tillader ikke, at effekten af entrectinib kan kategoriseres efter Medicinrådets metoder. Derfor sammenligner Medicinrådet entrectinib og crizotinib i en narrativ analyse. Nedenfor ses effektestimater, som indgår i den narrative analyse.

Tabel 4. Resultater for klinisk spørgsmål 1

Effektmål	Målenhed (MKRF)	Vigtighed	Entrectinib	Crizotinib	Aggregeret værdi for effektmålet
Overlevelse	Median overlevelse (MKRF: 3 mdr.)	Kritisk	Ingen modne data	Data af varierende modenhed – 17,2 - 51,4 måneder	Kan ikke kategoriseres
Behandlingsophør grundet uønskede hændelser	Andel patienter, der ophører behandlingen pga. uønskede hændelser (MKRF: 5 %)	Kritisk	Data for samlet patientpopulation (inkl. patienter med andre typer kræft behandlet i andre linjer) 9,1 %	Fra 0,8 % til 8,6 % i kliniske studier	Kan ikke kategoriseres
Tid til CNS-progression	Median (MKRF: 3 mdr.)	Vigtig	24,8 måneder	Ingen data	Kan ikke kategoriseres
Progressionsfri overlevelse	Median (MKRF: 3 mdr.)	Vigtig	15,7 måneder	5,5 måneder - 22 måneder	Kan ikke kategoriseres
Uønskede hændelser	Andel patienter, der oplever en grad 3-4 uønsket hændelse (5 %) Suppleres med narrativ gennemgang	Vigtig	Data for samlet patientpopulation (inkl. patienter med andre typer kræft behandlet i andre linjer) 61,1 %	52,8 %	Kan ikke kategoriseres
Livskvalitet	Gennemsnitlig ændring over tid i EORTC-QLQC30 (10 point)	Vigtig	Ingen data	Ingen data	Kan ikke kategoriseres

Konklusion	
Samlet kategori for lægemidlets værdi	Fagudvalget vurderer, at den samlede værdi af entrectinib sammenlignet med crizotinib til førstelinjebehandling af patienter med ROS1-positiv ikke-småcellet lungekræft **ikke kan kategoriseres**. På baggrund af det foreliggende datagrundlag og fagudvalgets kliniske erfaring formoder fagudvalget, at der ikke er klinisk relevante forskelle på crizotinib og entrectinib på de undersøgte effektmål.
Kvalitet af den samlede evidens	Meget lav

Overlevelse (kritisk effektmål)
Da der er tale om uhelbredelig sygdom, vurderes forbedret samlet overlevelse (OS) med mindst mulig toksicitet som afgørende. Derfor er OS et kritisk effektmål. Der findes mange relevante effektmål for overlevelse, og i denne sammenhæng har fagudvalget vurderet median OS som det mest relevante effektmål. Den mindste klinisk relevante forskel er 3 måneder.

For entrectinib eksisterer der data med en median opfølgningstid på 20,3 måneder for 94 patienter (15,8 måneder for 161 patienter) [17]. På dette tidspunkt var ca. en fjerdedel af patienterne i studiet døde. Dermed er median overlevelse ikke nået for entrectinib.

For crizotinib er data for median overlevelse ikke modne i alle studierne, da den øvre grænse for konfidensintervallet ikke er nået i fire ud af fem studier. De rapporterede medianværdier varierer mellem 17,2 måneder og 51,4 måneder [13–16]. Studierne har forskellige patientpopulationer og opfølgningstid. Derfor er det heller ikke muligt at angive et estimat for median overlevelse på crizotinib.

Fagudvalget vurderer, at forskelle mellem crizotinib og entrectinib på effektmålet ikke kan vurderes grundet manglende data. Effekten af entrectinib sammenlignet med crizotinib på effektmålet "overlevelse" kan **ikke kategoriseres**.

Fagudvalget bemærker som perspektivering, at de tilgængelige effektestimater indikerer, at overlevelsen for både entrectinib og crizotinib hos ROS1-positive NSCLC-patienter er væsentlig længere, end hvad der forventes for patienter med uhelbredelig ikke-planocellulær lungekræft *uden* targeterbare mutationer. Behandling af denne patientgruppe er undersøgt i KEYNOTE-189-studiet, og her var median overlevelse ca. 11 måneder for patienter behandlet med platinbaseret kemoterapi og ca. 22 måneder for patienter behandlet med pembrolizumab kombineret med platinbaseret kemoterapi [19]. De resultater bekræfter, at den tilgang, der benyttes i dansk klinisk praksis (beskrevet under "nuværende behandling") med først at behandle relevante patienter med targeterede lægemidler, er hensigtsmæssig.

Behandlingsophør grundet uønskede hændelser (kritisk effektmål)
Fagudvalget finder, at ophør med en potentielt effektiv behandling er kritisk for patienterne. For targeterede behandlinger forventes der ikke at være effekt efter ophør med behandlingen (som der kan være for *checkpoint inhibitor*-immunterapi), og patienterne kan risikere hurtig forværring af sygdommen, hvis behandlingen stoppes (*flare up*). Den mindste klinisk relevante forskel er 5 %-point.

For entrectinib er der rapporteret data i den integrerede analyse for behandlingsophør grundet uønskede hændelser for den samlede patientpopulation (dvs. 504 patienter, som enten har NTRK-fusion eller ROS1-positiv NSCLC). I alt 46 patienter (9,1 %) havde en uønsket hændelse, som førte til behandlingsophør [17]. Produktresuméet for entrectinib rapporterer, at 9 % af de ROS1-positive patienter ophørte behandling pga. uønskede hændelser (datasæt med 134 patienter fra maj 2018) [20]. Fagudvalget vurderer, at data fra den samlede patientpopulation svarer til data fra den ROS1-positive population.

For crizotinib er der rapporteret værdier, som varierer mellem 0,8 % og 8,6 % i de kliniske studier [13–16], mens produktresuméet for crizotinib rapporterer, at 18 % (samlet population af patienter med ALK-positiv og ROS1-positiv ikke-småcellet lungekræft) af patienterne ophørte med behandling pga. uønskede hændelser [21]. Studierne for entrectinib og crizotinib har forskellige patientpopulationer, forskellig rapportering af behandlingsophør og varierende opfølgningstid.

Effekten af entrectinib sammenlignet med crizotinib på effektmålet "behandlingsophør grundet uønskede hændelser" **kan ikke kategoriseres**. Fagudvalget vurderer, at der på det foreliggende datagrundlag ikke kan vurderes, om der er klinisk relevante forskelle mellem entrectinib og crizotinib hvad angår effektmålet.

CNS-progression (kritisk effektmål)
Patienter med ROS1-positiv NSCLC har ofte spredning til hjernen [8], hvilket medfører betydelig morbiditet. Derfor anser fagudvalget udvikling af sygdom i centralnervesystemet, CNS-progression, som et vigtigt effektmål.
Effektmålet omfatter både CNS-progression (forværring af eksisterende sygdom) hos patienter med hjernemetastaser på inklusionstidspunktet og patienter, der får hjernemetastaser under behandlingen. Fagudvalget vurderer, at 3 måneder er den mindste klinisk relevante forskel, når CNS-progression opgøres som et *time-to-event*-effektmål, hvilket foretrækkes.

For entrectinib var der i datasættet med 94 patienter 34 patienter med CNS-metastaser ved baseline. Den mediane tid til CNS-progression i det samlede datasæt var 24,8 måneder (16,1 måneder – NR) [17].
Generel PFS var markant kortere for patienter med CNS-metastaser ved baseline i forhold til patienter uden (9,9 måneder i forhold til 21,1 måneder) [17]. Disse data besvarer ikke som sådan det kliniske spørgsmål, men viser, at CNS-metastaser er en dårlig prognostisk faktor hos patienter, som behandles med entrectinib.
For crizotinib er der ikke information om CNS-metastaser ved baseline i PROFILE 1001 eller AcSé [13,14]. I EUCROSS var der 6 patienter med CNS-metastaser ved baseline, og deres generelle PFS var markant kortere end de patienter, der ikke havde CNS-metastaser (9,4 måneder versus 20 måneder) [15]. I METROS er der ikke rapporteret om endepunkter for de 6 patienter med CNS-metastaser ved baseline [16].

Effekten af entrectinib sammenlignet med crizotinib på effektmålet "CNS-progression" **kan ikke kategoriseres**. Fagudvalget vurderer, at der på det foreliggende datagrundlag ikke kan vurderes, om der er klinisk relevante forskelle mellem entrectinib og crizotinib hvad angår effektmålet.

Fagudvalget har klinisk erfaring med crizotinib til behandling af patienter med NSCLC med ALK-translokation og har oplevet, at effekten af crizotinib på CNS-progression er begrænset. Progression i CNS ses som første hændelse hos et stort antal patienter med targeterbar NSCLC. På det foreliggende datagrundlag finder fagudvalget det dog ikke dokumenteret, at entrectinib har en bedre effekt på CNS-progression end crizotinib.
Fagudvalget gør opmærksom på, at EMA har udbedt sig opfølgende studier af entrectinib

til patienter med CNS-metastaser. Resultaterne kan måske give anledning til, at konklusionen på dette effektmål skal revurderes.

Progressionsfri overlevelse (PFS) (vigtigt effektmål)
Progressionsfri overlevelse (PFS) bliver anvendt til at vurdere, hvor lang tid der går, inden sygdommen progredierer. PFS er defineret som tiden fra randomisering til første dokumentation af progression i henhold til Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 [22] eller dødsfald.

For entrectinib var median PFS 16,8 måneder (95 % CI, 12,0 - 21,4) for de 94 patienter (datasæt med længst opfølgningstid på 20,3 måneder) og 15,7 måneder (95 % CI, 11,0 - 21,1) for de 161 patienter (datasæt med opfølgningstid på 15 måneder) [17]. I begge tilfælde er PFS målt af en uafhængig komité.
For crizotinib varierer PFS i høj grad mellem de forskellige studier med værdier mellem 5,5 måneder og 22 måneder [13–16]. PFS er enten målt lokalt, af investigator eller af en uafhængig komité. Fagudvalget vurderer, at størrelsen på PFS for crizotinib varierer grundet især forskellige studiepopulationer og opfølgningstid i studierne, mens vurdering af effektmålet har mindre betydning.

Effekten af entrectinib sammenlignet med crizotinib på effektmålet PFS **kan ikke kategoriseres**. Fagudvalget vurderer, at der på det foreliggende datagrundlag ikke kan vurderes, om der er klinisk relevante forskelle mellem entrectinib og crizotinib hvad angår effektmålet.

Uønskede hændelser (vigtigt effektmål)
Forekomst af uønskede hændelser grad 3-4 er et udtryk for alvorlig toksicitet af lægemidlet [23]. På den baggrund vurderer fagudvalget, at uønskede hændelser er et vigtigt effektmål. Fagudvalget ønskede i protokollen data på nedenstående måleenheder.

Uønskede hændelser grad 3-4
Fagudvalget finder, at forskellen i andelen af patienter, som i løbet af opfølgningstiden oplever én eller flere hændelser af grad 3 eller 4, er relevant for vurderingen. Hændelser af grad 3-4 er defineret i henhold til National Cancer Institute CTCAE version 4.03 [23]. Den mindste klinisk relevante forskel er 5 %.

Kvalitativ gennemgang af uønskede hændelser
Fagudvalget ønskede at foretage en gennemgang af uønskede hændelser, der opstår ved behandling med entrectinib og crizotinib for at vurdere hændelsernes type, håndterbarhed og reversibilitet.

Uønskede hændelser grad 3-4 (vigtigt effektmål)
Fagudvalget er opmærksom på, at datagrundlaget for uønskede hændelser for entrectinib er baseret på et datasæt, hvor der indgår patienter med andre sygdomme end ikke-småcellet lungekræft, mens patienterne i studierne af crizotinib alle havde ikke-

småcellet lungekræft. Derudover er der forskel mellem studierne i forhold til, hvordan uønskede hændelser blev opgjort. Det vanskeliggør tolkningen af kvantitative data.

Ansøger har indleveret data, som viser, at i alt 61,1 % af patienterne (sikkerhedspopulationen, n=504) behandlet med entrectinib havde en grad ≥ 3 uønsket hændelse [17]. I EMAs EPAR for crizotinib er der rapporteret, at det var tilfældet for 52,8 % af patienterne behandlet med crizotinib for ROS1-positiv eller ALK-positiv ikke-småcellet lungekræft [24]. I EMAs EPAR foreligger der også tal for voksne patienter, hvor børn er frasorteret. Her oplevede 292 ud af 475 (61,5 %) af de voksne en grad 3-4 uønsket hændelse.

Grundet usikkerhed angående datagrundlag vurderer fagudvalget ikke, at der er dokumenteret en klinisk relevant forskel mellem de to lægemidler vedrørende antal patienter med grad 3-4 uønskede hændelser.
Fagudvalget vægter i højere grad den kvalitative vurdering af de to lægemidlers bivirkningsprofiler.

Kvalitativ gennemgang af uønskede hændelser

For entrectinib er der rapporteret neurologiske bivirkninger, både centrale (forvirring, dårlig hukommelse og hallucinationer) og perifere (neuropati). 5 % af patienterne i sikkerhedspopulationen oplevede at besvime, og 2,2 % havde hallucinationer. Uden en kontrolgruppe kan man ikke med sikkerhed vide, om de centrale neurologiske bivirkninger skyldes CNS-metastaser eller en virkning af entrectinib.
Desuden er der i studierne af entrectinib rapporteret hjertesvigt, forlænget QT-interval, pneumonitis, hæmatologiske forstyrrelser og frakturer. Sidstnævnte kan evt. skyldes knoglemetastaser. For laboratorietest kan leverfunktionstal og kreatinin være ændret, og nogle patienter får lav puls og blodtryk ved behandling med entrectinib. En del (13 %) patienter fik vægtøgning.
Samlet vurderer fagudvalget, at især de neurologiske og kardiale bivirkninger ved behandling med entrectinib giver anledning til forsigtighed og grundig monitorering. I lighed med EMAs EPAR vurderer fagudvalget, at sikkerhedsprofilen overordnet er håndterbar.

For crizotinib er de hyppigste uønskede hændelser hepatotoksicitet, gastrointestinale effekter, forlænget QT-interval, synsforstyrrelse og hæmatologiske bivirkninger.
Fagudvalget har stor klinisk erfaring med crizotinib til behandling af patienter med ALK-translokation og vurderer, at de mest alvorlige/generende bivirkninger er levertoksicitet og træthed.

Samlet vurderer fagudvalget på baggrund af datagrundlaget for entrectinib og kendskab til crizotinib at begge lægemidler kan medføre mange forskelligartede uønskede hændelser, heraf nogle, som er sjældne, men potentielt alvorlige.

Bivirkningsprofilerne er sammenlignelige hvad angår alvorlighed, og begge betragtes som håndterbare i dansk klinisk praksis.

Samlet vurdering af effektmålet uønskede hændelser

Effekten af entrectinib sammenlignet med crizotinib på effektmålet uønskede hændelser **kan ikke kategoriseres**. Fagudvalget vurderer, at begge lægemidler kan medføre en række uønskede hændelser, heraf nogle potentielt alvorlige eller meget generende for patienterne. Der er dog ikke datagrundlag eller klinisk erfaring for at skelne mellem de to lægemidler på dette effektmål.

Livskvalitet (vigtigt effektmål)

Livskvalitet kan for NSCLC-patienter måles med flere forskellige instrumenter. I dette tilfælde vil vurdering af livskvalitet blive baseret på følgende: European Organisation for Research and Treatment of Cancer Quality-of-life Questionnaire-Core 30 (EORTC QLQ-C30) [25,26].

Der foreligger meget sparsomme data på dette effektmål for både crizotinib og entrectinib. QLQ-C30 er rapporteret for 37 patienter, som fik entrectinib [17], og 33 patienter (fra EUCROSS-studiet), som fik crizotinib [15]. For begge grupper rapporteres en tendens til stigning i den globale score.

Effekten af entrectinib sammenlignet med crizotinib på effektmålet livskvalitet **kan ikke kategoriseres**. Fagudvalget vurderer, at der på det foreliggende datagrundlag ikke kan vurderes, om der er klinisk relevante forskelle mellem entrectinib og crizotinib hvad angår effektmålet.

5.1.5 Fagudvalgets konklusion

Fagudvalget vurderer, at den samlede værdi af entrectinib sammenlignet med crizotinib til førstelinjebehandling af patienter med ROS1-positiv ikke-småcellet lungekræft **ikke kan kategoriseres.**

På baggrund af det foreliggende datagrundlag og fagudvalgets kliniske erfaring formoder fagudvalget, at der ikke er klinisk relevante forskelle på crizotinib og entrectinib på de undersøgte effektmål.

Hvad angår klinisk effekt, er det ikke muligt at vurdere på det foreliggende datagrundlag, om der er forskelle mellem crizotinib og entrectinib på OS, PFS, CNS-progression eller livskvalitet. For OS er data ikke modne endnu, og median OS er ikke nået i flere af de inkluderede studier, deriblandt studiet af entrectinib. For CNS-progression og livskvalitet mangler der data for mange af studierne, som umuliggør en sammenligning. For PFS er der modne data fra alle studier, men på grund af forskelle mellem studierne hvad angår opfølgningstid og patientpopulationer, er det ikke muligt at drage konklusioner om en eventuel klinisk forskel mellem entrectinib og crizotinib. Sikkerhedsprofilerne for de to lægemidler er forskellige, men fagudvalget kan på baggrund af det eksisterende datagrundlag og klinisk erfaring ikke vurdere, om den ene bivirkningsprofil er mere fordelagtig for patienterne end den anden.

6. Andre overvejelser

Objektiv responsrate

I Medicinrådets protokol ønskede fagudvalget ikke at benytte objektiv responsrate (ORR) som et effektmål, der indgår i kategoriseringen af lægemidlet, men bad ansøger om at redegøre for ORR for ROS1-positive patienter behandlet med entrectinib og crizotinib i "andre overvejelser".

ORR var primært endepunkt i adskillige kliniske studier, som indgår i vurderingen, og ORR er et effektmål, der ofte bruges i sammenligning af single-arm-studier, da den ikke er afhængig af fx varierende opfølgningstid.
I det største datasæt for entrectinib (161 patienter) havde 67,1 % af patienterne et objektivt repons [17]. For studierne af crizotinib var ORR 72 % (PROFILE 1001) [13], 47,2 % (AcSé) [14], 73 % (EUCROSS) [15] og 65 % (METROS) [16]. Fagudvalget vurderer, at der ses en høj responsrate for begge lægemidler, og at der ikke er dokumentation for, at der er forskel på entrectinib eller crizotinib på dette effektmål. Fagudvalgets vurdering af ORR er i overensstemmelse med fagudvalgets konklusion på de effektmål, der indgår i vurderingen af entrectinibs kliniske værdi.

Efterfølgende behandlingslinjer

I protokollen ønskede fagudvalget også informationer, der kan belyse en vurdering af, hvorvidt og hvordan indførelsen af den ansøgte intervention i dansk klinisk praksis vil påvirke behandlinger i efterfølgende behandlingslinjer hvad angår type, varighed og forventet effekt.

I sin endelige ansøgning angiver ansøger, at kun få patienter, som tidligere var behandlet med crizotinib for ROS1-positiv ikke-småcellet lungekræft, fik respons på entrectinib [27]. Der er ikke på nuværende tidspunkt dokumentation for at benytte entrectinib som andenlinjebehandling til patienter med sygdomsprogression på crizotinib.
I de kliniske studier havde nogle af patienterne fået anden systemisk behandling før entrectinib eller crizotinib. Fagudvalget vurderer, at targeteret behandling som standard bør gives som førstelinjebehandling af uhelbredelig ikke-småcellet lungekræft til ROS1-positive patienter. Fagudvalget vurderer ikke, at behandling med entrectinib eller crizotinib vil give forskelle angående eventuel efterfølgende behandling.

Crizotinib

Fagudvalget gør opmærksom på, crizotinib ikke har været behandlet af Medicinrådet til ROS1-positive patienter, og at erfaringen med behandling på denne indikation er sparsom i Danmark. Til gengæld har fagudvalget klinisk erfaring med crizotinib til behandling af patienter med ALK-positiv ikke-småcellet lungekræft.

7. Relation til behandlingsvejledning

Den nuværende behandlingsvejledning for førstelinjebehandling af uhelbredelig ikke-småcellet lungekræft omfatter ikke ROS1-positive patienter. Fagudvalget formoder ud fra det eksisterende datagrundlag og klinisk erfaring, at entrectinib og crizotinib kan betragtes som ligestillede til patienter med ROS1-positiv ikke-småcellet lungekræft. Fagudvalget gør opmærksom på, at yderligere data, især angående effekten af entrectinib på CNS-progression, kan ændre denne vurdering.

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9. Sammensætning af fagudvalg og kontaktinformation til Medicinrådet

Medicinrådets fagudvalg vedrørende lungekræft

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

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

Medicinrådets sekretariat

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10. Versionslog

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

Final application for Rozlytrek (Entrectinib) for ROS1-positive Non-Small Cell Lung Cancer patients

Contents

1 Basic information

Table 1. Contact information	
Name	Andreas Fanø
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Area of responsibility	Market Access
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Table 2. Overview of the pharmaceutical	
Proprietary name	Rozlytrek
Generic name	Entrectinib
Marketing authorization holder in Denmark	Roche Registration GmbH Emil-Barrell-Strasse1 79639 Grenzach-Wyhlen, Germany
ATC code	LO1XE56
Pharmacotherapeutic group	Antineoplastic agents
Active substance(s)	Entrectinib
Pharmaceutical form(s)	Hard gelatin capsules of strengths of 100 mg and 200 mg
Mechanism of action	Entrectinib is an inhibitor of TRKA, TRKB, TRKC as well as ALK and ROS1. Preclinical studies have shown that entrectinib selectively inhibits proliferative activity of cells expressing NTRK-fusion proteins and can cause cell cycle arrest and apoptosis in these cells. This antiproliferative activity was correlated with inhibition of TRKA, TRKB, TRKC, ROS1, and ALK phosphorylation as well as the phosphorylation of key downstream mediators of the TRK signaling pathways (PLC]-γ, MAPK, and AKT) and ALK signaling pathways (STAT3, MAPK, AKT, and ERK1/2).

Dosage regimen	Adult: 600 mg, once daily
Therapeutic indication relevant for assessment (as defined by the European Medicines Agency)	*Rozlytrek as monotherapy is indicated for the treatment of adult patients with ROS1-positive, advanced non-small cell lung cancer (NSCLC) not previously treated with ROS1 inhibitors.*
Other approved therapeutic indications	Entrectinib is also approved for treatment of adult and paediatric patients (≥12 years of age) with NTRK-gene fusion positive solid tumours
Will dispensing be restricted to hospitals?	Yes
Combination therapy and/or co-medication	N/A
Packaging types, sizes/number of units, and concentrations	HDPE bottles containing 30 hard capsules 100mg entrectinib with a child- resistant, tamper- evident closure and silica gel desiccant integrated in the cap. HDPE bottles containing 90 hard capsules 200 mg entrectinib with a child- resistant, tamper- evident closure and silica gel desiccant integrated in the cap
Orphan drug designation	N/A

2 Abbreviations

Table 3. Abbreviations

AE	Adverse Event	NTRK	Neurotrophic Receptor Tyrosine Kinase
ALK	Anaplastic lymphoma kinase	ORR	Objective Response Rate
BICR	Blinded independent central review	OS	Overall survival
CI	Confidence interval	PCR	Polymerase chain reaction
CCoD	Clinical cut-off date	PD	Progressive disease
CNS	Central nervous system	PFS	Progression-free survival

DLCG	Danish Lung Cancer Group	QoL	Quality of life
DNA	Deoxyribonucleic acid	RECIST	Response evaluation criteria in solid tumors
DOLG	Danish oncology lung cancer group	RNA	Ribonucleic acid
ECOG	Eastern cooperative oncology group	ROS1	ROS proto-oncogene 1 receptor tyrosine kinase
ECOG PS	Eastern cooperative oncology group performance status	rtPCR	reverse transcriptase-polymerase chain reaction
FISH	Fluorescence in situ hybridization	rw	Real-world
HR	Hazard ratio	RWD	Real-world data
HRQoL	Health-related quality of life	rwPFS	Real-world Progression-free survival
IA	Investigator assessed	SAE	Serious adverse event
IC-ORR	Intracranial objective response rate	SCLC	Small cell lung cancer
IHC	Immunohistochemistry	SOC	System organ class
IRR	Independent radiologic review	TKI	Tyrosine kinase inhibitors
MAIC	Matching adjusted indirect comparison	TRK	Tropomyosin Receptor Kinase
NA	Not available	TRAE	treatment related adverse event
NE	Not estimated	TTD	Time To Discontinuation
NGS	Next-generation sequencing	QoL	Quality of Life

NR	Not reached	QLQ-C30	Core Quality of life questionnaire
NSCLC	Non-Small Cell Lung Cancer	QLQ-LC30	Quality of life questionnaire lung cancer module

3 Summary

The following application for Rozlytrek (entrectinib) was approved by the European Commission and the European Medicines Agency on 03.08.2020. **ROS1 positive NSCLC:** Rozlytrek as monotherapy is indicated for the treatment of adult patients with ROS1- positive, advanced non- small cell lung cancer (NSCLC) not previously treated with ROS1 inhibitors. **Aim:** To assess the added clinical benefit of entrectinib in ROS1 positive NSCLC patients without prior ROS1 TKI treatment. **Method:** As described in the protocol by the Danish Medicines Council the outcome measures evaluated were critical outcomes [1]; overall survival and treatment discontinuation due to AEs, and Important outcomes; CNS progression, PFS, Narrative description of AEs (both proportion of patients experiencing grade 3-4 (related) adverse events (AEs) including a qualitative summary of AEs) and Quality of life. The Medicines Council states in the protocol that no publication with a direct comparison of entrectinib and crizotinib was found. Additional literature search was performed in order to find other relevant publications for narrative or indirect comparison. The application is based on an integrated analysis of three single-arm trials (ALKA, STARTRK-1 and STARTRK-2) evaluating the efficacy and safety of entrectinib in ROS1 positive NSCLC [2]. Five single-arm trials examining crizotinib in ROS1 NSCLC were found [3-7]. Additionally two indirect comparisons between entrectinib and crizotinib were found [8,9]. **Results:** Results from the outcomes defined by the Medicines Council is presented in this section. Overall survival: Median OS for entrectinib in the integrated analysis was not reached at the CCoD [2]. For crizotinib median OS were reported between 17.2-51.4 months [3-7]. We are not able to conclude if there is a minimal clinically relevant difference of 3 months in median OS between entrectinib and crizotinib. Treatment discontinuation due to AEs: 9.1% of patients in the integrated analysis had treatment discontinuation due to AEs [2]. For crizotinib discontinuation rates were reported between 5.9 and 18% [3-7,10]. Resulting in a minimal clinically relevant difference in favour of entrectinib. CNS progression: Entrectinib had a median time to CNS progression of 24.8 months. It was not reported in any of the crizotinib studies, but a retrospective study showed similar time to progression [3-7,11]. It was not possible to determine whether there is a minimal clinically relevant difference. PFS: Entrectinib had a median PFS of 16.8 months by BICR [2]. For crizotinib the reported median PFS was between 5.5-22.8 months [3-7]. We are not able to conclude if there is a minimal clinically relevant difference of 3 months in median PFS between entrectinib and crizotinib. Narrative description of AEs: Data from crizotinib compared with the integrated analysis suggested a difference between the two rates is 8.2% in favor of crizotinib and thus above the minimal clinical relevant difference for grade 3-4 AEs. The safety profiles of entrectinib and crizotinib are comparable, however it was seen that patients in crizotinib treatment more often have AEs leading to discontinuation or death. Quality of life: Quality of life was measured using QLQ-C30 for both entrectinib and crizotinib. The available data does not suggest major differences, however, the mean change in global HRQoL for entrectinib is not yet published.

4 ROS1-positive NSCLC

Knowledge about molecular alterations and biomarkers in oncology has increased in recent years and some of these alterations have been identified as oncogenic drivers. One of them is ROS proto-oncogene 1 receptor tyrosine kinase (ROS1). The frequency of rearrangement in the receptor tyrosine kinase ROS1 has been reported between 0.3-2.8% of non-small cell lung cancers (NSCLC), representing a lower frequency than other known oncogenic drivers in NSCLC [12-16]. Currently 22 different ROS1 fusion variants have been reported in NSCLC and the most common ROS1 fusion partner is CD74-ROS1 (less than 50% of ROS1 fusion variants) [17]. ROS1-fusions are rarely overlapping with other oncogenic drivers [16,18].

Similar to anaplastic lymphoma kinase (ALK)-positive NSCLC patients, ROS1-positive NSCLC patients will often experience central nervous system (CNS) progression. Studies have suggested high incidence rates of 19-53% in CNS-metastases among patients diagnosed with ROS1-positive NSCLC [11,19,20]. CNS-metastases are generally associated with poorer prognosis and quality of life (QoL) [21-23].

Studies have shown that approximately 30-47% (depending on disease stage) of ROS1-positive NSCLC patients treated with crizotinib with no baseline CNS metastasis are expected to develop CNS metastasis [11,17]. There is therefore an unmet need for new treatments within ROS1-positive NSCLC with proven CNS penetration and efficacy.

4.1 Testing and treatment of ROS1 positive NSCLC in Denmark

Lung cancer is one of the most frequent cancers in Denmark and in 2018 4775 patients were diagnosed [24]. Among these patients, the majority (approximately 85%) was diagnosed with NSCLC [24].

Only recently, has routine testing for ROS1 been recommended for adenocarcinomas and non-small cell carcinomas and implemented in the Danish Lung Cancer Group's (DLCG) pathology guidelines [25]. Therefore, ROS1 testing is not included in earlier annual DLCG reports [25]. Feedback from clinicians reveal that although NSCLC patients in Denmark are currently being tested for ROS1, only few ROS1-positive patients are found each year [26]. Combined with the experiences of the frequency of Danish ALK-positive patients, this could indicate a relatively low incidence of ROS1 mutations among NSCLC patients in Denmark compared to the incidence reported in peer-reviewed literature.

Of the total number of new lung cancer cases per year of 4775, it is estimated that approximately 60% have stage IIIB-IV disease, which results in a population of 2865 patients. With the proportion of 85% NSCLC patients this equals 2435 patients [27]. The calculated number of patients with ROS1-positive NSCLC will then depend on the incidence deemed to be the most realistic in a Danish setting. As mentioned above, frequencies from 0.3%-2.8% have been reported [12-16]. Based on this and the experiences with ROS1 testing so far as well as experience with ALK testing, an incidence of approximately 0.3% seems to be the most realistic estimate. With 0.3% of NSCLC patients potentially having ROS1 mutations, this will result in ≈7 patients per year that are candidates for treatment with entrectinib. However, with the increasing implementation of comprehensive genome sequencing in Denmark (e.g. NGS or whole-genome sequencing) at the point of diagnosis the estimated patient number could increase in the future.

5 Rationale for entrectinib in ROS1 positive NSCLC

Entrectinib is an oral, CNS-active, selective inhibitor of the tropomyosin receptor kinases (TRK) A/B/C, ROS1, and ALK. Gene rearrangements (fusions) in each of the genes encoding these target kinases can result in fusion proteins that constitutively activate downstream signaling and drive oncogenesis in different tumour types. The binding of entrectinib leads to inhibition of the downstream pathways (MAPK, PI3K/AKT and PKC) resulting in inhibition of cell proliferation and tumour growth [28].

Entrectinib has been studied in three phase 1 or 2 trials with ROS1-positive NSCLC patients: ALKA-372-001, STARTRK-1 and STARTRK-2. All of these showed a treatment effect significantly beyond historic controls, which led to the application and anticipated regulatory approval.

Targeting treatment to specific mutations is generally considered effective, and is well known in lung cancer where treatments targeting ALK and EGFR have been proven to be effective. In addition other targeted treatments are currently being developed for known oncogenic drives like EGFR, RET, MET and KRAS among many others. Due to the limited number of ROS1 patients, comparative studies are not available, and not likely to become available in the near future, so treatment effect is often only compared to historical controls, where targeted treatments compare favourably.

6 Literature search

The protocol for the assessment of entrectinib in ROS1-positive NSCLC (dated: 11th of June 2020) is used as the guide for performing a literature search. Since the Medicines Council has not found any full text articles that contain a direct comparison between entrectinib and crizotinib, the application has to include a literature search for relevant studies for an indirect comparison.
The search strategy was defined by the Medicines Council. Electronic searches were carried out in MEDLINE (via PubMed) and in CENTRAL (via Cochrane Library). The search contains terms descriptive of the area.

The strategy and results of the literature search has been described in more detail in appendix 1.
After removal of duplicates, two employees independent of each other screened all references on title and abstract level according to established in- and exclusion criteria in a reference management tool. The selected articles went through a full text review to establish their relevance for the assessment.

Search date: Searches made on the 05th of July 2020 in PubMed/MEDLINE and in Central/Cochrane library.

Figure 1. Literature search – PubMed/MEDLINE

Search	Actions	Details	Query	Results	Time
#11	•••	›	Search: **(#8 NOT (#9 OR #10))**	149	13:36:28
#10	•••	›	Search: **(Case Reports[pt] OR Comment[pt] OR Editorial[pt] OR Guideline[pt] OR Letter[pt] OR Review[pt])**	6,288,419	13:36:14
#9	•••	›	Search: **(case report[ti] OR review of the literature[tiab] OR retrospective[ti] OR observational[ti])**	430,926	13:35:59
#8	•••	›	Search: **((#1 OR #2) AND (#3 OR #4 OR #5 OR #6) AND #7)**	289	13:35:46
#7	•••	›	Search: **ROS1[tiab] OR ROS-1[tiab] OR ROS proto-oncogene 1[tiab]**	1,411	13:35:29
#6	•••	›	Search: **(nonsmall cell[tiab] or non-small cell[tiab] or squamous cell [tiab] or large cell[tiab]) AND (cancer[tiab] or carcinoma[tiab] or carcinomas[tiab] OR adenocarcinoma*[tiab])**	169,695	13:35:11
#5	•••	›	Search: **adenocarcinoma of lung[mh]**	8,387	13:34:59
#4	•••	›	Search: **carcinoma, non-small-cell lung[mh]**	52,989	13:34:46
#3	•••	›	Search: **NSCLC[tiab]**	43,055	13:34:30
#2	•••	›	Search: **crizotinib[mh] OR crizotinib*[tiab] OR Xalkori*[tiab]**	2,369	13:33:57
#1	•••	›	Search: **entrectinib[nm] OR entrectinib[tiab] OR Rozlytrek*[tiab] OR NMS-E628[tiab] OR RXDX-101[tiab]**	111	13:33:35

Figure 2. Literature search - Central/Cochrane

− +	#1	(entrectinib or Rozlytrek* or "NMS E628" or "R2XDX 101"):ti,ab,kw	Limits	10
− +	#2	(crizotinib or Xalkori*):ti,ab,kw	Limits	313
− +	#3	(ROS1 or ROS-1 or "ROS next proto next oncogene 1"):ti,ab,kw	Limits	104
− +	#4	(#1 OR #2) AND #3	Limits	33
− +	#5	"conference abstract":pt	Limits	157292
− +	#6	#4 not #5	Limits	7

6.1 Relevant studies

Table 4. Relevant studies included in the assessment

Reference (title, author, journal, year)	Trial name(s)	Study number(s)	Dates of study (start and expected completion date)	Relevant for clinical question
Entrectinib in ROS1 fusion-positive non-small-cell lung cancer: integrated analysis of three phase 1-2 trials; Drilon A et al; Lancet oncol; 2020	ALKA-372-001, STARTRK-1, STARTRK-2	EudraCT 2012-000148-88, NCT02097810, NCT02568267	STARTRK-2 Study start date: 19-nov-2015 Estimated study completion date: 02-dec-2024	All/1
Crizotinib in ROS1-rearranged advanced non-small-cell lung cancer (NSCLC): updated results, including overall survival, from PROFILE 1001	PROFILE 1001	NCT00585195	Study start date: 19-apr-2006 Estimated study completion date: 31-dec-2022	All/1
Phase II Safety and Efficacy Study of Crizotinib in East Asian Patients With ROS1 Positive, ALK Negative Advanced NSCLC; Wu et al; J Clin Oncol; 2018	OX-ONC	NCT01945021	Study start date: September 30, 2013 Study completion date: January 22, 2020	All/1
Crizotinib in c-MET or ROS1-positive NSCLC: results of the AcSé phase II trial;Moro-sibilot et al; Annals of oncology; 2019	AcSé phase II trial	EudraCT2013-000885-13	Study start date: August, 2013 Estimated study completion date: July, 2022	All/1
Safety and Efficacy of Crizotinib in patients With Advanced or Metastatic ROS1-Rearranged Lung Cancer (EUCROSS): A European Phase II Clinical Trial; Michels et al; J Thorac Oncol; 2019	EUCROSS	EudraCT2013-002737-38	Study start date: May, 2014 Estimated study completion date: January 2020	All/1
Crizotinib in MET-Deregulated or ROS1-Rearranged Pretreated Non-Small Cell Lung Cancer (METROS): A Phase II, Prospective, Multicenter, Two-Arms Trial; Landi, L. et al; Clin Cancer Res; 2019	METROS	NCT02499614	Study start date: December, 2014 Estimated study completion date: December 2018	All/1
Time-to-treatment discontinuation (TTD) and real-world progression-free survival (rwPFS) as endpoints for comparative efficacy analysis	ALKA-372-001, STARTRK-1, STARTRK-2	N/A	N/A	All/1

between entrectinib trial and crizotinib real-world ROS1 fusion-positive (ROS1+) NSCLC patients; Doebele et al; J Clin Oncol; 2019				
Matching-adjusted indirect comparison: entrectinib versus crizotinib in ROS1 fusion-positive non-small cell lung cancer; Chu, P. et al; J Comp Eff Res	ALKA-372-001, STARTRK-1, STARTRK-2, PROFILE 1001, PROFILE 1007, ASCEND-4	N/A	N/A	All/1

6.2 Main characteristics of included studies

Entrectinib

Data on entrectinib in ROS1-positive NSCLC is described in an integrated analysis of the ALKA-372-001, STARTRK-1 and STARTRK-2 [2,29]. In the pooled analysis, the efficacy and safety of entrectinib in patients with ROS1-positive, locally advanced or metastatic NSCLC not previously treated with ROS1 inhibitors was examined.

ALKA-372-001 is a first-in-human, phase I study of entrectinib – an oral pan-TRK, ROS1, and ALK inhibitor – in patients with advanced solid tumours with relevant molecular alterations. STARTRK-1 is a study of oral RXDX-101 in adult patients with locally advanced or metastatic cancer targeting neurotrophic receptor tyrosine kinase (NTRK) 1, NTRK2, NTRK3, ROS1, or ALK molecular alterations. STARTRK-2 is an open-label, multicentre, global phase 2 basket study of entrectinib for the treatment of patients with locally advanced or metastatic solid tumours that harbour NTRK1/2/3, ROS1, or ALK gene rearrangements.

Inclusion criteria was investigator assessed (IA) measurable disease (according to Response Evaluation Criteria in Solid Tumours [RECIST] version 1.1); a Eastern Cooperative Oncology Group (ECOG) performance status (ECOG PS) of 0–2; that patients received at least 600 mg (one dose) of entrectinib and a life expectancy of at least 3 months (ALKA-372-001 and STARTRK-1) or at least 4 weeks (STARTRK-2); and adequate organ function. Furthermore, ROS1 fusions were confirmed by local molecular profiling or central RNA-based next-generation sequencing depending on the trial. Patients could be included if they had either asymptomatic or previously treated and controlled brain metastases. Previous treatments were allowed in ALKA-372-001 (excluding previous ROS1 inhibitors); STARTRK-1 (Including crizotinib, ceritinib and investigational drug) and in STARTRK-2 (excluding approved and investigational ROS1 inhibitors).

Exclusion criteria was any of the following comorbidities:

- History of other previous cancer or currently active second malignancy
- Prolonged QTc interval
- Active infections

- Gastrointestinal disease
- Interstitial lung disease
- Interstitial fibrosis, or history of tyrosine kinase inhibitor (TKI) induced pneumonitis
- Peripheral neuropathy grade 2 or worse

The efficacy population submitted to EMA consists of three different analysis sets [2]. The initial MAA analysis includes n=53 patients enrolled up to 30 April 2017. Of the n=53 patients, 9 were in ALKA, 7 in STARTRK-1 and 37 in STARTRK-2. A second larger dataset of n=94 subjects enrolled up to 30 Nov 2017 was provided per CHMP request (not pre-specified in the iSAP and considered exploratory). In addition to the n=53 patients above, this dataset includes further 41 patients enrolled between 30 April 2017 and 30 Nov 2017, all treated within the STARTRK-2 study. The latest dataset includes n=161 patients which has been submitted by Roche as per CHMP request, had >6 months of follow up (enrolled up to 31 Oct 2018, CCoD 1 May 2019). The dataset with 53 patients is available in the article by Drilon et al. [29], while the larger datasets are available through the Rozlytrek EPAR [2].

For the primary dataset (n=94) median duration of follow-up was 20.3 months (95% Cl, 19.2-22.8) and for the second dataset (n=161) median duration of follow-up was 15.8 months (95% Cl, 14.49-18.23). As the scientific committee has requested data on the longest follow-up period, the dataset with 94 patients has been deemed to be the most relevant dataset for answering the clinical question, however given the relative population size, the dataset with 161 will also be presented when available as a supplement in the assessment.

The safety population is also divided into different populations with both an overall population across both NTRK fusion-positive tumours and ROS1-positive NSCLC as well as smaller separate populations:

Overall safety population:

- The initial overall safety population (n=355) marketing authorisation application.
- The overall safety population (n=504): Includes patients from ALKA, STARTRK-1, STARTRK-2 and STARTRK-NG who received at least one dose of entrectinib.

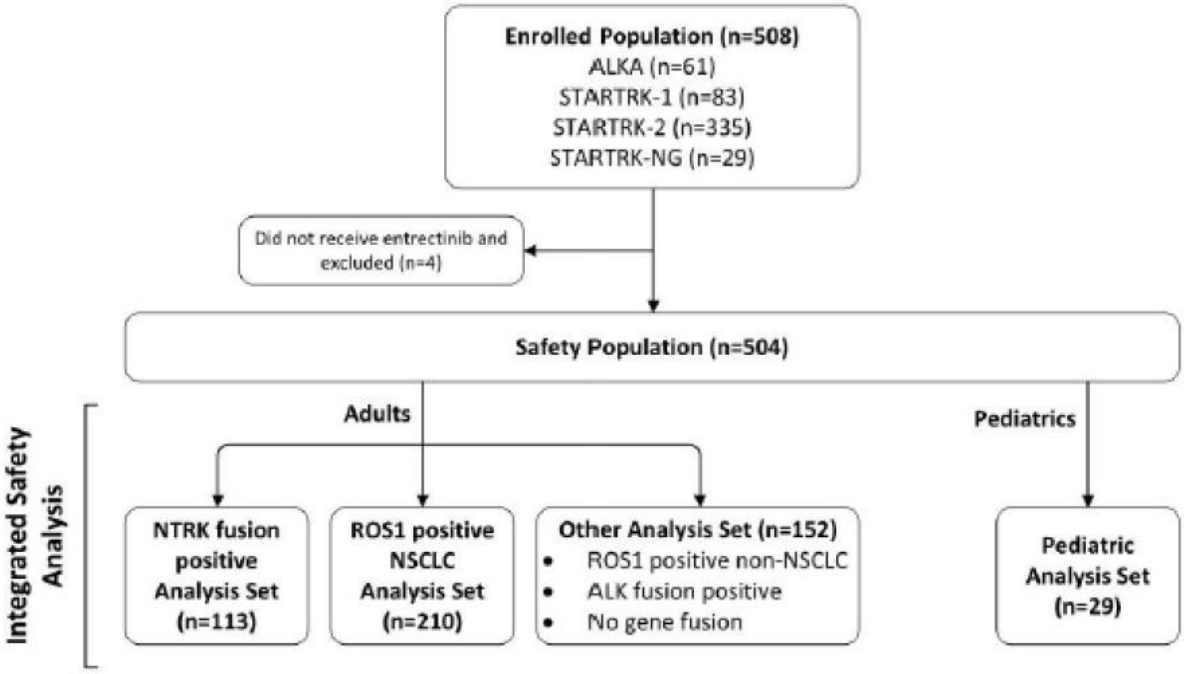
Adult analysis sets:

- NTRK fusion-positive analysis set (n=113): Includes patients from ALKA, STARTRK-1, and STARTRK-2 with NTRK fusion-positive tumours. All of the patients included in the analysis set were ≥18 years of age.
- ROS1-positive NSCLC analysis set will be presented as either the initial dataset (n=134) or the newer updated dataset (n=210): Includes patients from ALKA, STARTRK-1, and STARTRK-2 with ROS1-positive NSCLC.
- Other analysis set (n=152): Includes patients from ALKA, STARTRK-1, and STARTRK-2 with either ROS1-positive non-NSCLC, ALK fusion-positive tumours, or with no identified gene fusion.

Pediatric analysis set:

- Pediatric analysis set (n=29): Includes patients from the dose escalation portion (Phase I), or dose expansion (Phase Ib) stages of the STARTRK-NG study

Figure 3. Safety populations of the integrated analysis



ALK; anaplastic lymphoma kinase; NSCLC; non-small cell lung cancer; NTRK; Neurotrophic tyrosine receptor kinase; ROS1; ROS proto-oncogene 1 receptor tyrosine kinase.

The description of the safety profile for entrectinib in this application will be based on the data from the overall safety population of 504 adult and paediatric patients, if data is available on the ROS1-positive NSCLC analysis set of 210 patients from ALKA, STARTRK-1, and STARTRK-2 will also be described. In general, pooling of the safety data from the four studies is valid since all four studies had similar designs, treatment regimens, collection of safety data, and patient population (with the exception of STARTRK-NG, which solely included paediatric patients).

Please see Table 5, where baseline characteristics from the included trials are presented together with the two different datasets.

Crizotinib

Five studies including crizotinib in ROS1-positive NSCLC were found in the literature search.

A phase 1/1b single-arm study, PROFILE 1001, which included 53 patients with ROS1-rearranged advanced NSCLC. An update on antitumor activity, overall survival (OS) and safety data (additional 46.2 months follow-up) was presented in an article by Shaw et al. from 2019 [3]. All patients were treated with 250 mg crizotinib twice daily and had their ROS1 status confirmed with either Fluorescence In Situ Hybridization (FISH) or reverse transcriptase-Polymerase Chain Reaction (rtPCR). The primary endpoints were: 1) Number of participants with adverse events (AE) and serious adverse events (SAE), 2) Area under the concentration-

time curve, and 3) Maximum tolerated dose. Secondary endpoints were percentage of participants with objective response; area under the Concentration-Time Curve (AUC) for PF-02341066 when co-administered with rifampin; Area under the Concentration-Time Curve (AUC) for PF-02341066 when co-administered with itraconazole [30]. In the updated publication by Shaw et al. the following was descripted as endpoints: Best overall response, ORR, DOR, time to first tumor response, PFS, OS, and probability of survival at 6, 12, 24, 36, and 48 months [3].

A phase 2 single-arm, the OX-ONC study, including 127 East-Asian patients was described in an article by Wu et al. from 2018 [4]. ROS1 status was verified using rtPCR. Patients were to receive oral crizotinib at a starting dose of 250 mg twice daily and continued treatment until Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1–defined progression (by independent radiology review [IRR]), unacceptable toxicity, or withdrawal of consent. The primary endpoint was objective response rate (ORR) by IRR.

A phase 2 single-arm, the AcSé study, included 37 patients, where patients received 250 mg crizotinib twice daily. The study results have been reported in an article by Moro-Sibilot et al. from 2019 [5]. The ROS1 status was determined using immunohistochemistry (IHC) and confirmed by FISH (with a threshold of ≥15% positive cells in ≥100 nuclei). Efficacy was assessed using the ORR after two cycles of crizotinib as the primary outcome. Secondary outcomes included disease control rate at four cycles, best ORR, progression-free survival (PFS), OS, and drug tolerance.

EUCROSS is a European single-arm phase 2 study of crizotinib in ROS1-positive NSCLC. 34 patients were included in the study, but 4 were excluded from the efficacy analysis. The results have been reported in an article by Michels et al from 2019 [6]. Key eligibility criteria included patients who were 18 years of age or older with advanced/metastatic lung cancer and centrally confirmed ROS1-rearranged lung cancer (diagnosed using FISH). Treatment included 250 mg crizotinib twice daily. The primary endpoint was investigator-assessed ORR by IA (RECIST, version 1.1). Key secondary endpoints were PFS, OS, and efficacy by independent radiologic review, safety, health-related quality of life, and molecular characterization of tumour tissue.

The last study included for crizotinib is METROS, a phase 2 single-arm study with 26 ROS1-positive patients included and results were reported in an article by Landi et al. from 2019 [7]. Patients with pre-treated advanced NSCLC and evidence of ROS1 rearrangements (Cohort A) or MET deregulation (amplification, ratio MET/CEP7 >2.2 or MET exon 14 mutations, Cohort B) were treated with crizotinib 250 mg BID orally. The co-primary end-point was the ORR in the two cohorts.

Please see Table 5 where baseline characteristics from the included trials are presented.

Table 5. Demographics and baseline disease characteristics of the included studies for ROS1-positive patients

	PROFILE-1001 (n=53) [3]	OX-ONC (n=127) [4]	AcSé trial (n=37) [5]	EUCROSS (n=34) [6]	METROS (n=26) [7]	Integrated analysis (n=94) [2]	Integrated analysis (n=161) [2]
Women, N (%)	30 (57)	73 (57.5)	26 (70.3)	19 (56)	16 (62)	60 (63.8)	104 (64.5)
Median age, years (range)	55 (25-81)	51.5 (23-80)	62 (33-81)	56 (33-84)	68 (28-64)	53 (33-86)	54 (20-86)
Ethnicity, N (%) caucasian asian other	 30 (57) 21 (40) 2 (4)	 127 (100)	NA	 31 (91) 2 (6) 1 (3)		 46 (48.9) 41 (43.6) 5 (5.3)	 71 (44.1) 73 (45.3) 17 (10.6)
ECOG, N (%) 0 1 2	 23 (43) 29 (55) 1 (2)	 34 (26.8) 93 (73.2) 0 (0)	 11 (29.7) 16 (43.2) 9 (24.3)	 12 (35) 20 (59) 2 (6)	 18 (62) 7 (27) 1 (4)	 35 (37.2) 48 (51.1) 11 (11.7)	 66 (41) 79 (49.1) 16 (9.9)
Smoking history, N (%)	13 (25)	36 (28.3)	11 (31)	11 (32)	12 (46)	38 (40.4)	60 (37.3)
Metastatic disease at inclusion, N (%)	NA	121 (95.3)	35 (95)	34 (100)		93 (98.9)	158 (98.1)
CNS metastasis at baseline, N(%)	NA	23 (18.1)	8 (21)	7 (21)	6 (23)	40 (42.6)	53 (32.9)
Number of prior therapies 0 1 2 ≥3 Median (range)	 7 (13)[b] 22 (43)[b] 12 (23)[b] 12 (23)[b] 2 (1-6)[b]	 24 (18.9) 53 (41.7) 31 (24) 19 (15)	 NA NA NA NA 2 (1-7)	 7 (21) 12 (35) 5 (15) 10 (29) NA	 - 20 (76) 3 (12) 3 (12) NA	 34 (36.2) 36 (38.2) 12 (12.8) 12 (12.8) NA	 60 (37)[a] 64 (40)[a] 18 (11)[a] 19 (12)[a] NA

		NA					

[a]Lines of therapy are determined from the time of metastatic disease diagnosis. Patients may have received other therapies in the adjuvant or neo-adjuvant setting that would not count as a line of therapy in this population; [b]Based on patients who received 1 prior advanced/metastatic regimen; ECOG - Eastern Cooperative Oncology Group; NA - Not available

In addition to these studies, two indirect comparisons for entrectinib vs. crizotinib in ROS1-positive NSCLC were found (presented below).

Indirect comparisons

To bring additional evidence to support the narrative comparison of entrectinib and crizotinib, two indirect comparisons were included in this application:

- A real world comparative analysis comparing of the integrated clinical data (from STARTRK-2, STARTRK-1, and ALKA studies) for entrectinib with real world data (RWD) for crizotinib tracked through the Flatiron Health Analytic Database [8].
- Aa Matched Adjusted Indirect Comparison (MAIC) comparing data from the integrated analysis of entrectinib in ROS1-positive NSCLC to PROFILE 1001 as presented by Shaw et al (2019) [9].

Both publications use data from the initial dataset submitted to EMA (n=53). Please see Table 6 where baseline characteristics from the included indirect comparisons are presented.

Table 6. Demographic and baseline disease characteristics of the included indirect comparisons

	Flatiron comparative efficacy analysis		MAIC analysis	
	Entrectinib (Integrated analysis, n=53) [8]	**Crizotinib** (real-world, n=69) [8]	**Entrectinib** (integrated analysis, n=53)[2]	**Crizotinib** (Profile 1001, n=53) [9]
Female, N (%)	34 (64.1)	39 (50.5)	34 (64.2)	30 (56.6)
Race, n(%) Caucasian Asian Other/Missing	 31 (58.5) 19 (35.9) 3 (5.7)	 41 (59.4) 6 (8.7) 22 (31.9)	 31 (58.5) 19 (35.8) 3 (5.7)	NA
Median Age, Years (IQR)/(range)	53 (46-61)	65 (55-73)	53 (27-73)	55 (25-81)
Smoking history, N (%)	22 (41.5)	38 (55.1)	22 (41.5)	13 (24.5)
ECOG PS*, N (%) 0	 20 (37.7)	 16 (23.2)	 20 (37.7)	 23 (43.4)

1 2 Missing	27 (50.9) 6 (11.3) 0	8 (11.6) 7 (10.1) 38 (55.1)	27 (50.9) 6 (11.3) 0	29 (54.7) 1 (1.9) 0
CNS metastases at baseline, N (%)	23 (43.4)	17 (24.6)	23 (43.4)	NA
Prior therapy, N (%) ≤2 prior lines of therapy Prior targeted therapy[†] Prior chemotherapy	40 (75.5) 9 (17.0) 34 (64.2)	63 (91.3) 11 (15.9) 21 (30.4)	NA	First line 7 (13.2)
*Assessed within 30 days before the first treatment start date for the crizotinib arm; [†]Includes previous treatment with TKIs; does not include targeted treatment with TRK or ROS1 inhibitors; IQR - Interquartile range; NA - Not available; ECOG PS - Eastern cooperative oncology group performance status, MAIC - Matching adjusted indirect comparison				

Methods of the Flatiron analysis

An analysis of the relative efficacies of entrectinib and crizotinib was performed by comparing data from the integrated analysis of entrectinib (ALKA, STARTRK-1 and STARTRK-2 trials) to real world data for crizotinib tracked using the Flatiron database. The analysis has been described in a poster presented on ISPOR 2019 by Doebele et al. [8] and in the Rozlytrek EPAR [2]. The Flatiron database is a US nationwide database that tracks de-identified patient level data from electronic health registries. The database includes more than 280 cancer clinics and represents >2.2 million US cancer patients available for analysis.

An overview of the selection criteria for the entrectinib and the crizotinib arm as well as the selection flowchart for the crizotinib arm can be seen in table 7 and figure 4. Overall, 150 ROS1-positive advanced NSCLC patients were found in the Flatiron database. The analysis incorporated 69 of these patients and of these 54 patients were derived using propensity score matching for a matched crizotinib arm for use in the comparative analysis. The included patients were found after applying the inclusion and exclusion criteria derived from the STARTRK-2 study (used also for the integrated efficacy analysis set of entrectinib).
The entrectinib arm was the ROS1 NSCLC Efficacy Evaluable analysis set obtained by integrating data from STARTRK-2, STARTRK-1, and ALKA studies (n=53) - an earlier clinical cut-off date (CCoD) (from 26-Oct-2012 to 27-Mar-2018). The baseline characteristics for the Flatiron analysis can be seen in Table 6.

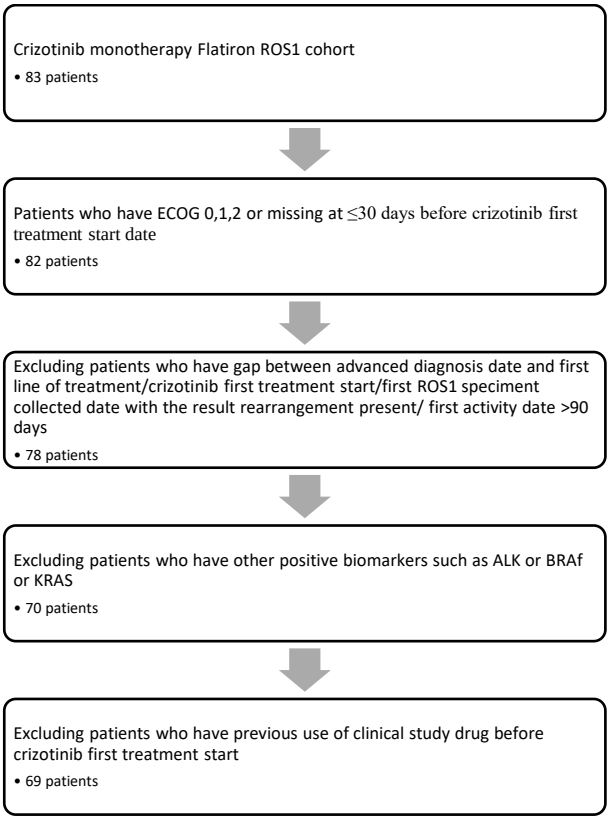
Table 7. Treatment arms in the Flatiron analysis [2].

	Entrectinib arm	Crizotinib arm
Baseline demographics	Patients with locally advanced or metastatic NSCLC ≥18 years of age	Patients with locally advanced or metastatic NSCLC ≥18 years of age

Performance status	ECOG performance status of 0-2	ECOG performance status of 0-2. Patients with missing ECOG were allowed
Testing	ROS1-positive rearrangement confirmed via NGS or other nucleic acid based diagnostic tests	ROS1-positive rearrangement confirmed, confirmed via NGS, FISH, IHC as per U.S. clinical pratice
Prior therapies	Prior anticancer therapy such as chemotherapy allowed, and no previous exposure to another ROS1 inhibitor such as crizotinib	Prior anticancer therapy such as chemotherapy allowed; patients who had a gap between advanced diagnosis date and a crizotinib first treatment start date of more than 90 days and no information on treatment prior crizotinib start were excluded

ECOG – Eastern Cooperative Oncology Group; FISH – flourecence in situ hybridization; IHC – immunohistochemistry; NGS – next generation sequencing; NSCLC – non-small cell lung cancer; U.S. – united states.

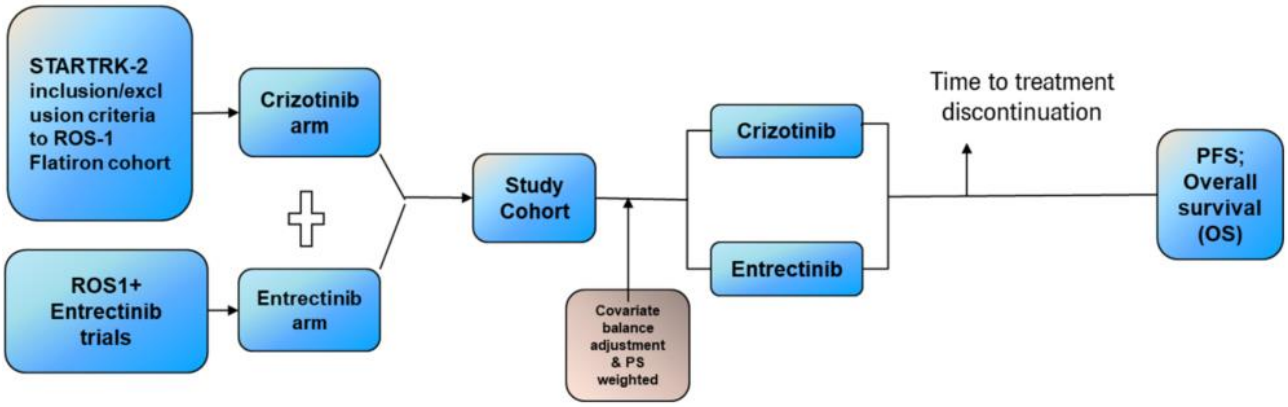
Figure 4. Inclusion process of the Flatiron analysis [2]



Time-to-event analyses were carried out on a propensity score matched population. Kaplan-Meier analyses and Cox regression models were used to compare the effect of entrectinib and crizotinib on the included

outcomes. The study design can be seen in Figure 5. Primary endpoint was Time to Treatment Discontinuation (TTD) and secondary objectives included PFS and OS as well as a description of demographics, clinical characteristics and outcomes of the ROS1-positive NSCLC patients with and without CNS metastases at baseline (including time to CNS progression).

Figure 5. Design of the Flatiron analysis



Methods of the Matching-Adjusted Indirect Comparison

A MAIC was done by Chu et al. to compare entrectinib to crizotinib in ROS1-positive NSCLC [9].

The MAIC assigned statistical weights to the individual entrectinib-treated patients to adjust for their representation relative to that observed in crizotinib-treated patients in PROFILE 1001. Propensity weights were assigned to entrectinib patients, as this was the only source with individual data available, and a propensity score logistic regression model estimated the odds of being enrolled into the comparative evidence source. After weighting, the average baseline characteristics were balanced between the entrectinib arm and the baseline characteristics of PROFILE 1001. The final baseline characteristics selected for matching based on known factors were sex, ECOG status, smoking history (yes/no), age, disease stage at enrollment and prior treatment (treatment-naive vs. prior treatment).

As the percentage with CNS metastases at baseline was not reported in PROFILE 1001, the analysis was set up as three different scenarios that differ on the assumed proportion of patients with CNS metastases. The assumed proportion in PROFILE 1001 is in each scenario based on rates observed in available literature. An overview of the sources for each scenario can be seen in Table 8. The analysis of safety outcomes (AEs and discontinuations) used the ROS1 safety population of 134 patients for entrectinib instead of the efficacy population of 53 patients [9].

Table 8. Sources for each of the three scenarios in the MAIC analysis

	Scenario 1	**Scenario 2**	**Scenario 3**
Assumed proportion with CNS metastases in PROFILE 1001	18.1%	24.64%	43.4%

Source	Wu et al.[4]	Doebele et al. [8]	Entrectinib integrated analysis [2]
Population	East-Asian patients (n=127)	US patients (n=69)	n=53

Kaplan-Meier curves were generated and OS and PFS probabilities were obtained. Hazard ratios were calculated using weighted Cox proportional hazards models. Odds ratios were estimated for AEs and treatment discontinuations using the derived weights. Confidence intervals were estimated using bootstrap sampling. The procedure was repeated multiple times to obtain a distribution of hazard ratio (HR) and the 2.5 and 97.5 percentiles were used to generate the limits of a confidence interval (CI).

Please also refer to Appendix 10.2 for main characteristics of the included study.

7 Clinical questions

7.1 What is the clinical benefit of entrectinib compared to crizotinib as a first line treatment of patients with incurable ROS-positive NSCLC

7.1.1 Presentation of the relevant study and results

The following section contains a comparative analysis of entrectinib versus crizotinib, which the Scientific Committee has appointed as the relevant comparator in this assessment.

For entrectinib, the results of the integrated analysis of ALKA, STARTRK-1, STARTRK-2 are used as the primary source of data for efficacy in ROS1-positive NSCLC. The included data for both entrectinib and crizotinib is based on single-arm studies and no relevant independent direct head-to-head comparison is published. Individual evaluations of the studies show indications of important differences in study populations and particularly reporting practices, that are difficult to account for in standardized cross-trial comparisons. Results from the included studies will therefore be presented in a narrative comparative analysis. In addition hereto, evidence from previously described indirect comparisons will be presented for the relevant endpoints when available.

Differences and limitations in the trials and indirect comparisons

In this section, differences and limitations between the included studies will be discussed.

As mentioned above, the included trials are all single arm trials without a direct comparator which limits the availability of direct and indirect comparisons. Across the trials, there are significant differences in the studied populations e.g. follow-up period, ECOG PS, CNS metastases at baseline, race, molecular testing and methods of the assessments.

The included studies also report different follow-up periods and the treatment duration of the trials are quite different. Entrectinib treatment duration is a mean of 5.5 months (ranging from 0.0-42.1 months) in the integrated analysis (n=504) and a median 7.4 months (ranging from 0.0-42.1 months) in the ROS1 specific subgroup (n=210) [2]. Wu et al reports 18.4 months of median treatment duration and PROFILE 1001 reports a median 22.4 months, AcSé 11.1 months, METROS 15.2 months, while EUCROSS does not report treatment duration [3-7].

ECOG PS is varying in all three subgroups. In ECOG PS 0 the reported numbers of patients is ranging from 26.8% to 43%, in ECOG PS 1 it is ranging from 27% to 73.2% and lastly ECOG PS 2 is reported from 2% to 24.3% [2-7].

For the included crizotinib trials, the reported CNS metastases at baseline were similar (18.1-23%), but both the integrated analysis and STARTRK-2 had CNS metastases at baseline at approximately 33% [2-7]. In PROFILE 1001, the proportion of patients with CNS metastases at baseline was not reported, which represents a further limitation in indirect comparisons. In the OX-ONC trial, no caucasian patients were included and all patients were of asian ethnicity [4]. This should be taken into account when comparing the other included trials where the caucasian population varied from 41.1% to 91% [2,3,5-7]. PFS results from the integrated analysis for entrectinib will mainly be presented as blinded independent central review (BICR) results, but data for investigator assessed PFS is also available [2]. The crizotinib studies are mainly assessed by investigator in in EUCROSS and METROS [6,7]. In OX-ONC and EUCROSS Independent radiology review IRR was used and in AcSé it was not reported [4-6]. In PROFILE 1001 the method of assessment is not stated [3]. These are all differences that significantly affect the reported outcomes and make naïve comparisons difficult.

For the MAIC analysis, certain limitations should be taken into account when interpreting the PROFILE 1001 trial versus the entrectinib integrated analysis; i) the proportion of patients with CNS metastasis at baseline for PROFILE 1001 was not reported and might be significantly lower or higher than entrectinib integrated analysis, ii) it was unclear whether PFS was assessed by BICR or IA in PROFILE 1001, iii) patients in entrectinib had a median survival follow-up of 15.84 months compared to 62.6 months in PROFILE 1001.

For the Flatiron real world comparative analysis, the main limitations include divergent derivation methods for both PFS and rwPFS as well as differences in frequencies and types of biomarker tests used in the trials (Next-generation sequencing [NGS]-based) and rw-setting (FISH-based) and the limited known ECOG status available (45%) in the crizotinib arm [8].

7.1.2 Overall survival - Critical outcome

In the protocol for the assessment of entrectinib in ROS1-positive NSCLC, the Scientific Committee states that OS should be measured as median OS and that a median difference of 3 months is clinically relevant.

Narrative comparison

OS for entrectinib has been assessed with a median of 20.3 months of follow-up (see Table 9). In the primary dataset (n=94) 25 patients (26.6%) had died, while it was 38 (23.6%) in the expanded dataset (n=161). The

median OS has not been reached (CI 28.3-NR) in any of the newer datasets in the integrated analysis of entrectinib [2].

Table 9. Kaplan-Meier event free rates for OS in ROS1-positive NSCLC patients treated with Rozlytrek in the integrated analysis and crizotinib in PROFILE 1001

	Integrated analysis (n=161) [31]	Profile 1001 (n=53)[3]
6 months Event free probability, (95% CI)	0.91 (0.87; 0.96)	0.91 (0.79-0.96)
9 months Event free probability, (95% CI)	0.86 (0.81; 0.92)	N/A
12 months Event free probability, (95% CI)	0.81 (0.74; 0.87)	0.79 (0.65-0.88)
N/A - Not Available		

The latest update of the PROFILE 1001 study showed a median OS of 51.4 months (95% CI, 29.3-not reached) [3]. The OX-ONC trial reports a median OS of 32.5 months (95% CI, 32.5-NR), but adds that they consider the data not to be mature [4]. In the AcSé trial the reported median OS was 17.2 months (95% CI, 6.8-32.8) [5]. For the EUCROSS trial, the reported median OS (95% CI, 17.1-NR) was not met at the CCoD [6]. Lastly the METROS trial did not reach median OS either and no confidence interval was reported [7].

As mentioned earlier, there are big differences across the studies regarding the proportion of patients with ECOG PS 2, which might affect the results. PROFILE 1001 with the highest reported median OS has included 2% with ECOG PS 2 and AcSé with the lowest reported median OS has included 25% ECOG PS 2.

The impact of patient characteristics is only speculative, with differences in follow-up periods, treatment lines and proportion of performance status 2 patients, which is higher in the entrectinib analysis and the AcSé trial. With no clear indication of a more tolerable drug, the different treatment durations may indicate prognostic differences in the study populations.

With the median OS for entrectinib not yet reached, it is difficult to measure the minimal clinically relevant difference of 3 months. Furthermore, the size of the studies and resulting in statistical uncertainty makes it difficult to conclude on the results of the published studies when comparing medians.

Indirect comparisons

In the MAIC analysis, OS was analysed for three scenarios; each assuming a different proportion of baseline CNS metastases in PROFILE 1001. It was however not possible to calculate a median in any scenario due to the low number of events. The HR was in all three scenarios indicative of a reduction in risk of death in favour of entrectinib. The results of the MAIC analysis of OS can be seen in Table 10.

Table 10. MAIC - Overall Survival (OS)[9]

Intervention	Scenario	Number of patients (sum of weights)	Number of events	Median 95% CI, months	Hazard Ratio (95% CI)	Median difference (entrectinib vs crizotinib, months)
Crizotinib	Original	53	26	51.5 (29.87, NE)	-	-
Entrectinib	Original	53	9	NE (28.32,NE)	-	-
Entrectinib	Reweighted (Scenario 1)	(39.98)	5.30	NE (NE, NE)	0.47 (0.11-1.03)	NE
Entrectinib	Reweighted (Scenario 2)	(42.57)	5.92	NE (NE, NE)	0.50 (0.13.1.06)	NE
Entrectinib	Reweighted (Scenario 3)	(44.91)	7.16	NE (NE, NE)	0.61 (0.16, 1.27)	NE

NE - Not estimable.

As seen in Table 10, the MAIC shows a statistically non-significant benefit in favour of entrectinib, but since the median is not yet reached, a difference can only be shown in the hazard ratio. CNS metastases at baseline affect the OS results in the reweighted scenarios. This indicates that the difference in CNS metastases at baseline could be a significant confounder when attempting to compare the study results directly.

OS data was also compared in the real world analysis of Flatiron data [8]. The unweighted median OS for crizotinib was 19.9 months (95% CI, 15.1-NE), while the weighted median OS was 18.5 months (95% CI, 15.1-19.9). At the time of the analysis, the median OS for entrectinib could not be estimated (at 15.5 months of follow-up).

As the median OS for entrectinib has not been reached it is difficult to compare entrectinib and crizotinib in terms of median OS in the indirect comparisons. The hazard ratio results in the MAIC analysis could however suggest an OS benefit of using entrectinib but results are not significant.

Conclusion

Based on the presented median OS and the trial differences described earlier, we are not able to conclude if there is a minimal clinically relevant difference of 3 months in median OS between entrectinib and crizotinib. The MAIC has however displayed hazard ratios that suggest a favourable profile of entrectinib in all three scenarios, however, results were not statistically significant.

A significant variance was seen in the reported median OS data for crizotinib ranging from 17.2 months in the AcSé study to 51.4 months in the PROFILE 1001. The 51.4 months in PROFILE 1001 is markedly higher than the reported median OS in all other trials. These differences could be indicative of the differences in reporting methods and the low proportion of patients with ECOG PS 2. As the proportion of patients with CNS metastases at baseline is not reported in PROFILE 1001, the influence of this difficult to ascertain.
An overview of the reported and estimated median OS data for entrectinib and crizotinib can be seen in Table 11.

Table 11. Overview of the reported and estimated median OS data for entrectinib and crizotinib

	Drug (study population, N)	Median OS (95% CI, Months)
Narrative comparison	**Entrectinib** (Integrated analysis, n=94 and n=161)[a]	NE (28.3-NE)
	Crizotinib (PROFILE 1001, n=53)[b]	51.4 (29.3-NR)
	Crizotinib (OX-ONC, n=127)[a]	32.5 (32-NR)
	Crizotinib (AcSé trial, n=37)	17.2 (6.8-32.8)
	Crizotinib (EUCROSS trial, n=30)	NR (17.1-NR)
	Crizotinib (METROS trial, n=26)	NR
MAIC analysis	**Entrectinib reweighted (Scenario 1 and 2)**	NE (NE-NE)
	Crizotinib	51.5 (29.8-NE)
FLATIRON analysis	**Crizotinib unweighted** (n=69)	19.9 (15.1-NE)
	Crizotinib weighted (n=54)	18.5 (15.1-19.9)

[a]Kaplan-Meier estimate; [b]Based on the Brookmeyer and Crowley method; NR - Not reached; NE - not estimate

7.1.3 Adverse events leading to discontinuation of treatment - Critical outcome

Adverse events leading to discontinuation of treatment is listed as a critical outcome in the protocol for the assessment. The minimal clinically relevant difference is set to 5%-points. For a description of the overall safety profiles of entrectinib and crizotinib, please refer to section 7.1.5 Adverse events. As requested in the protocol a list of all AEs that leads to discontinuation and the relevant frequencies will be presented later in this section.

Narrative comparison

For the integrated analysis (overall, n=504) it was reported that 46 (9.1%) of patients experienced an AE that led to discontinuation [2]. Discontinuation of treatment due to an adverse reaction was reported in 4.4% of patients in the entrectinib SmPC (n=504) [31].

In PROFILE 1001 and the publication by Shaw et al only treatment-related adverse events are reported, and it is described that no patients discontinued due to treatment-related adverse events [3]. In the NICE assessment (TA529) of crizotinib in ROS1-positive NSCLC based on PROFILE 1001 (n=53), it was, however, reported that 4 patients (7.5%) had permanent treatment discontinuation due to an adverse event [32]. OX-ONC reported 1 patient (0.8%) discontinuing due to treatment-related AEs (TRAE) [4]. In the AcSé trial, discontinuation due to toxicity was reported in 3 patients (8.6%) [5]. In the EUCROSS trial, 2 patients (5.9 %) were reported to discontinue treatment due to AEs [6]. In the METROS trial, 3 patients (6%) were reported to have permanent discontinuations due to TRAEs [7]. In relation to these results, it is important to keep the difference between the trials in mind as well as the limitations in what is reported. In the SmPC of crizotinib (n=1722) it is reported that in all-causality adverse events associated with permanent treatment discontinuation occurred in 302 (18%) patients, including both ALK+ and ROS1 patients [10].

For comparison, the ALEX study, comparing alectinib to crizotinib in ALK+ NSCLC, reported that 19 patients (12.5%) experienced treatment discontinuation due to AEs with 17.6 months median duration of follow-up [33]. The populations of these two diseases would otherwise be considered similar, potentially suggesting underreporting for the ROS1 specific population in the PROFILE 1001 study.

There are no minimal clinically relevant differences in the reported discontinuation rates in the included studies, when excluding TRAEs (5.9-9.1%) [2-7]. However when comparing the overall safety populations for entrectinib and crizotinib, which represents the most comprehensive knowledge about the safety of the products, there is a difference of 8.9%, which is above the 5% minimal clinically relevant difference between entrectinib (9.1%) and crizotinib (18%).

Indirect comparison

Treatment discontinuations due to adverse events were also evaluated in the MAIC analysis based on the ROS1-positive NSCLC patient population of 134 patients [9].

Results of the analysis of all three scenarios can be seen in Table 12. The scenarios had only small differences. Overall the results indicated a lower percentage of patients with discontinuation of treatment due to AEs when treated with entrectinib, but the confidence intervals of the ORs are wide suggesting that the estimate is uncertain. The mean difference is also lower than the clinically significant 5%.

Table 12. MAIC - Discontinuations due to adverse events [9]

Intervention	Scenario	Number of patients (sum of weights)	Number with discontinuation due to AEs	% with discontinuation due to AEs	Odds ratio (95% CI)	Median difference (entrectinib vs crizotinib, %)
Crizotinib	Original	53	4	7.5%	-	-
Entrectinib	Original	134	-	-	-	-
Entrectinib	Reweighted (Scenario 1)	(93.4)	6.36	6,8%	0.90 (0.23, 1.91)	-0.7
Entrectinib	Reweighted (Scenario 2)	(101.6)	6.77	6.7%	0.87 (0.25, 1.83)	-0.8
Entrectinib	Reweighted (Scenario 3)	(115.9)	7.04	6.1%	0.79 (0.29, 1.44)	-1.4

In relation to the general discontinuation of the treatment, the Flatiron comparative analysis finds that the median time to discontinuation in general is 8.4 months for the crizotinib real world arm and 14.6 months for the entrectinib arm, it was not reported if and to what degree AEs affected this difference in time to treatment discontinuation.

List of AEs resulting in treatment discontinuations

The list of AEs resulting in treatment discontinuations was requested by the scientific committee as part of a narrative description of adverse events. In the interest of cohesion, the section will however be presented here instead. The rates of AEs leading to treatment discontinuation is described and compared in section 7.1.2. In this section the list of related AEs and their frequencies will be presented and discussed.

As mentioned, AEs leading to discontinuation of treatment were rare (9.1%) in the total safety population (n=504) [2]. The most frequently reported adverse events leading to discontinuation (≥1% of patients) in system organ class (SOC) were as follows: Respiratory thoracic and mediastinal disorders (2.2%), cardiac disorders (1.8%), general disorders and administration site conditions (1.6%), and nervous system disorders (1.2%) [2]. There was no predominant AE that led to withdrawal of entrectinib treatment. A list of all adverse events leading to treatment discontinuation can be seen in Table 13.

As mentioned, for crizotinib all-causality AEs associated with permanent treatment discontinuation occurred in 302 (18%) patients of which the reported terms were interstitial lung disease (1%), elevated transaminases (1%) and neutropenia (<1%) [10]. In the 53 patients in the PROFILE 1001 study (data from EPAR), discontinuations due to adverse events occurred in 4 patients (7.5%): Disease progression (2 patients, 3.8%), Nausea (1 patients, 1.9%), and pericardial effusion (1 patients, 1.9%) [34].

Table 13. Adverse events leading to treatment discontinuation for entrectinib and crizotinib

Event	**Entrectinib** (Overall safety population, n=504)[2]	**Crizotinib** (SmPC, n=1722) [10]
	Number of patients, N (%)	
Total number of patients with at least one adverse event leading to discontinuation	46 (9.1%)	302 (18%)
Interstitial lung disease	NA	17 (1%)
Elevated transaminases	NA	17 (1%)
Neutropenia	NA	<17 (<1%)
Respiratory, thoracic and mediastinal disorders	11 (2.2%)	NA
Cardiac disorders	9 (1.8%)	NA
General disorders and administration site conditions	8 (1.6%)	NA
Nervous system disorders	6 (1.2%)	NA
NA - Not applicable		

Conclusion

Based on the reported rates of AEs leading to discontinuation from the narrative comparisons, it can be concluded that there is a difference of 8.9 %-points between the integrated analysis for entrectinib (n=504) and the SmPC for crizotinib. This difference is above the minimal clinically relevant threshold, which means that there is a minimal clinically relevant difference in favour of entrectinib. This was not consistent with the MAIC that found a difference <5% in favor of entrectinib. However, the indirect comparison only compared PROFILE 1001 and the integrated analysis of entrectinib, and not the entire crizotinib safety profile.

An overview of the reported and estimated discontinuation due to adverse events data for entrectinib and crizotinib can be seen in Table 14.

Table 14. Overview of the reported discontinuation of entrectinib and crizotinib due to adverse events

	Drug (study population, N)	Discontinuation rate (%)
Narrative comparison	**Entrectinib** (Integrated analysis, EPAR (overall), n=504)	9.1
	Entrectinib (Integrated analysis, SmPC (overall), n=504)	(4.4)*
	Crizotinib (PROFILE 1001, n=53)	7.5[a]
	Crizotinib (OX-ONC, n=127)[a]	(0.8)*
	Crizotinib (AcSé trial, n=37)	8.6[b]
	Crizotinib (EUCROSS trial, n=34)	5.9
	Crizotinib (METROS trial, n=26)	(6)*
	Crizotinib (SmPCl, n=1722)	18
MAIC analysis	**Entrectinib reweighted**	Scenario 1 6.4%
		Scenario 2 6.8%
		Scenario 3 7.0%
	Crizotinib	7.5

[a]reported in crizotinib EPAR; [b]reported at toxicity; *treatment related adverse event

7.1.4 CNS-progression - Important outcome

CNS progression is listed as an important outcome in the protocol for the assessment. The outcome should be measured as the median CNS PFS (time-to-event) and the minimal clinically relevant difference is set to 3 months.

Narrative comparison

For entrectinib, the integrated analysis (n=94) included 34 patients with CNS progression at baseline and 60 patients without. The median time to CNS progression assessed by BICR was 24.8 months (95% CI, 16.1-NR) for integrated analysis (n=94) [2]. Patients with baseline CNS disease in the integrated analysis had a PFS of 9.9 (95% CI, 4.6-17.4) months versus 21.1 months (95% CI, 14.8-30.8) in patients with no CNS disease. ORR was similar in baseline CNS disease (67.6%) versus no CNS disease (76.7%) [2].

For crizotinib, there is not reported any information on CNS disease from the PROFILE 1001 study or AcSé trial [3,5]. The OX-ONC trial reports a PFS in patients with baseline CNS disease of 10.2 months vs 18.8 months in non-CNS patients as well as 73.9% ORR in patients with CNS metastasis versus 71.2% ORR in patients without CNS metastasis [4]. For the six patients (21%) with CNS metastasis at baseline in EUCROSS, median PFS was shorter for patients with CNS metastasis at 9.4 months (95% CI, 1.7-NR) versus 20.0 months (95% CI, 10.1-NR) for patients without CNS metastasis at baseline [6]. ORR was similar for patients with or without CNS metastasis at baseline. In METROS, 6 patients had CNS metastasis at baseline and responses were only observed in one ROS1 patient. No outcomes were reported for the patients with CNS metastasis [7].
In addition to the presented crizotinib trials, a retrospective analysis on the incidence of CNS metastasis was published by Patil et al. [11]. In this study, 19 ROS1 stage IV patients were eligible for analysis of CNS progression on crizotinib. Median duration of follow-up was 30 months. CNS was found to be the first and sole site of progression in 9 patients (47%) and within 24 months 50% of the ROS1 patients without CNS metastasis prior to crizotinib had progressed within the CNS.

For comparison, the study ALEX, comparing alectinib to crizotinib in ALK+ NSCLC, reported 45% of crizotinib treated ALK+ patients had an CNS progression event [33]. Furthermore, the 12 months cumulative incidence rate of CNS progression was 41.4% (95% CI, 33.2 to 49.4). As previously mentioned the populations of ALK+ and ROS1 would otherwise be considered somewhat similar, suggesting a lower time to CNS progression for crizotinib than reported in the retrospective study by Patil et al [11].

In terms of the molecules themselves, Entrectinib is also reported to be a weak P-gp subtract that can maintain CNS exposure in *in vitro* and *in vivo* experiments [35]. Crizotinib on the other hand was found to be a stronger P-gp substrate, leading to poorer brain distribution [35].

Indirect comparison

None of the indirect analyses included time to CNS progression as an outcome, however, the Flatiron analysis included a subgroup analysis. Of the 69 crizotinib-treated patients included in the Flatiron analysis, 17 patients were identified to have brain metastasis. For these patients, the estimated median PFS was 4.6 months and median OS was 15.5 months [2].

Conclusion

Based on lack of data on crizotinib's median time to CNS progression it is not possible to determine whether or not there is a minimal clinically relevant difference between entrectinib and crizotinib. The retrospective study by Patil et al. on crizotinib found a median time to CNS progression of 24 months [11]. This result should however be interpreted with caution due to the differences in study design (prospective versus retrospective) and sample size (94 patients versus 19 patients). No matter the approach, a comparative analysis with PROFILE 1001 is difficult to perform, as the study does not report CNS disease or activity.

Entrectinib has shown a median time to CNS progression at 24.8 months, which is an important outcome based on the high incidence rates of developing CNS metastasis reported for crizotinib (approximately 30-47%, depending on disease stage) [11,17]. The lack of and differences in reporting makes it difficult to make any clear differentiation between the two drugs. From the results in ALK and ROS1-positive NSLC, the results of the ALEX study could however be indicative of a low CNS efficacy of crizotinib.

An overview of the reported and estimated CNS progression entrectinib and crizotinib can be seen in Table 15.

Table 15. Overview of the reported and estimated CNS progression of entrectinib and crizotinib

	Drug (study population, n)	Median time to CNS progression (CI 95%, months)	PFS in patients with CNS disease at baseline (95% CI, months)
Narrative comparison	**Entrectinib** (Integrated analysis, n=161)	24.8 months (16.1-NR)[a]	9.9 months (4.6-17.4)
	Crizotinib (PROFILE 1001, n=53)	N/A	N/A
	Crizotinib (OX-ONC, n=127)	N/A	10.2 months (5.6-13.1)
	Crizotinib (AcSé trial, n=37)	N/A	N/A
	Crizotinib (EUCROSS trial, n=30)	N/A	9.4 months (1.7-NR)

	Crizotinib (METROS trial, n=26)	N/A	N/A
Flatiron analysis	**Crizotinib** n=63 (Brain metastasis subgroup: n=17) [34]	N/A	4.6 months
[a]Blinded independent central review (BICR); NA-Not available			

7.1.5 Progression-free survival - Important outcome

The protocol lists PFS as an important outcome. Data should be compared using median PFS with a minimal clinically relevant difference of 3 months median PFS.

Narrative comparison

Median PFS assessed by BICR was 16.8 months (95% CI, 12.0-21.4) for the integrated analysis (n=94) [2]. Median PFS was also assessed for entrectinib in the newest dataset (n=161) with a median PFS by BICR of 15.7 months (95% CI, 11.0-21.1) [2]. Investigator-assessed median PFS is not available in any of the publications for the newer datacuts. For the previous datacut (31 May 2018, n=53) the median PFS was 15.5 months (95% CI, 10.0-19.0) in the integrated analysis [2].

For crizotinib, the PROFILE 1001 trial does not report the method of assessment, but shows a median PFS of 19.3 months (95% CI, 15.2-39.1) [3]. In the OX-ONC trial, PFS was assessed by IRR and median PFS reported as 15.9 months (95% CI, 12.9-24.0) [4]. In the AcSé trial method of assessment is not reported, but the median PFS was 5.5 months (95% CI, 4.2-9.1) [5]. In the EUCROSS trial median PFS was 20 months (95% CI, 10.1-NR) as assessed locally and 20 months (95% CI, 9.6-NR) as assessed by IRR [6]. Median PFS in the METROS trial was 22.8 months (95% CI, 15.2-30.3) and was assessed by investigator [7].

As seen in the reported median OS, the reported PFS medians for crizotinib varies greatly between the trials, ranging from 5.5 months to 19.3 months [2-7]. PROFILE 1001 had the highest reported median PFS with 2% ECOG PS 2 and no reported proportion of CNS metastases at baseline, whereas AcSé with the lowest reported median PFS had 25% with ECOG PS 2 and 21% CNS metastasis at baseline.
The OX-ONC, EUCROSS, and METROS trials showed median PFS of 15.9, 20 and 22.8 months respectively. All three trials also had low share of ECOG PS 2 patients with 0 patients in OX-ONC, 2 patients (6%) in EUCROSS and 1 patient (4%) in METROS. All three studies had comparable proportions with CNS metastases at baseline ranging from 18.1-23% (however markedly lower than the 32.9% reported in the integrated analysis for entrectinib). This suggests that prognostic factors in the study populations are highly influential.
The reported median PFS of crizotinib in PROFILE 1001, METROS, OX-ONC, and EUCROSS are all considerably higher than what was reported in the ALEX trial where 151 patients were treated with crizotinib. Here the reported median PFS by independent review was 10.4 months (95% CI, 7.7-14.6) [33]. Considering the

similarities between ALK-positive and ROS1-positive NSCLC patients it is unclear why crizotinib has demonstrated PFS results of such variance in ROS1 setting. The population in the ALEX study has a similar proportion of ECOG PS 2 patients (7%) and CNS metastases at baseline (38%) to those seen in the integrated analysis for entrectinib [2,33].

These differences in the included populations are plausible explanations for the variance seen in the results. It is noteworthy that the proportion of patients with ECOG PS 2 is low in the studies that reported the longest median PFS for crizotinib. The BICR assessed PFS of the entrectinib integrated analysis at 16.8 months is relatively high when taking into consideration that 11 patients (11.7%) had ECOG PS 2 and 34 patients (37.8%) had CNS metastasis at baseline. Given the differences in crizotinib results, it is not possible to separate the two drugs based on PFS with the available data.

Indirect comparison

PFS for both crizotinib and entrectinib was analysed in the MAIC analysis. The analysis was carried out on PFS assessed by BICR in the integrated analysis. A limitation in the analysis, however, is the fact that the methodology (e.g. BICR or IA), is unclear in PROFILE 1001 [3]. Another limitation is again the unreported proportion of patients with brain metastases at baseline in PROFILE 1001. As seen in the results (Table 16 and Table 17), the estimated median differs significantly depending on the specific scenario and what proportion of brain metastases the entrectinib data is reweighted to.

As mentioned previously, Scenario 1 and 2 assumes a proportion of brain metastases of 18.1% [4] and 24.64% [8] respectively while Scenario 3 assumes a proportion of 43.4% [2]. If the analysis assumes a proportion of CNS metastases at baseline in PROFILE 1001 of 43.4%, the median PFS of entrectinib of 19.0 months is almost similar to the crizotinib median PFS of 19.33 months with a difference of -0.33 months. If choosing either Scenario 1 or 2, the estimated median PFS on entrectinib treatment is 26.3 months and the difference compared to crizotinib PFS is 6.97 months, crossing the minimal clinically relevant difference.

Table 16. MAIC - Progression-Free Survival (PFS) by BICR [9]

Intervention	Scenario	Number of patients (sum of weights)	Number of events	Median 95% CI, months	Hazard Ratio (95% CI)	Median difference (entrectinib vs crizotinib, months)
Crizotinib	Original	53	36	19.33 (15.27, 33.15)		
Entrectinib	Original	53	25	19.0 (12.2,36.6)		
Entrectinib	Reweighted	(40.0)	16.4	26.3	0.94 (053,	6.97

	(Scenario 1)			(19.0,NE)	1.43)	
Entrectinib	Reweighted (Scenario 2)	(42.6)	17.3	26.3 (15.7, NE)	0.96 (0.56, 1.45)	6.97
Entrectinib	Reweighted (Scenario 3)	(44.9)	18.1	19.0 (15.7, NE)	1.05 (0.64, 1.60)	-0.33

When the analysis is performed on IA PFS, the results favours crizotinib, with the median difference in scenario 3 crossing the minimal clinically significant difference.

Table 17. MAIC - Progression-Free Survival (PFS) by IA [9]

Intervention	Scenario	Number of patients (sum of weights)	Number of events	Median 95% CI, months	Hazard Ratio (95% CI)	Median difference (entrectinib vs crizotinib, months)
Crizotinib	Original	53	36	19.33 (15.27, 33.15)	-	-
Entrectinib	Original	53		15.5 10.0-19.0	-	-
Entrectinib	Reweighted (Scenario 1)	(40.0)	22.5	17.71 (15.51, NE)	1.29 (1.84, 1.82)	-1.62
Entrectinib	Reweighted (Scenario 2)	(42.6)	24.3	17.51 (14.49, NE)	1.35 (0.90, 1.86)	-1.82
Entrectinib	Reweighted (Scenario 3)	(44.9)	27.1	15.51 (12.22, NE)	1.54 (1.06, 2.11)	-3.82

Overall, it is difficult to assess the most realistic scenario for the proportion of brain metastases at baseline in PROFILE 1001. The proportion of patients with CNS metastases at ROS1 diagnosis has been reported with different rates in the literature spanning from 19-53% [11,19,20]. It is furthermore also difficult to determine the most relevant assessment method for PFS when comparing entrectinib data to PROFILE 1001 as this was unknown for PROFILE 1001, and the results differ depending on which methodology is chosen in the analysis.

PFS was also compared in the real world analysis of Flatiron data [8]. The unweighted median rwPFS by BICR for crizotinib was 8.5 months (95% CI, 6.2-10.1), while the weighted median rwPFS by BICR for crizotinib was 8.8 months (95% CI, 8.2-9.9). At the time of the analysis and using the earlier CCOD (n=53, 27-mar-2018), the

median PFS by BICR of entrectinib was 19.0 months (95% CI, 12.2-NE). This results in a difference in a difference of median PFS of 10.5 and 10.2 respectively, which is above the minimal clinically relevant difference of 3 months. Using the most recent datacut of the 1st of May 2019 (dataset with 94 patients), the median PFS of entrectinib (by BICR) is 16.8 months (95% CI, 12.0-21.4) in the integrated analysis. Compared to the two rwPFS estimates of crizotinib, this results in a difference of 8.3 months for the unweighted scenario and 8.0 months for the weighted scenario, which are both above the difference of 3 months.

Conclusion

The differences in baseline characteristics, reporting methodologies and assessments make direct naïve treatments comparisons difficult and hard to interpret. As seen in the MAIC analysis, the baseline characteristics can have a significant influence on the results and the unknown proportion of CNS metastases at baseline and the unclear methodology in the assessment of PFS in PROFILE 1001 can affect the results. In addition to this, the integrated analysis for entrectinib had a proportion of 11.7% ECOG performance status 2 and 36.2% CNS metastases at baseline. The 36.2% with CNS metastases in the integrated analysis for entrectinib is the highest reported proportion across all studies included in this application.

Due to these challenges, indirect methods of comparisons such as MAIC and propensity score matching become important tools. In this case however, the lack of knowledge regarding the patient population in PROFILE 1001 and the performed analysis, makes it difficult to ascertain the most realistic scenario in the MAIC analysis. It is also worthy of note that the reported PFS of crizotinib in PROFILE 1001, OX-ONC, and EUCROSS is markedly higher than what was seen in the real-world data analysis in the Flatiron database, the AcSé trial, and also considerably higher than the reported PFS by BICR of crizotinib on 151 ALK patients in the ALEX trial which was 10.4 months (95% CI, 7.7-14.6). Overall, it is not possible to conclude if there is a minimal clinically relevant difference of 3 months in median PFS between entrectinib and crizotinib.

An overview of the median PFS and rwPFS of both the narrative and the indirect comparisons can be seen in Table 18.

Table 18. Median (rw)PFS data of entrectinib and crizotinib

	Drug (study population, N)	Median (CI 95%, months)
Narrative comparison	**Entrectinib** (Integrated analysis, n=94)	16.8 (12.0-21.4)[b]
	Entrectinib (Integrated analysis, n=53)	15.5 (10.0-19.0)[a]
	Entrectinib	15.7 (11.0-21.1)[b]

	(Integrated analysis, n=161)	
	Crizotinib (PROFILE 1001, n=53)	19.3 (15.3-39.1)
	Crizotinib (OX-ONC, n=127)	15.9 (12.9-24.0)[c]
	Crizotinib (AcSé trial, n=37)	5.5 (4.2-9.1)*
	Crizotinib (EUCROSS trial, n=30)	20.0 (9.6-NR)[c]
	Crizotinib (METROS trial, n=26)	22.8 (15.2-30.3)
MAIC analysis	**Entrectinib reweighted**	Scenario 1 (BICR) 26.3 (19.0, NE)
		Scenario 2 (BICR) 26.3 (15.7-NE)
		Scenario 3 (BICR) 19.0 (15.7,-NE)
		Scenario 1 (IA) 17.7 (15.5-NE)
		Scenario 2 (IA) 17.5 (14.5,NE)
		Scenario 3 (IA) 15.5 (12.2-NE)
	Crizotinib (PROFILE 1001)	19.3 (15.3 - 33.2)
Flatiron analysis (rwPFS)	**Entrectinib** (n=53)	19 (12.2-NE)
	Crizotinib unweighted (n=69)	8.5 (6.2-10.1)
	Crizotinib weighted (n=54)	8.8 (8.2-9.9)

[a]Investigator assessed (IA); [b]Blinded independent central review (BICR) assessed; [c]Independent radiology review (IRR); *Specific assessment not reported; rwPFS - Real-world PFS; NR- Not reached; NE - not estimated

7.1.6 Adverse events - Important outcome

"Adverse events" is listed as an important outcome in the protocol. The outcome should be measured as both the proportion of patients experiencing at least 1 grade 3-4 AE as well as a narrative assessment of the safety profiles of both entrectinib and crizotinib. For grade 3-4 AEs the minimal clinically relevant difference is 5%-points. Below is an overall description of the safety profile of entrectinib and crizotinib respectively.

Safety populations

Entrectinib

As mentioned previously, the description of the safety profile for entrectinib in this application will be based on the data from the overall safety populations of adult and pediatric patients (n=504), if data are available for either of the ROS1-positive NSCLC analysis set (n=134 or 210) from ALKA, STARTRK-1, and STARTRK-2, it will also be described. For a few of the narrative comparisons, the initial safety population (n=355) is the only available dataset [2,31].

Crizotinib

For the available crizotinib publications in general there was only sparse reporting on AEs and the available publications seems to mainly report treatment-related adverse events in their description of the safety profile [3-7]. The most comprehensive description of AEs for crizotinib was found in the crizotinib EPAR containing the previous PROFILE 1001 datacut of the 30th of November 2014 (n=53) [34]. In addition to the EPAR, the overall safety population of crizotinib in both ROS1-positive and ALK-positive NSCLC (n=1722) will be described using the SmPC for crizotinib [10].

7.1.7 Proportion of patients experiencing at least one grade 3-4 AEs

In the publication by Shaw et al. presenting the data from the most recent PROFILE 1001 datacut (30th of June 2018), only treatment-related AEs are reported [3]. Instead the crizotinib EPAR of the ROS1 indication was consulted [34]. As mentioned, this report has however not been updated with the recent datacut and contains data from the previous datacut of 30th of November 2014 from the PROFILE 1001 trial. No indirect comparisons were available for this specific endpoint.

Narrative comparison

For entrectinib, grade 3-4 events have been reported in the overall safety population (n=504). 61.1 % of the patients experienced grade ≥3 [2]. The most frequently reported grade 3-4 AEs (≥2%) in the initial safety population (n=355) is presented in table 19. In terms of SAEs, 39.9% of patients in the overall safety population (n=504) experienced at least one SAE (any grade). Treatment-related SAEs (any grade) occurred in 9.7% of patients. The most common SAEs regardless of causality by SOC (≥2% of patients, any grade) were: dyspnoea (4.6%), pleural effusion (3.0%), pulmonary embolism (2.0%), pneumonia (4.0%) [2]. There were a total of 123 patients (24.4%) that died within the overall safety population (n=504) [2]. The majority of grade 5 AEs were respiratory AEs that occurred in patients with lung cancers or lung metastases. The majority of grade 5 AEs were reported in a context of worsening of underlying disease or complications of the underlying malignancy.

Table 19. Grade ≥3 AEs for entrectinib with an incidence rate of ≥2%	
Event	**Entrectinib** (Total safety population,n=355)
	Number of patients, n (%)
Weight increased	23 (6.5)
Aspartate aminotransferase increased	12 (3.4)
Alanine aminotransferase increased	11 (3.1)
Neutrophil count decreased	9 (2.5)
Lipase increase	7 (2.0)
Dyspnea	22 (6.2)
Pulmonary embolism	12 (3.7)
Hypoxia	12 (3.4)
Pleural effusion	11 (3.1)
Anaemia	38 (10.7)
Neutropenia	9 (2.5)
Syncope	9 (2.5)
Pneumonia	14 (3.9)
Sepsis	8 (2.3)
lung infection	7 (2.0)
Hypophosphatemia	10 (2.8)

Hypokalaemia	7 (2.0)
Hyponatremia	7 (2.0)
Fatigue	15 (4.2)
Diarrhoea	7 (2.0)
Hypotension	7 (2.0)

The reported number of patients with grade 3-4 AEs in the crizotinib EPAR (with previous datacut of 30th of November 2014) was 52.8% (28/53) [34]. Crizotinibs population is small and does not include the comprehensive overview of grade 3-4 AEs reported in the ROS1 population. The difference between the two rates is 8.3% and thus above the minimal clinical relevant difference. As mentioned, no grade 3-4 AEs was reported in any of the crizotinib studies as all publications only reported TRAEs.

When comparing to the ALEX study in ALK+ NSCLC patients, the crizotinib arm had 50% grade 3-5 AEs with a shorter treatment duration, which could suggest some underreporting of AEs in the ROS1 crizotinib studies [33].

For crizotinib, the most common grade 3 or 4 adverse events are described in Table 20. As some frequencies may have been underestimated by reliance on a single preferred term, the analysis in the EPAR was done in aggregate using clustered terms (presented in capital letters). 22 patients (41.5%) experienced at least one SAE (any grade). The most common (≥2 patients) were disease progression (9 patients (19%), pneumonia (3 patients, 5.7%), headache (2 patients, 3.8%), and nausea (2 patients, 3.8%). Treatment-related SAEs were seen in 2 patients (3.8%) and included bradycardia and gastrointestinal amyloidosis. Grade 5 adverse events occurred in 9 patients (17.0%). No treatment-related grade 5 adverse events were recorded.

Table 20. Grade 3 or 4 adverse events for crizotinib

	All causality		Treatment-related	
	Grade 3 n (%)	Grade 4 n (%)	Grade 3 n (%)	Grade 4 n (%)
Any grade 3 or 4 AE	28 (52.8%)		16 (30.2%)	

Hypophosphataemia	8 (15.1%)	0	7 (13.2%)	0
NEUTROPENIA	5 (9.4%)	0	5 (9.4%)	0
Headache	4 (7.5%)	0	0	0
DYSPNOEA	3 (5.7%)	0	0	0
Syncope	3 (5.7%)	0	0	0
Vomiting	3 (5.7%)	0	1 (1.9%)	0
Electrocardiogram QT prolonged	2 (3.8%)	0	1 (1.9%)	0
Elevated transaminases	2 (3.8%)	0	2 (3.8%)	0
Pneumonia	2 (3.8%)	0	0	0
PULMONARY EMBOLISM	0	6 (11.3%)	0	0

Looking at the reported TRAEs from both products. TRAEs for entrectinib, Drilon et al reported (based on May 31 2018 datacut, n=53) that 41 patients (31%) experienced grade 3 TRAEs, while 5 (4%) experienced grade 4 TRAEs [29].

In the publication of Shaw et al. a proportion of 36.0% of patients is reported for grade 3 treatment-related adverse events (no grade 4 TRAEs were seen) [3]. In OX-ONC, 32 patients (25.2) experienced grade 3-4 TRAEs [4]. In AcSé the AEs were only summarized as a graphical representation, and the numerical value is not available [5]. In EUCROSS, 8 patients (21%) had grade 3 TRAE [6]. For METROS, 3 patients (11.5%) experienced grade 3-4 TRAEs [7].

The data suggests that there are differences in the reporting of AEs between the studies making comparison difficult, but overall there is no evidence suggesting large differences in safety between the two drugs. In addition sample sizes are small and baseline characteristics are different, therefore a certain variation is to be expected, particularly for the crizotinib studies.

For both entrectinib and crizotinib, gastrointestinal adverse reactions are fairly common, as are elevation of liver enzymes and some changes in lab values. Crizotinib may have a higher occurrence of vision disorders and neutropenia, while anemia and weight increase is associated with entrectinib.

Conclusion

Because of the lacking reports on all-causality grade 3-4 AEs from the crizotinib studies it is difficult to compare entrectinib and crizotinib grade 3-4 AE safety profile. The rates reported for crizotinib in PROFILE

1001 are considerably lower than what was reported in ALK-positive NSCLC in the ALEX trial. Data from crizotinib EPAR (earlier dataset, n=53) compared with the integrated analysis suggested a difference between the two rates is 8.3% in favour of crizotinib and thus above the minimal clinical relevant difference. The data from entrectinib is shown as ≥3 grade and for the overall population, which will affect the number when comparing with crizotinib. This difference is however shown in an earlier datacut and it is unknown whether the current proportion of patients with a grade 3-4 AE is equal or higher in the updated analysis of PROFILE 1001.

7.1.8 Narrative description of the safety profile

Summary of safety profiles

For the overall safety population most patients had received all their planned doses of entrectinib with few missed doses (median of 1.0, CI: 0.0, 50.0) and ROS1-positive NSCLC population (median of 1.0, CI: 0.0, 25.0). Treatment with entrectinib was generally well tolerated with a manageable safety profile. Most of the AEs in the overall safety population (n=504) that required intervention were managed with either dose interruption (45.8%) or dose reduction (26.0%) [2].

Most (99%) patients in the overall integrated safety population (n=504) had at least one AE. The most frequently reported AEs by system organ class was nervous system disorder (82.5%); gastrointestinal (81.5%); general disorders and site conditions (73.4%); respiratory, thoracic and mediastinal disorders (~60%); musculoskeletal and connective tissue disorders and investigations (~55%) [2].

An overview of the safety profile in both the ROS1-positive NSCLC population and the overall safety population can be seen in Table 21. For all three population the summary of the safety profile resembles one another.

Table 21. Summary of Adverse Events in the safety population

	ROS1-positive NSCLC (n=134)	Overall safety population (n=355)	Overall safety population (n=504)
Any Adverse Events	134 (100.0)	353 (99.4)	499 (99)
Related Adverse Events	125 (93.3)	325 (91.5)	-
Grade ≥3 Adverse Events	82 (61.2)	217 (61.1)	308 (61.1)
Related Grade ≥3 Adverse Events	46 (34.3)	110 (31.0)	-
Adverse Events Leading to Death	9 (6.7)	20 (5.6)	24 (4.8)
Serious Adverse Events	50 (37.3)	137 (38.6)	
Adverse Events Leading to Discontinuation of Trial Drug	6 (4.5)	30 (8.5)	46 (9.1)

In the safety analysis for crizotinib described in the EPAR some preferred terms are aggregated to clustered terms [34]. This approach was taken, since some frequencies might have been underestimated, when relying on a single preferred term. Clustered terms are presented in capital letters.

All patients experienced an adverse event at some point during crizotinib treatment. The most frequently reported AEs (≥25%) included vision disorder (86.8%), nausea (58.5%), edema (58.5%), vomiting (50.9%), diarrhoea (45.3%), constipation (43.4%), dizziness (39.6%), upper respiratory infection (39.6%), elevated transaminases (35.8%), fatigue (32.1%), neuropathy (30.2%), dyspnea (28.3%), rash (26.4%), and bradycardia (26.4%).

28 of patients had a dose interruption (any missed dose for more than 1 day in a cycle) which was a maximum of less than a week for 13 (46.4%) of patients. 7 (13.2%) patients had a dose reduction below 500 mg/day lasting more than 1 day.

An overview of the safety profile of Crizotinib in PROFILE 1001 can be seen in Table 22.

Table 22. Summary of Adverse Events in the Safety Analysis Population for crizotinib

	ROS1-positive NSCLC (n=53)
Any Adverse Events	53 (100%)
Related Adverse Events	52 (98.1%)[a]
Grade 3 or 4 AEs	28 (52.8%)
Related Grade 3 or 4 Adverse Events	16 (30.2%)
Adverse Events Leading to Death	9 (17.0%)
Serious Adverse Events	22 (41.5%)
Adverse Events Leading to Discontinuation of Trial Drug	4 (7.5%)

[a]All 53 patients (100%) had experienced a related AE in the 30th of June 2018 datacut [34]

Based on these summarized data for crizotinib and entrectinib there are certain similarities, besides grade 3-4 adverse events reported above. However there is a substantial difference in the reported adverse events leading to death with 17% reported for crizotinib (n=53) and 6.7% reported in the ROS1 population for entrectinib (n=134) and even lower 4.8% for the newer overall population (n=504).

Presentation of all AEs for entrectinib and crizotinib treatment

As requested by the protocol, this section will present a review of all AEs that occur in treatment with entrectinib and crizotinib in order to assess the type of events, manageability and reversibility of the AEs. For the narrative description of entrectinib and crizotinib, SmPCs for both entrectinib and crizotinib were used to report the general safety profile related to the treatment [10,31]. The safety population in the integrated analysis is the same as the safety population described in the SmPC for entrectinib.

Tabulated list of adverse reactions in entrectinib and crizotinib

The adverse reactions listed in table 23 are presented by system organ class and frequency categories, defined using the following convention: very common (1/10); common (1/100 to <1/10), uncommon (1/1,000 to <1/100), rare (1/10,000 to <1/1,000), very rare (<1/10,000), not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 23. Adverse reactions reported in entrectinib (n=504) and crizotinib (n=1722) clinical studies

System organ class	**Drug**	Very common	Common	Uncommon
Infections and infestations	Entrectinib	Lung infection[1] (13.1%) Urinary tract infection (12.7%)		
	Crizotinib			
Blood and lymphatic system disorders	Entrectinib	Anaemia (28.2%) Neutropenia[2] (11.3%)		
	Crizotinib	Neutropenia[a] (22%) Anaemia[b] (15%) Leukopenia[c] (15%)		
Metabolism and nutrition disorders	Entrectinib	Weight increased (26.4%) Decreased appetite (11.9%)	Hyperuricemia (9.1%) Dehydration (7.9%)	Tumour lysis syndrome (0.2%)
	Crizotinib	Decreased appetite (30%)	Hypophosphatemia (6%)	
Nervous system disorders	Entrectinib	Dysgeusia (42.3%) Dizziness[3] (39.7%) Dyaesthesia[4] (29.0%) Cognitive disorders[5] (24.2%) Headache (17.5%) Peripheral sensory neuropathy[6] (15.7%) Ataxia[7] (15.7%) Sleep disturbances[8] (13.5%)	Mood disorders[5] (9.1%) Syncope (4.6%)	

	Crizotinib	Neuropathy[d] (25%) Dysgeusia (21%)		
Eye disorders	Entrectinib	Vision blurred[10] (11.9%)		
	Crizotinib	Vision disorder[e] (63%)		
Cardiac disorders	Entrectinib		Congestive heart failure[11] (3.0%) Electrocardiogram QTc prolonged (2.0%)	
	Crizotinib	Dizziness[f] (26%) Bradycardia[g] (13%)	Cardiac failure[h] (1%) Electrocardiogram QT prolonged (4%) Syncope (3%)	
Vascular disorders	Entrectinib	Hypotension[12] (16.5%)		
	Crizotinib			
Respiratory, thoracic and mediastinal disorders	Entrectinib	Dyspnoea (27.0%) Cough (21.4%)	Pleural effusion (6.9%)	
	Crizotinib		Interstitial lung disease[i] (3%)	
Gastrointestinal disorders	Entrectinib	Constipation (42.9%) Diarrhoea (33.5%) Nausea (32.1%) Vomiting (23.2%) Abdominal pain (11.1%) Dysphagia (10.1%)		
	Crizotinib	Vomiting (51%) Diarrhoea (54%) Nausea (57%) Constipation (43%) Abdominal pain[j] (21%)	Oesophagitis[k] (2%) Dyspepsia (8%)	Gastrointestinal perforation[l] (<1%)
Hepatobiliary disorders	Entrectinib	AST increased (17.5%) ALT increased (16.1%)		
	Crizotinib	Elevated transaminases[m] (32%)	Blood alkaline phosphatase increased (7%)	Hepatic failure (<1%)

Skin and subcutaneous tissue disorders	Entrectinib	Rash[13] (11.5%)	Photosensitivity reaction (2.8)	
	Crizotinib	Rash (13%)		
Musculoskeletal and connective tissue disorders	Entrectinib	Myalgia (19.6%) Arthralgia (19.0%) Muscular weakness (12.3%)	Fractures[14] (6.2%)	
	Crizotinib			
Renal and urinary disorders	Entrectinib	Blood creatinine increased (25.4%) Urinary retention[15] (10.9%)		
	Crizotinib		Renal cyst[n] (3%) Blood creatinine increased[o] (8%)	
General disorders and administration site conditions	Entrectinib	Fatigue[16] (45.0%) Oedema[17] (37.3%) Pain[18] (24.4%) Pyrexia (20.0%)		
	Crizotinib	Oedema[p] (47%) Fatigue (30%)		
Investigations	Entrectinib			
	Crizotinib		Blood testosterone decreased[q] (2%)	
Please see description of elevated letters and numbers in the relevant SmPCs of entrectinib and crizotinib [10,31].				

Description of selected adverse events

Entrectinib

This section and the selected is based on the SmPC for entrectinib [31]. The reported frequencies are based on the total safety population of 504 patients.

Cognitive disorders

A range of cognitive disorders was reported across the entrectinib clinical trials including confusional state (7.3%), cognitive disorders (6.3%), memory impairment (4.2%), disturbance in attention (3.8%), amnesia (2.8%), mental status changes (1.2%), hallucination (1.0%), delirium (0.8%), visual hallucination (0.4%) and mental disorder (0.2%). The frequency of cognitive disorders was higher in patients with CNS disease at

baseline (29.7%) compared to those without (23.1%). Grade 3 cognitive disorders were seen in 4.4% of patients. The median time to onset of cognitive disorders was 0.92 months. The majority of grade 3 cognitive disorders were manageable and resolved with entrectinib dose interruption and/or reduction. Most patients were able to continue treatment and only 1 event described as "cognitive disorder" led to discontinuation of entrectinib.

Fractures

Fractures were observed in 5.3% of adult patients (25/475). The assessment of tumour involvement at the site of fracture was in general inadequate - however radiologic abnormalities that could indicate tumour involvement were reported in some adult patients. Most fractures were hip or other lower extremity fractures (e.g. femoral or tibial). Some fractures occurred in adult patients due to a fall or other trauma to the affected area. The median time to fracture was 3.4 months (95% CI, 0.26-18.5) in adults. Of the adult patients that experienced fractures, treatment was interrupted in 36.0% of cases. No patients discontinued treatment with entrectinib due to fractures.

None of the fracture events led to discontinuation of entrectinib treatment and in the majority of cases did not result in any actions regarding the study drug. At the time of CCoD, the majority of fractures had resolved.

Ataxia

Ataxia (including ataxia, balance disorders, and gait disturbances) was reported in 15.7% of patients. Median time to onset was 0.4 months (95% CI, 0.03-28.19) with a median duration of 0.7 months (95% CI, 0.03-11.99). The majority of patients (67.1% of cases) recovered from ataxia. AEs related to ataxia was more frequently observed in elderly patients (23.8 of patients) compared to patients below 65 years of age (12.8%).

Syncope

Syncope was reported in 4.6% of patients. Syncope was in some patients reported with concurrent hypotension, dehydration, or QTc prolongation. All grade 3 events (3.0%) had been resolved by the time of CCoD.

QTc interval prolongation

Among the 504 patients that received at least 1 dose of entrectinib 4% of patients with at least one post-baseline ECG assessment experienced QTcF interval prolongation of >60 ms after starting treatment with entrectinib and 2.8% of patients had a QTcF interval of ≥500 ms. All AEs of prolonged QT were non-serious and all except one grade 1 case had resolved at time of CCoD.

Peripheral sensory neuropathy

15.7% of patients experienced peripheral sensory neuropathy with a median time to onset of 0.49 months (CI: 0.03 months-20.93 months) and a median duration of 0.8 months (95% CI, 0.07-6.01). The majority of patients (55.7%) recovered from peripheral neuropathy. Most events were grade 1 or 2 in severity and these events were generally resolved without any dose interruption and/or reduction. Few patients (5 [1.0%]) experienced grade 4 events of peripheral sensory neuropathy. These were resolved with entrectinib dose interruption and/or reduction.

Eye disorders

In terms of eye disorders vision blurred (8.5%), diplopia (2.6%), and visual impairment (1.6%) was reported across the clinical trials. Median time to onset was 1.9 months (95% CI, 0.03-14.49). Of the patients that experienced eye disorders, the majority of patients (61.7%) recovered. The majority of events were grade 1. 2 cases of grade 3 eye disorder events were reported, however, both had resolved at CCOD.

Crizotinib

This section and the selected is based on the SmPC for Crizotinib [10]. The reported frequencies are based on the total safety population of 1722 patients.

Hepatotoxicity

Transaminase elevations generally occurred within the first 2 months of treatment. Across studies with crizotinib in patients with either ALK-positive or ROS1-positive NSCLC, the median time to onset of increased Grade 1 or 2 transaminases was 23 days. Median time to onset of increased Grade 3 or 4 transaminases was 43 days. Increases to Grade 3 or 4 ALT or AST elevations were observed in 187 (11%) and 95 (6%) of patients, respectively. Seventeen (1%) patients required permanent discontinuation from treatment associated with elevated transaminases, suggesting that these events were generally manageable by dosing modifications. Grade 3 and 4 transaminase elevations were generally reversible upon dosing interruption. Across studies with crizotinib in patients with either ALK-positive or ROS1-positive NSCLC (n=1722), dose reductions associated with transaminase elevations occurred in 76 (4%) patients. Seventeen (1%) patients required permanent discontinuation from treatment. Patients should be monitored for hepatotoxicity and managed as recommended.

Gastrointestinal effects

The most commonly reported all-causality gastrointestinal events was nausea (57%), diarrhoea (54%), vomiting (51%), and constipation (43%). Most events were mild to moderate in severity. Median times to onset for nausea and vomiting were 3 days, and these events declined in frequency after 3 weeks of treatment. Supportive care should include the use of antiemetic medicinal products. Median times to onset for diarrhoea and constipation were 13 and 17 days, respectively. Supportive care for diarrhoea and constipation should include the use of standard antidiarrheal and laxative medicinal products, respectively. In clinical studies with crizotinib, events of gastrointestinal perforations were reported. There were reports of fatal cases of gastrointestinal perforation during post-marketing use of crizotinib

QT interval prolongation

Across studies in patients with either ALK-positive or ROS1-positive advanced NSCLC, QTcF (corrected QT by the Fridericia method) ≥500 msec was recorded in 34 (2.1%) of 1619 patients with at least 1 postbaseline ECG assessment and a maximum increase from baseline in QTcF ≥60 msec was observed in 79 (5.0%) of 1585 patients with a baseline and at least 1 postbaseline ECG assessment. 13 All-causality Grade 3 or 4 Electrocardiogram QT prolonged was reported in 27 (1.6%) out of 1722 patients. QT prolongation can result in arrhythmias and is a risk factor for sudden death. QT prolongation may clinically manifest as bradycardia, dizziness, and syncope. Electrolyte disturbances, dehydration and bradycardia may further increase the risk

of QTc prolongation and thus, periodic monitoring of ECG and electrolyte levels is recommended in patients with GI toxicity.

Bradycardia
In studies with crizotinib, all-causality bradycardia was experienced by 219 (13%) of 1722 patients treated with crizotinib. Most events were mild in severity. A total of 259 (16%) of 1666 patients with at least 1 postbaseline vital sign assessment had a pulse rate <50 bpm. The use of concomitant medicinal products associated with bradycardia should be carefully evaluated. Patients who develop symptomatic bradycardia should be managed as recommended.

Interstitial lung disease/pneumonitis
Severe, life-threatening, or fatal interstitial lung disease (ILD)/pneumonitis can occur in patients treated with crizotinib. Across studies in patients (n=1722), 50 (3%) patients treated with crizotinib had any grade all-causality ILD, including 18 (1%) patients with Grade 3 or 4, and 8 (<1%) patients with fatal cases. According to an independent review committee (IRC) assessment of patients with ALK-positive NSCLC (n=1669), 20 (1.2%) patients had ILD/pneumonitis, including 10 (<1%) patients with fatal cases. These cases generally occurred within 3 months after the initiation of treatment. Patients with pulmonary symptoms indicative of ILD/pneumonitis should be monitored. Other potential causes of ILD/pneumonitis should be excluded.

Visual effects
All-causality, all grade, vision disorder, most commonly visual impairment, photopsia, vision blurred, and vitreous floaters, was experienced by 1084 (63%) of 1722 patients treated with crizotinib. Of the 1084 patients who experienced vision disorder, 95% had events that were mild in severity. Seven (0.4%) patients had temporary treatment discontinuation and 2 (0.1%) patients had a dose reduction associated with vision disorder. There were no permanent discontinuations associated with vision disorder for any of the 1722 patients treated with crizotinib. In clinical studies with crizotinib (n=1722), Grade 4 visual field defect with vision loss has been reported in 4 (0.2%) patients. Optic atrophy and optic nerve disorder have been reported as potential causes of vision loss (see section 4.4).
Based on the Visual Symptom Assessment Questionnaire (VSAQ-ALK), patients treated with crizotinib in Study 1007 and Study 1014 reported a higher incidence of visual disturbances compared to patients treated with chemotherapy. The onset of vision disorders generally started within the first week of drug administration. The majority of patients on the crizotinib arm in randomised Phase 3 Studies 1007 and 1014 (>50%) reported visual disturbances; which occurred at a frequency of 4 to 7 days each week, lasted up to 1 minute, and had mild or no impact (scores 0 to 3 out of a maximum score of 10) on daily activities as captured by the VSAQ-ALK questionnaire. 14 An ophthalmology substudy using specific ophthalmic assessments at specified time points was conducted in 54 patients with NSCLC who received crizotinib 250 mg twice daily. Thirty-eight (70.4%) of the 54 patients experienced an Eye Disorders System Organ Class treatment-emergent all causality adverse event of which 30 patients had ophthalmic examinations. Of the 30 patients, an ophthalmic abnormality of any type was reported in 14 (36.8%) patients and no ophthalmic finding was seen in 16 (42.1%) patients. The most common findings concerned slit lamp biomicroscopy (21.1%), fundoscopy (15.8%) and visual acuity (13.2%). Pre-existing ophthalmic abnormalities and concomitant medical conditions which could be contributory to ocular findings were noted in many patients, and no conclusive causal

relationship to crizotinib could be determined. There were no findings related to aqueous cell count and anterior chamber aqueous flare assessment. No visual disturbances associated with crizotinib appeared to be related to changes in best corrected visual acuity, the vitreous, the retina, or the optic nerve. In patients with new onset of Grade 4 visual loss, crizotinib treatment should be discontinued and ophthalmological evaluation should be performed. Ophthalmological evaluation is recommended if vision disorder persists or worsens in severity.

Nervous system effects
All-causality neuropathy was experienced by 435 (25%) out of 1722 patients treated with crizotinib. Dysgeusia was also very commonly reported in these studies, and was primarily Grade 1 in severity.

Renal cyst
All-causality complex renal cysts were experienced by 52 (3%) of 1722 patients treated with crizotinib. Local cystic invasion beyond the kidney was observed in some patients. Periodic monitoring with imaging and urinalysis should be considered in patients who develop renal cysts.

Neutropenia and leukopenia
Across studies in patients with either ALK-positive or ROS1-positive advanced NSCLC (n=1722), Grade 3 or 4 neutropenia was observed in 212 (12%) patients treated with crizotinib. Median time to onset of any grade neutropenia was 89 days. Neutropenia was associated with dose reduction or permanent treatment discontinuation for 3% and <1% of patients, respectively. Less than 0.5% of patients experienced febrile neutropenia in clinical studies with crizotinib. Across studies in patients with either ALK-positive or ROS1-positive advanced NSCLC (n=1722), Grade 3 or Grade 4 leukopenia was observed in 48 (3%) patients treated with crizotinib. Median time to onset of any grade of leukopenia was 85 days. Leukopenia was associated with a dose reduction for <0.5% of patients, and no patients permanently discontinued crizotinib treatment associated with leukopenia. In clinical studies of crizotinib in patients with either ALK-positive or ROS1-positive advanced NSCLC, shifts to Grade 3 or 4 decreases in leukocytes and neutrophils were observed at frequencies of 4% and 13%, respectively. Complete blood counts including differential white blood cell counts should be monitored as clinically indicated, with more frequent repeat testing if Grade 3 or 4 abnormalities are observed, or if fever or infection occurs.

<u>Summary of the safety profile for entrectinib and crizotinib</u>
The safety of entrectinib has been evaluated in 504 patients in clinical studies [31]. The most common serious adverse drug reactions were: lung infection, dyspnoea , cognitive impairment, and pleural effusion. The most common adverse drug reactions (≥20%) with entrectinib were: fatigue, constipation, dysgeusia, oedema, dizziness, diarrhoea, nausea, dysaesthesia, dyspnoea, anaemia, increased weight, increased blood creatinine, pain, cognitive disorders, vomiting, cough, and pyrexia.

The safety for crizotinib has been evaluated in 1722 patients [10]. The most common serious adverse drug reactions were: Hepatotoxicity, ILD/pneumonitis, neutropenia, and QT interval prolongation. The most common adverse drug reactions (≥25%) with crizotinib were: Vision disorder, nausea, diarrhoea, vomiting, oedema, constipation, elevated transaminases, fatigue, decreased appetite, dizziness, and neuropathy.

EMAs conclusion on safety

In EMAs assessment of the safety of entrectinib it was stated that although the safety database of the claimed indications was of limited extent, the safety profile was considered overall manageable. Safety data for adolescents was deemed to be limited but the safety profile was similar to the overall entrectinib safety profile. The recorded grade ≥3 events in adolescents included neutropenia and headache. In view of the conditional MA, the MAH should submit the results of an interim safety and efficacy analysis of the NTRK-efficacy-evaluable adult and pediatric patients including adolescents that are available as per integrated statistical analysis plan.

In EMAs assessment of the safety of crizotinib in the variation assessment report for ROS1 from 2016 (n=53) it was concluded that no new safety signals were identified from patients with ROS1-positive NSCLC. The reported AEs and laboratory abnormalities were consistent with the established safety profile as described in the current Pfizer reference product label information for crizotinib. The safety profile of crizotinib in the 53 patients with ROS1-positive NSCLC in PROFILE 1001 was consistent with the known overall crizotinib safety profile.

Conclusion on the narrative description of the safety profiles

In this narrative comparison of entrectinib and crizotinib it can be concluded, that the safety profiles of entrectinib and crizotinib are comparable. Crizotinib has a longer follow-up period and has a longer time on market, and therefore the safety population is larger. However when looking at the crizotinib studies with ROS1-positive patients, the safety reporting is often sparsely reported and not detailed in the updated publications. Experiences from the ALK population in crizotinib shows higher reported frequencies in grade 3-5 AEs than seen in the ROS1 population.

Based on the presented data, it seems that patients experience more grade 3-4 AEs on entrectinib, but more often have AEs leading to discontinuation or death on crizotinib. For AEs leading to discontinuations there is a 8.9% difference in favour of entrectinib and for AEs leading to deaths the difference is 11.4% in favour of entrectinib. This suggests entrectinib having more grade 3-4 AEs, but that they are more manageable than crizotinib therefore leading to less discontinuations and deaths.

7.1.9 Quality of life - important outcome

The scientific committee requests data on the following parameter for quality of life (QoL) with a clinically meaningful average change over time at 10 points. No indirect comparisons were available for this outcome.

Narrative comparison

PRO data was only evaluated in the STARTRK-2 study and results have only been published in the EPAR for the datacut of the 30th of May 2018 [2]. The STARTRK-2 population comprised 37 patients of the 53 patients included in the integrated analysis.

All patients completed the QLQ-C30 and the QLQ-LC13 questionnaire on cycle 1 day 1 and answered at least 1 question on an onstudy timepoint thereafter. The number of patients with evaluable QLQ-C30 and QLC-

LC13 results at baseline were 34 (91.9%) and 33 (89.2%) respectively. Completion rates for both questionnaires remained above 80% at most study visits but was 42% at the EOT (End of Treatment) visit.

At baseline, patients reported moderate-to-high functioning scores for QLQ-C30 (global health status [57.84], physical functioning [68.87], role functioning [60.29], and cognitive functioning [81.86]). During treatment with entrectinib patients tended to either maintain or improve on high baseline health-related quality of life (mean changes from 37.50-11.74 on global health status). Patients continued to report moderate-to-high scores for functional scales (e.g. physical functioning, role functioning, and cognitive functioning), at most study visits with a trend towards clinical improvement. An exception to this was cognitive functioning, which trended towards worsening at specific timepoints that were above the clinical meaningful threshold of 10 points (worst mean change score was -41.76 at cycle 22 day 1).

In terms of the QLQ-LC13 questionnaire, patients tended to report moderate symptom burden at baseline (chest pain [mean score=17.17], dyspnea [mean score=38.05]), with trends towards immediate meaningful improvement. Severe cough was reported at baseline (mean score of 44.44), followed by immediate meaningful improvement (mean change from baseline score of -17.86 on cycle 2 day 1).
No PRO or QoL data was collected in the PROFILE 1001, AcSé or METROS trials [3,5,7]. HRQoL was measured in both OX-ONC and EUCROSS using QLQ-C30 and QLQ-LC13 [4,6]. None of the studies reported their exact baseline QoL measurements which makes the direct comparability limited and results difficult to interpret.

In both the OX-ONC trial and the EUCROSS trial, the numerical changes in mean global EORTC QLQ-C30 scores were not reported. Instead a graphical representation could be found in the supplementary appendices of both articles. In both articles, QoL is reported for the first 20 cycles in OX-ONC and for the first 24 cycles in EUCROSS [4,6]. For the OX-ONC trial, QLQ-C30 was measured on 122 patients with QoL data on 68 patients at the last measurement at cycle 20. The baseline QLQ-C30 scores were not reported. The graph showed changes compared to the baseline global QoL standardized score. The mean global QoL scores increased to approximately 7.1 points from baseline in cycle 3 before stabilizing at approximately 4-5 points higher than the baseline up until cycle 20. The improvement was stated to be statistically significant for cycle 3-5, 7, and 10. From cycles 2-20 most patients had either improved their global QoL during therapy (≥10 point improvement from baseline; 30.4%-37.0%) or stable (< 10 point change from baseline; 38.4%-46.8%).

In the EUCROSS trial, QLQ-C30 was measured on 33 patients. The baseline QLQ-C30 scores were approximately 57. The mean global scores were found to improve slightly during the cause of treatment. A large improvement was seen between cycles 3 and 4 where the mean global score increased to approximately 67. The mean global scores remained stable from cycle 5 up until cycle 24 with values varying between approximately 70-75. The highest measured mean global score was seen after cycle 24 at approximately 80. At this point in time, only 9 of the 33 patients had their QoL measured.

Conclusion
Overall the data does not suggest differences in QoL between the two treatments. The limited QoL data reported and the lack of direct comparative analyses between the two treatments makes it difficult to compare the efficacy on QoL between the two treatments.

8 Other considerations

8.1 Effect of entrectinib on treatment lines

The scientific committee requested information on how the implementation of entrectinib in clinical practice will affect later treatment lines in regards to type, duration and expected effect.

In general, about 35% of patients did not receive any other prior systemic treatment in the metastatic setting [2]. Treatment with entrectinib was allowed to continue after disease progression if the patient was perceived by the investigator to derive clinical benefit, which occurred in up to half of the patients. However, based on available data it is not possible to evaluate the benefit of post-progression treatment with entrectinib.

In a publication on ALKA and STARTRK-1 by Drilon et al. from 2017, it was found that no responses were observed in the 6 patients with recurrent gene rearrangements involving ROS1, who had previously received a ROS1 inhibitor (crizotinib) prior to entrectinib [36]. Additionally, the integrated analysis reported a total of 27 subjects who received entrectinib after other ROS1 inhibitors, of which only 3 responded (3/27=11.1%) [2]. These 27 ROS1-positive NSCLC patients previously treated with crizotinib (9 in STARTRK-1 and 18 in STARTRK-2) included 19 patients who previously experienced CNS-only progression and 8 overall systemic progression while on crizotinib [2]. A total of 2 responses were observed among the 19 patients with CNS-progression as the sole site of progression (RR 10.5%), and 1 response among 8 patients with overall systemic progression (RR 12.5%) [2]. This information implies that post-crizotinib or treatment after other ROS1 targeted treatments is not effective. Both entrectinib and crizotinib have been approved as a first line treatment. Currently second-line ROS1 inhibitors are in clinical development, but not approved. It would therefore be anticipated that ROS1-positive patients progressing with secondary mutations in ROS1 or other targets on their first-line ROS1 TKI treatment, would be able to either participate in a clinical study; receive chemotherapy or experimental treatment; or best supportive care after their first line ROS1 TKI treatment. There is insufficient available data to conclude anything on treatment based on specific resistance mutation.

In the entrectinib studies, there is information on efficacy based on the line of therapy. Efficacy is generally preserved through later lines after chemotherapy, and across treatment types (chemotherapy, immunotherapy, radiation and more), although the sample size drops somewhat post second line [2]. The efficacy per line of treatment is not reported in some of the crizotinib trials [3-5].EUCROSS reported that number of prior treatment lines had no detectable effect on ORR, PFS and OS, and in METROS they only reported as second-line or later treatmen [6,7].

The entrectinib studies as well as the PROFILE 1001 studies were analysed for specific fusion partners with ROS1 but no clear differences, and low sample sizes, makes it difficult to interpret the data and there is no clear difference on individual fusion partners [2,3].

In conclusion, ROS1 TKI treatment should be given up front, or after chemotherapy if the rearrangement is detected in later lines. The data suggest that entrectinib efficacy drops after prior use of crizotinib, with no data available for crizotinib. Second line post ROS1 TKI treatment is therefore not supported by data currently.

8.2 Objective response rate

The scientific committee requests data on the ORR of entrectinib and crizotinib as a perspective in the categorization.

Narrative comparison

For the integrated analysis (either BICR or IA) and intracranial ORR (IC-ORR) has been reported [2]. In the initial updated integrated analysis (n=94) entrectinib has an ORR of 73.4% (95% CI, 63.3, 82.0). 7 patients (7.4%) had CR, 62 patients (66.0%) had PR and 7 (7.4%) had stable disease. 10 (10.6%) patients had disease progression, 0 patients had non-complete/partial responses and for 8 (8.5%) response was missing or unevaluable The newest integrated analysis (n=161) for entrectinib has an ORR of 67.1 % (95% CI, 59.3-74.3) by BICR (entrectinib EPAR). 14 patients (8.7%) had CR, 94 patients (58.4%) had PR and 14 (8.7%) had stable disease. 15 (9.3%) patients had disease progression, 10 (6.2%) patients had non-complete/partial responses and for 14 (8.7%) response was missing or unevaluable. For patients in the integrated analysis (n=161), 46 had CNS disease at baseline. IC-ORR was 52.2% (24/46) (95%CI 36.95, 67.1), which includes 8 CR (17.4%). Of those, 24 had measurable CNS disease by BIRC, in whom IC-ORR was 79.2% (19 responders) (95%CI 57.85, 92.9); IC-DOR in the 19 responders was 12.9 months (95%CI 6.8, 22.1).

In the PROFILE 1001 trial, the ORR for crizotinib in 53 patients was 72% (95% CI, 58-83) and included 6 confirmed CR, 32 confirmed PR and 10 with stable disease [3]. ORRs were consistent across different patients subgroups. For the 127 patients in the OX-ONC trial ORR by IRR was 71.7 % (95% CI, 63.0-79.3) with 17 CR and 74 PR [4]. ORR was similar independent of prior lines of therapy. ORR was similar in patients with CNS metastasis at 73.9 % (95% CI, 51.6-89.8), but had a shorter median PFS (please see CNS progression section 7.1.3.). In the 36 patients in the AcSé trials ORR was 47.2% (95 % CI, 30.4-64.5) at two cycles [5]. After two cycles of crizotinib 17 patients had partial response (PR) and after 4 cycles 21 patients had tumour responses (1 complete response (CR) and 20 PR). In the EUCROSS trial ORR determined by local assessment was 70% (95% CI, 51-85; n=21 of 30 patients) and ORR determined by IRR was 73% (95% CI, 54-88; 22 of 30 patients) [6]. For the six patients (21%) with CNS metastasis at baseline had similar ORR, but a shorter median PFS (please see CNS progression section 7.1.3.). 65% (95% CI, 44-82) ORR was reported in the METROS trial [7]. One patient (4%) had CR, 16 (61%) had PR and six patients (23%) obtained stable disease. Median DOR was 21.4 months (95% CI, 12.7-30.1).

In general the reported ORRs were similar ranging from 65%-73.4%, excluding the AcSé trial reporting the lowest ORR at only 47.2%. In none of the included crizotinib trials reported IC-ORR and it is therefore not possible to say anything regarding crizotinibs IC-ORR. Entrectinib showed IC-ORR at 52.2% and 79.2% in patients with measurable CNS disease by BIRC.

Indirect comparison

ORR for both entrectinib and crizotinib was analysed in the MAIC analysis [9]. The adjusted population and ORR clearly favor entrectinib and indicate that entrectinib may be substantially more effective than crizotinib in terms of ORR in alle three scenarios (See Table 24).

Table 24. MAIC - Objective Response Rate by BICR [9]						
Intervention	Scenario	Number of patients (sum of weights)	Number of events	% with ORR	Odds Ratio (95% CI)	Difference (entrectinib vs crizotinib, %)
Crizotinib	Original	53	38	71.7		
Entrectinib	Original	53	41	77		
Entrectinib	Reweighted (Scenario 1)	(40.0)	32.7	81.9	2.74 (1.4,8.6)	10.2
Entrectinib	Reweighted (Scenario 2)	(42.6)	34.6	81.3	2.6 (1.3-7.7)	9.6
Entrectinib	Reweighted (Scenario 3)	(44.9)	35.9	80.0	2.4 (1.2-7.0)	8.3

Conclusion

Based on the indirect comparison of ORRs described above, entrectinib has a higher objective response rate than crizotinib. Both entrectinib and crizotinib have shown similar ORR in the narrative comparison of patients with and without CNS metastasis. IC-ORR have not been reported in any of the crizotinib studies and it was therefore not possible to compare this endpoint for entrectinib and crizotinib.

Table 25. (Intracranial-)Objective Response Rate of entrectinib and crizotinib		
	Drug (study population, n)	(IC-)ORR (CI 95%, %)
Narrative comparison	**Entrectinib** (Integrated analysis, n=161)	67.1 (59.3-74.3)[b]
		52.2 (37.0-67.1)(IC-ORR)[b]
	Entrectinib (Integrated analysis, n=94)	73.4 (63.3-82.0)[c]
	Crizotinib (PROFILE 1001, n=53)	72 (58-83)
	Crizotinib (OX-ONC, n=127)	71.7 (63.0-79.3)[a]

	Crizotinib (AcSé trial, n=37)	47.2 (30.4-64.5)
	Crizotinib (EUCROSS trial, n=30)	73 (54-88)[a]
	Crizotinib (METROS trial, n=26)	65 (44-82)
MAIC analysis	**Entrectinib reweighted**	Scenario 1 81.9
		Scenario 2 81.3
		Scenario 3 80.0
	Crizotinib	71.7
[a]Independent radiological review (IRR); [b]Blinded independent central review (BICR); [c]investigator assed; IC-ORR - Intracranial objective response rate		

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10 Appendices

10.1 Literature search – Inclusion and exclusion criteria and PRISMA flow diagram

Table 26. Inclusion and exclusion criteria

	Inclusion criteria	**Exclusion criteria**
Population	Adult ROS-1-positive NSCLC patients	Other populations
Intervention and comparator	Entrectinib 600 mg orally once daily and/or Crizotinib 250 mg orally twice daily	Other interventions
Outcomes	At least one relevant for protocol (OS, Treatment discontinuation due to AEs, CNS progression, PFS, AEs, QoL)	Outcomes out of PICO scope
Design	Contains prospective data Study on human patients	Retrospective, observational, review Animal study, in vitro study
Language	English, Scandinavian	Other language
Publication date	Not specified	Not specified

Table 27. Overview of excluded full text articles

Author	**Journal and year**	**Title**	**Reason**	**Search**

Shaw, A. T. et al	N Engl J Med, 2015	Crizotinib in ROS1-rearranged non-small-cell lung cancer	Replaced by publication of later datacut	PubMed/MEDLINE
Kazandjian, D. et al	Oncologist, 2016	Benefit-Risk Summary of Crizotinib for the Treatment of Patients With ROS1 Alteration-Positive, Metastatic Non-Small Cell Lung Cancer	Review	
Drilon, A. et al	Cancer Discov, 2017	Safety and Antitumor Activity of the Multitargeted Pan-TRK, ROS1, and ALK Inhibitor Entrectinib: Combined Results from Two Phase I Trials (ALKA-372-001 and STARTRK-1)	Replaced by publication of later datacut	PubMed/MEDLINE
Zhang, L. et al	Onco Targets Ther, 2019	High feasibility of cytological specimens for detection of ROS1 fusion by reverse transcriptase PCR in Chinese patients with advanced non-small-cell lung cancer	Outcomes not relevant for assessment	PubMed/MEDLINE
Chiari, R. et al	Clin Lung Cancer, 2020	ROS1-rearranged Non-small-cell Lung Cancer is Associated With a High Rate of Venous	Outcomes not relevant for assessment	PubMed/MEDLINE

		Thromboembolism : Analysis From a Phase II, Prospective, Multicenter, Two-arms Trial (METROS)		
Clark, J. et al	Future Oncol, 2020	Dose-escalation trial of the ALK, MET & ROS1 inhibitor, crizotinib, in patients with advanced cancer	Dose escalation; dose not relevant for assessment	PubMed/MEDLINE
Metha, A. et al	Lung Cancer (Auckl), 2020	Incidence of ROS1-Rearranged Non-Small-Cell Lung Carcinoma in India and Efficacy of Crizotinib in Lung Adenocarcinoma Patients	Outcomes not relevant for assessment	PubMed/MEDLINE

Figure 6. PRISMA Flow Diagram MEDLINE via PubMed

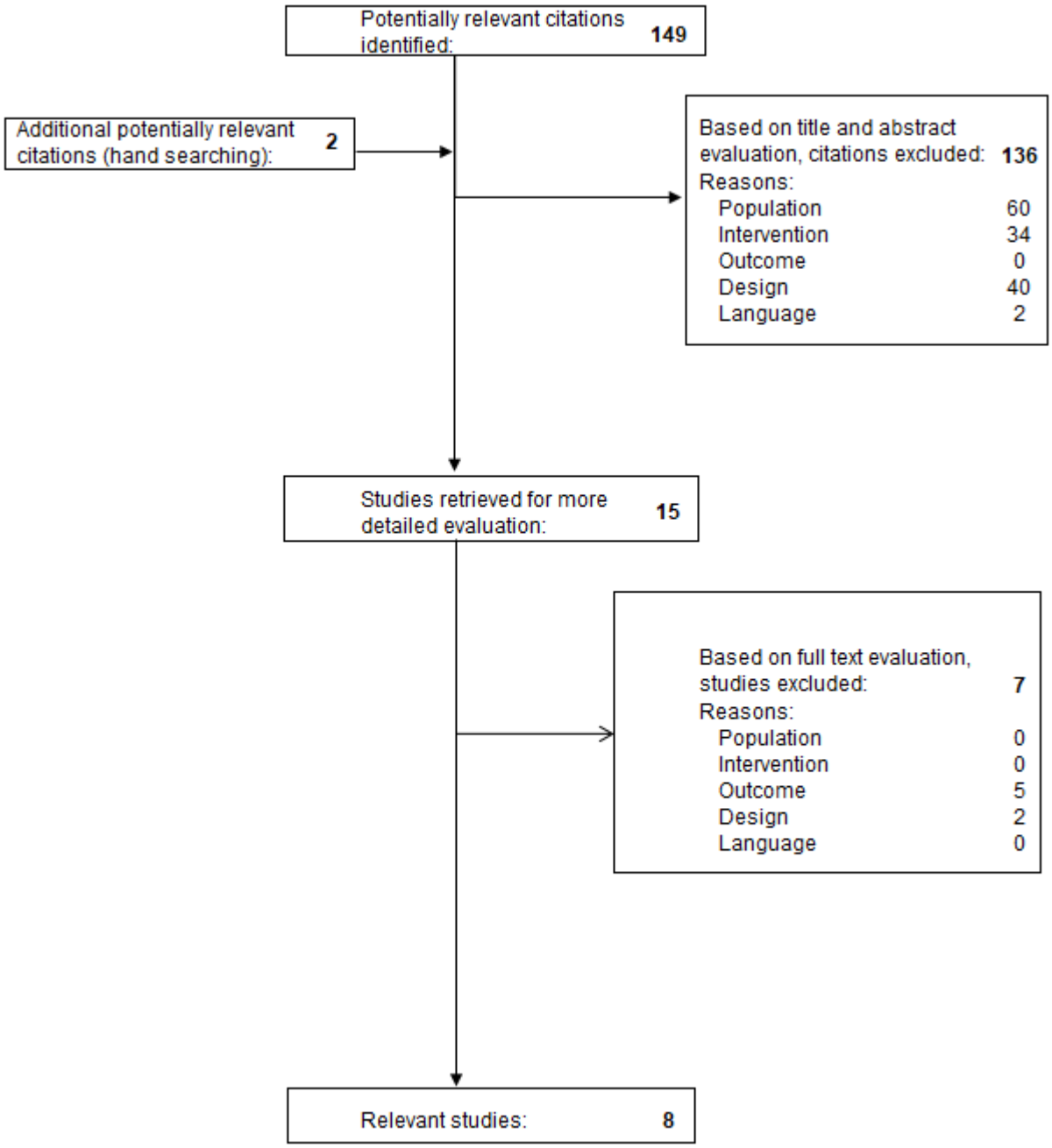
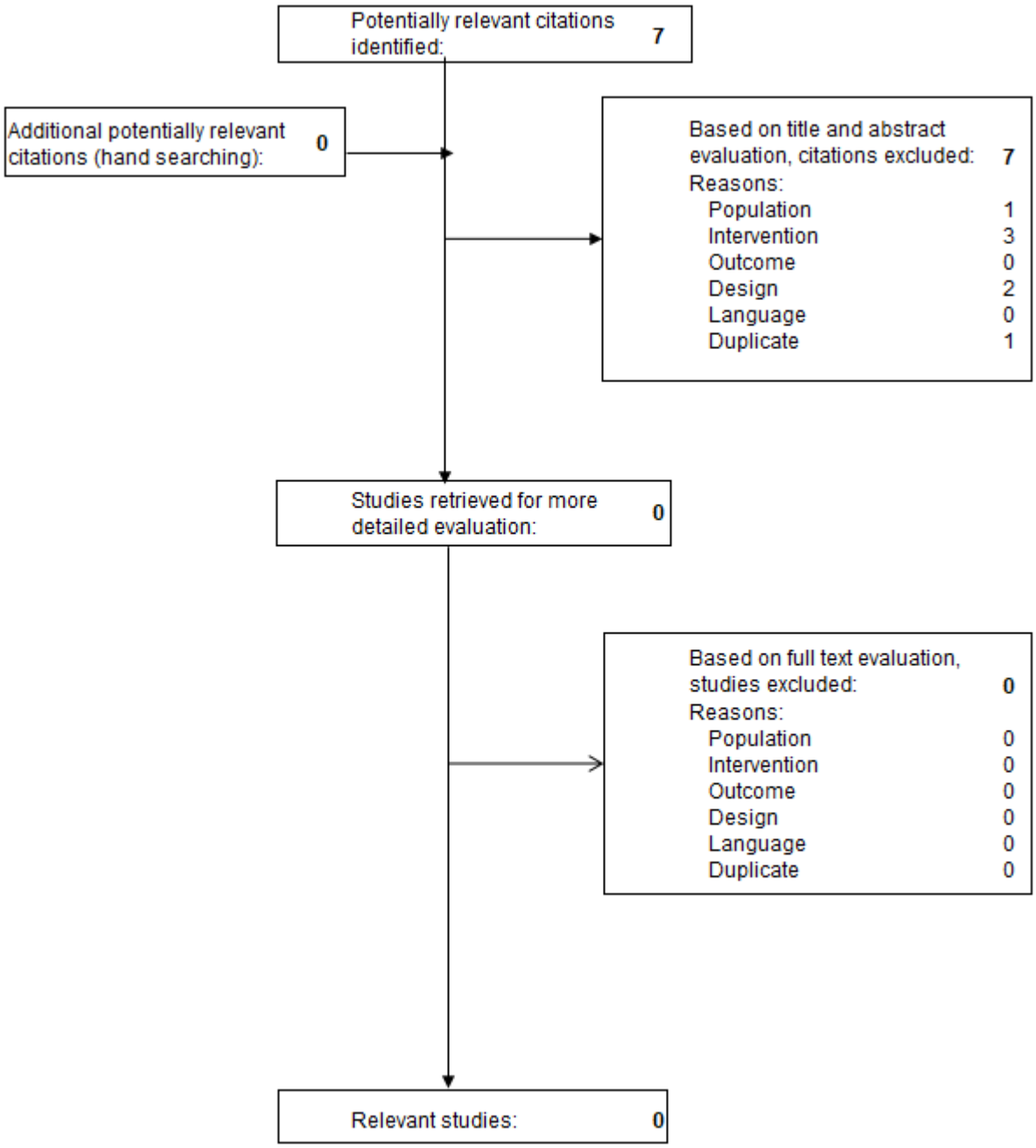


Figure 7. PRISMA Flow Diagram CENTRAL via Cochrane Library



10.2 Main characteristics of included studies

Table 28. Main study characteristics of the integrated analysis of entrectinib	
Trial name	First-in-human, phase I study of entrectinib – an oral pan-trk, ROS1, and ALK inhibitor – in patients with advanced solid tumors with relevant molecular alterations (ALKA-372-001) A Phase 1, Multicenter, Open-Label Study of Oral Entrectinib (RXDX-101) in Adult Patients With Locally Advanced or Metastatic Cancer Confirmed to be Positive for NTRK1, NTRK2, NTRK3, ROS1, or ALK Molecular Alterations (STARTRK-1) An Open-Label, Multicenter, Global Phase 2 Basket Study of Entrectinib for the Treatment of Patients With Locally Advanced or Metastatic Solid Tumors That Harbor NTRK1/2/3, ROS1, or ALK Gene Rearrangements (STARTRK-2)
NCT number	EudraCT 2012-000148-88 (ALKA-372-001) NCT02097810 (STARTRK-1) NCT02568267 (STARTRK-2)
Objective	Safety, clinical efficacy, pharmacokinetics
Publications – title, author, journal, year	Entrectinib in patients with advanced or metastatic NTRK fusion-positive solid tumours: Integrated analysis of three phase 1-2 trials. Doebele et al, The Lancet 2020 EPAR data, clinical cut-off date, 01-May-2019
Study type and design	Basket study, Dose finding
Follow-up time	Median follow-up: 20.3 months
Population (inclusion and exclusion criteria)	The integrated analysis included patients from 10 different histologies, covering both high and low frequencies. Patients received at least one dose of entrectinib (≥600 mg once daily), had measurable disease assessed by the investigator according to Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1 (regardless of line of therapy), had an ECOG PS of 2 or less, a life expectancy of at least 3 months in the phase 1 studies or at least 4 weeks in the phase 2 basket trial and adequate organ function and were TRK inhibitor naive (although previous treatment with other cancer therapies was allowed). Patients with brain metastases were included in the integrated analysis if they had previous

	treatment resulting in control of symptoms or were asymptomatic. Patients requiring steroids for their brain metastases were allowed to continue their steroid treatment, but had to have received stable or decreasing doses for at least 2 weeks before the start of entrectinib treatment. Exclusion criteria in the integrated analysis included following comorbidities: History of other previous cancer or currently active second malignancy; prolonged QTc interval; active infections; gastrointestinal disease; interstitial lung disease, interstitial fibrosis, or history of tyrosine kinase inhibitor-induced pneumonitis; or peripheral neuropathy grade 2 or worse.
Intervention	Entrectinib
Baseline characteristics	See Table 5
Primary and secondary endpoints	Primary endpoint: ● Objective response rate Secondary endpoints: ● Duration of response ● Time to response ● Clinical benefit scale ● Intracranial tumor response ● CNS progression-free survival ● Progression-free survival ● Overall survival
Method of analysis	Summary statistics with response data confidence intervals estimated using Clopper-Pearson. Time-to-event estimated using Kaplan-Meier method. Descriptive statistics for safety
Subgroup analyses	None

Table 29. Main study characteristics of PROFILE 1001

Trial name	PHASE 1 SAFETY, PHARMACOKINETIC AND PHARMACODYNAMIC STUDY OF PF-02341066, A MET/HGFR SELECTIVE TYROSINE KINASE INHIBITOR, ADMINISTERED ORALLY TO PATIENTS WITH ADVANCED CANCER
NCT number	00585195
Objective	Efficacy (response rate), Safety, PK
Publications – title, author, journal, year	Crizotinib in ROS1-Rearranged Non-Small-Cell Lung Cancer, Shaw, A. et al., N Engl J Med, 2014 Crizotinib in ROS1-rearranged advanced non-small-cell lung cancer (NSCLC): updated results, including overall survival, from PROFILE 1001. Shaw, A. et al., Ann Oncol, 2019
Study type and design	Phase I basket study
Follow-up time	The median duration of follow-up was 62.6 months
Population (inclusion and exclusion criteria)	Eligible patients had histologically confirmed, advanced NSCLC with a ROS1 rearrangement. In 49 of 50 patients (98%), ROS1 rearrangement identified using break-apart FISH, the remaining patient using a RT-PCR assay.. Other eligibility criteria included an age of at least 18 years, an Eastern Cooperative Oncology Group performance status of 0 to 2, adequate organ function, and measurable disease according to RECIST version 1.0.19
Intervention	crizotinib n=53
Baseline characteristics	See Table 5.
Primary and secondary endpoints	Primary endpoints: ● Objective response rate Secondary endpoints: ● Duration of response ● Time to first tumor response ● Progression-free survival ● Overall survival ● Probability of survival at 6, 12, 24, 36, 48 months
Method of analysis	Time-to-event using Kaplan-Meier method. Confidence intervals generated vi Brookmeyer-Crowley method. Confidence intervals for ORR estimated using binomial method based on F-distribution.

Subgroup analyses	None

Table 30. Main study characteristics of the AcSé trial	
Trial name	Phase 2 Study Assessing Efficacy and Safety of Crizotinib in Patients Harboring an Alteration on ALK, MET or ROS1 AcSé
NCT number	*02034981*
Objective	Assessing anti-tumor activity of crizotinib; efficacy and safety
Publications – title, author, journal, year	Crizotinib in c-MET- or ROS1-positive NSCLC: results of the AcSé phase II trial, Moro-Sibilot, D. et al., Ann Oncol, 2019
Study type and design	Biology driven, trans-tumoral, multicentric phase II trial
Follow-up time	Not reported - only available in graphical representation
Population (inclusion and exclusion criteria)	Inclusion: ● Male and female ≥ 1 year of age ● Unresectable locally advanced or metastatic malignant tumor of any histological type (but NSCLC with an ALK translocation) and not amenable to any other validated therapeutic option. (for pediatrics a relapse after a first well-conducted standard treatment or a situation without any standard treatment and a survival <10%). ● One proven specific alterations among ALK, MET, RON and ROS1 genes determined on the primary and/or the metastatic lesion ● Measurable disease according to RECIST 1.1 ● For patients with primary cerebral tumors (adults or children), measurable disease defined by bi-dimensional measurements : two perpendicular diameters of at least 10 mm on CT or MRI scan, outside of a previously radiated field within the last 3 months, to observe pseudoprogression ● Hematologic function (ANC ≥ $1.0x10^9$/L, platelets ≥ $75x10^9$/L, platelets ≥ $50x10^9$/L for ALCL with bone marrow involved ; platelets ≥ $100x10^9$/L for primary or secondary cerebral tumors; Hb ≥ 8g/L), renal function (creat cl ≥ 50 mL/min Cockcroft and Gault) and hepatic function (serum bilirubin ≤ 1.5x ULN unless due to Gilbert's syndrome ; ASAT and ALAT ≤ 5x ULN if liver metastasis or ≤ 3x ULN if liver metastasis with advanced fibrosis (FibroTest>0.48) or ≤ 3x ULN without liver metastasis) ● Normal values for calcium, magnesium and potassium levels ● Able to swallow and retain oral medication

	• ECOG PS of 0 to 2, or Karnofsky scale > 50 % or Lansky Play scale (< 12 years) > 50%, (for CNS tumors, the neurological deficiency due to the disease itself) • Life expectancy ≥ 3 months Exclusion: • Male and female ≥ 1 year of age • Unresectable locally advanced or metastatic malignant tumor of any histological type (but NSCLC with an ALK translocation) and not amenable to any other validated therapeutic option. (for pediatrics a relapse after a first well-conducted standard treatment or a situation without any standard treatment and a survival <10%). • One proven specific alterations among ALK, MET, RON and ROS1 genes determined on the primary and/or the metastatic lesion • Measurable disease according to RECIST 1.1 • For patients with primary cerebral tumors (adults or children), measurable disease defined by bi-dimensional measurements : two perpendicular diameters of at least 10 mm on CT or MRI scan, outside of a previously radiated field within the last 3 months, to observe pseudoprogression • Hematologic function (ANC ≥ $1.0x10^9$/L, platelets ≥ $75x10^9$/L, platelets ≥ $50x10^9$/L for ALCL with bone marrow involved ; platelets ≥ $100x10^9$/L for primary or secondary cerebral tumors; Hb ≥ 8g/L), renal function (creat cl ≥ 50 mL/min Cockcroft and Gault) and hepatic function (serum bilirubin ≤ 1.5x ULN unless due to Gilbert's syndrome ; ASAT and ALAT ≤ 5x ULN if liver metastasis or ≤ 3x ULN if liver metastasis with advanced fibrosis (FibroTest>0.48) or ≤ 3x ULN without liver metastasis) • Normal values for calcium, magnesium and potassium levels • Able to swallow and retain oral medication • ECOG PS of 0 to 2, or Karnofsky scale > 50 % or Lansky Play scale (< 12 years) > 50%, (for CNS tumors, the neurological deficiency due to the disease itself) • Life expectancy ≥ 3 months
Intervention	Crizotinib Patients will receive oral crizotinib, daily continuously, until progression or unacceptable toxicity develops. -250 mg twice daily for adults ≥ 18 years of age • 280 mg/m² twice daily for children and adolescents aged from 1 to 17 (except ALCL).

	• 165 mg/m² twice daily for ALCL patients aged from 1 to 17.
Baseline characteristics	See Table 5.
Primary and secondary endpoints	Primary endpoints: • Objective response Secondary endpoints: • Safety profile • Disease control rate • Response duration • Progression-free survival • Overall survival
Method of analysis	Time-to-event measured via Kaplan-Meier method with Rothman confidence intervals
Subgroup analyses	None

Table 31. Main study characteristics of OX-ONC

Trial name	Phase II Safety and Efficacy Study of Crizotinib in East Asian Patients With ROS1 Positive, ALK Negative Advanced NSCLC
NCT number	*01945021*
Objective	To assess treatment effectiveness and safety of oral crizotinib administered to East Asian patients with Advanced Non-Small Cell Lung Cancer (NSCLC) that is confirmed to be positive for a ROS1 positive gene mutation (translocation or inversion) and confirmed negative for an ALK mutation
Publications – title, author, journal, year	Phase II Study of Crizotinib in East Asian Patients With ROS1-positive Advanced Non-Small-Cell Lung Cancer, Wu, Y. et al., J Clin Oncol, 2018
Study type and design	Open-label, Multinational, Single-arm, Multicenter Phase II Clinical Trial
Follow-up time	Median follow-up: 21.4 months
Population (inclusion and exclusion criteria)	Inclusion: • Histologically or cytologically proven diagnosis of NSCLC that is locally advanced or metastatic • treatment-naïve or have received no more than 3 systemic treatment regimen(s) • Positive for translocation or inversion events involving the ROS1 gene

	● Negative for translocation or inversion events involving the ALK gene ● Patients with brain metastases are eligible if asymptomatic, or if treated, must be neurologically stable for at least 2 weeks and are not taking any contraindicated medications ● Any prior treatment (chemotherapy, radiation [except for palliative], or surgery) must have been completed at least 2 weeks prior to initiation of study medication ● At least 1 measurable tumor lesion as per RECIST v1.1 ● Female or male, 18 years of age or older ● ECOG performance status 0 to 1 ● Adequate organ function ● Signed and dated informed consent ● Willingness and ability to comply with scheduled visits, treatment plans, laboratory tests, and other study procedures, including completion of the PRO measures ● Agree to use effective contraception during the study period and for at least 90 days after completion of the study treatment Exclusion: ● Current treatment on another therapeutic clinical trial ● Prior therapy specifically directed against ALK or ROS1 fusion genes ● Spinal cord compression unless treated with the patient attaining good pain control and stable or recovered neurologic function, carcinomatous meningitis, or leptomeningeal disease ● known interstitial fibrosis or interstitial lung disease ● myocardial infarction, severe/unstable angina, coronary/peripheral artery bypass graft, congestive heart failure, or cerebrovascular accident including transient ischemic attack within 3 months prior to start of study treatment ● Ongoing cardiac dysrhythmias of NCI CTCAE v4.03 Grade >/=2, uncontrolled atrial fibrillation of any grade, or QTc >470 msec ● Pregnant or breast feeding ● Use of drugs or foods that are known potent CYP3A4 inhibitors or inducers ● Use of other anti-cancer drugs including traditional Chinese medicine on the SFDA list ● Evidence of active malignancy within last 3 years
Intervention	Crizotinib

Baseline characteristics	See Table 5.
Primary and secondary endpoints	Primary endpoints: ● ORR Secondary endpoints: ● Duration of response ● Time to first response ● Disease control rate ● Progression-free survival ● Overall survival ● Type, incidence, severity, seriousness and relationship to study medications of adverse events and any laboratory abnormalities ● Number of patients with a shift in hematology laboratory results from grade </=2 to Grade 3 or Grade 4 ● Number of patients with a shift of chemistry laboratory results from grade </= 2 to Grade 3 or Grade 4 ● Change from baseline scores on the european organization for research and treatment of cancer (EORTC) quality of life (QoL) questionnaire core 30 (QLQ-C30) ● Change from baseline scores on the european organization for research and treatment of cancer (EORTC) quality of life questionnaire lung cancer module 13
Method of analysis	ORR (percentage of patients with a best overall response of a confirmed complete or confirmed partial response) and DCR (percentage of patients with a confirmed complete or confirmed partial response or stable disease) by IRR were evaluated in the response-evaluable population, and the 95% CIs were calculated using the exact method on the basis of the *F*-distribution. OR was summarized by Kaplan-Meier method and descriptive statistics; TTR was summarized using descriptive statistics only. DOR and TTR were assessed only in the subgroup of responder-patients in the response-evaluable population. In the safety analysis population, the Kaplan-Meier method was used to estimate median PFS and OS; two-sided 95% CIs are provided. PRO end points were analyzed in the PRO-evaluable population (all patients in the safety analysis population who completed a baseline and one or more post–baseline PRO assessments)
Subgroup analyses	None

Table 32. Main study characteristics of EUCROSS	
Trial name	EUCROSS: European Trial on Crizotinib in ROS1 Translocated Lung Cancer (EUCROSS)
NCT number	*02183870*
Objective	To evaluate the efficacy and safety of crizotinib in patients with adenocarcinoma of the lung harbouring ROS1 translocations
Publications – title, author, journal, year	Safety and Efficacy of Crizotinib in Patients With Advanced or Metastatic ROS1-Rearranged Lung Cancer (EUCROSS): A European Phase II Clinical Trial, Michels, S. et al., J Thorac Oncol, 2019
Study type and design	Multicenter, single-arm phase II trial
Follow-up time	Median follow-up: 20.6 months
Population (inclusion and exclusion criteria)	Inclusion: ● Patients with adenocarcinoma of the lung that is locally advanced or metastatic independent from the number of prior lines of therapy, i.e. including non-pretreated patients (UICC stage IIIB or IV) ● Positive for ROS1 translocation by central FISH-testing ● Ability to swallow pills ● Age > 18 years ● ECOG PS 0 to 2 ● Life expectancy of at least 12 weeks ● Disease measurable per Response Evaluation Criteria in Solid Tumors (RECIST, version 1.1) ● Any prior treatment (chemotherapy, radiation or surgery) must have been completed at least 2 weeks prior to initiation of study medication ● Adequate bone marrow, liver and renal function as assessed by the following laboratory requirements to be conducted within 14 days prior to screening: ● Hemoglobin ≥ 8.0 g/dL ● Absolute neutrophil count (ANC) ≥ 1,000 /mm3 ● Platelet count ≥ 50 000/µL

	• Total bilirubin ≤ 2 x upper limit of normal (ULN) • Alanine aminotransferase (ALT), aspartate aminotransferase (AST) and alkaline phosphatase (AP) ≤ 2,5 x ULN or ≤ 5 x ULN in case of liver involvement • PT-INR/PTT ≤ 1.5 x ULN • Serum creatinine ≤ 2 times ULN • Calculated creatinine clearance (CLcr) ≥ 40 ml/min (Cockcroft-Gault formula) • Written informed consent • Negative serum pregnancy test within 3 days prior to start of dosing premenopausal women. Women of non-childbearing potential may be included without serum pregnancy test if they are either surgically sterile or have been postmenopausal for ≥ 1 year. Exclusion: • Previous treatment with specific ALK or ROS1 inhibitors • Current treatment within another therapeutic clinical trial • Other history of ongoing malignancy that would potentially interfere with the interpretation of efficacy (early stage or chronic disease is allowed if not requiring active therapy or intervention and being under control) • Pregnancy or breastfeeding • Use of drugs or foods that are known potent CYP3A4 inhibitors, including but not limited to atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, troleandomycin, voriconazole and grapefruit or grapefruit juice • Use of drugs that are known potent CYP3A4 inducers, including but not limited to carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin, and St. John's wort • Use of drugs that are CYP3A4 substrates with narrow therapeutic indices, including but not limited to dihydroergotamine, ergotamine, pimozide, astemizole, cisapride, and terfenadine • Active CNS metastases. Patients with brain metastasis are eligible if asymptomatic for ≥ 14 days before starting study medication and off corticosteroids.

	• History of or known carcinomatous meningitis or leptomeningeal disease • Known diagnosis of HIV, active hepatitis B and/or C (testing is not mandatory) • Any person being in an institution on assignment of the respective authority against his/her own will • Any medical, mental or psychological condition which in the opinion of the investigator would not permit the patient to complete the study or understand the patient information • Ongoing cardiac dysrhythmias of CTCAE grade ≥2, uncontrolled atrial fibrillation of any grade or QTcF interval > 470ms • Patients with known interstitial fibrosis or interstitial lung disease • Any of the following within 3 months prior to first crizotinib administration: Myocardial infarction, severe/unstable angina, symptomatic congestive heart failure, cerebrovascular accident or transient ischemic attack
Intervention	Crizotinib 250 mg twice daily
Baseline characteristics	See Table 5.
Primary and secondary endpoints	Primary endpoints: • ORR Secondary endpoints: • Progression-free survival (PFS) • Overall survival (OS) • Duration of response (DR) • Time to tumor response • Disease control rate • Safety/adverse events and tolerability in all patients treated with crizotinib • Patient reported outcomes (PRO) • Objective response rate (ORR)
Method of analysis	Time-to-event data were summarized using a Kaplan-Meier estimator. The statistical significance for differences in time-to-event endpoints between strata

	was calculated using the log-rank test and for differences in proportions using Fischer's exact test. AEs were described by the frequency of patients exhibiting a specific event and by grade. AEs were summarized according to the Medical Dictionary for Regulatory Activities preferred term. cores collected within the HRQoL questionnaires were tested using a repeat measures model for linear time trends and summarized by mean and standard-error per time-point (2-cycle intervals until cycle 24 and aggregated as one timepoint thereafter) and analyzed for time trends using a repeat measures model.
Subgroup analyses	Response-evaluable population Sequencing-positive population

Table 33. Main study characteristics of METROS

Trial name	Crizotinib in Pretreated Metastatic Non-small-cell Lung Cancer With MET Amplification or ROS1 Translocation (METROS) (METROS)
NCT number	*02499614*
Objective	Investigating activity of crizotinib in patients harboring MET or ROS1 alterations
Publications – title, author, journal, year	Crizotinib in MET-Deregulated or ROS1-Rearranged Pretreated Non-Small Cell Lung Cancer (METROS): A Phase II, Prospective, Multicenter, Two-Arms Trial, Landi, L. et al., Clin Cancer Res, 2019
Study type and design	Phase II, prospective, two arms, parallel, non comparative study
Follow-up time	Median follow-up: 21 months

Population (inclusion and exclusion criteria)	Inclusion: ● Histologically confirmed diagnosis of NSCLC ● Availability of tumor tissue for ROS1 and MET analyses ● Patient positive for ROS1 translocation or MET amplification ● At least one radiological measurable disease according to RECIST criteria (Response Evaluation Criteria in Solid Tumors) ● At least 1 previous standard chemotherapy regimen ● Performance status 0-2 (ECOG) ● Patient compliance to trial procedures ● age ≥ 18 years ● Written informed consent ● Adequate BM function (ANC ≥ 1.5x109/L, Platelets ≥ 100x109/L, HgB > 9g/dl) ● Adequate liver function (bilirubin <G2, transaminases no more than 3xULN/<5xULN in present of liver metastases). ● Normal level of alkaline phosphatase and creatinine. ● If female: childbearing potential either terminated by surgery, radiation, or menopause, or attenuated by use of approved contraceptive method [intrauterine contraceptive device (IUD), birth control pills, or barrier device] during and for ninety(90) days after end of treatment. Exclusion: ● No tumor tissue available or patient negative for ROS1 translocation or MET amplification ● Absence of any measurable lesion ● For ROS1+ patients: Previous therapy with crizotinib or any anti-ALK agent ● For MET amplified patients: Evidence of MET amplification in tumor tissue collected in EGFR mutant patient at time of EGFR-TKI acquired resistance occurrence. An EGFR mutant patient is eligible if MET amplification is detected in a tumor specimen collected before starting an EGFR-TKI ● No previous chemotherapy ● Concomitant radiotherapy or chemotherapy. ● Previous radiotherapy on the target lesion(s). If all sites were included in radiotherapy fields patient is eligible only if there is evidence of progressive disease after completion of radiotherapy. ● Symptomatic brain metastases ● Diagnosis of any other malignancy during the last 5 years, except for in situ carcinoma of cervix uteri and squamous cell carcinoma of the skin ● Pregnancy or lactating

	• Other serious illness or medical condition potentially interfering with the study
Intervention	Crizotinib 250 mg twice daily
Baseline characteristics	See Table 5.
Primary and secondary endpoints	Primary endpoints: • Response rate Secondary endpoints: • Progression-free survival (PFS) • Overall survival (OS) • Toxicity analysis: Incidence of grade 3-4 toxicity • Correlation with additional tumor biomarkers in tumor tissue or blood • Response according to different levels of ROS1 translocation or MET amplification
Method of analysis	Associations among factors were evaluated with the $\chi 2$ test while differences in distribution of quantitative variables were measured with the Mann–Whitney test. Confidence interval (95%) for ORR was calculated according to the exact method. PFS and OS were calculated from the date of starting therapy to the date of first evidence of either disease progression or death of the patient in the absence of documented disease progression (PFS), or death for any cause (OS). Patients without an event were censored at the date of last follow-up. Survival times were estimated using Kaplan–Meier analysis and expressed as medians with corresponding two-sided 95% confidence intervals (CI). Differences between curves were evaluated using the log-rank test
Subgroup analyses	MET-amplification Exon 14-mutated

Table 34. Main study characteristics of Flatiron comparative analysis	
Trial name	Time-to-treatment discontinuation (TTD) and real-world progression-free survival (rwPFS) as endpoints for comparative efficacy analysis between entrectinib trial and crizotinib real-world ROS1 fusion-positive (ROS1+) NSCLC patients
NCT number	*N/A*

Objective	To compare the efficacy of entrectinib as reported in clinical trials to crizotinib, the current standard of care, using retrospective electronic health records (EHR) from a real-world cohort of patients with ROS1+ NSCLC.
Publications – title, author, journal, year	Time-to-treatment discontinuation (TTD) and real-world progression-free survival (rwPFS) as endpoints for comparative efficacy analysis between entrectinib trial and crizotinib real-world ROS1 fusion-positive (ROS1+) NSCLC patients; Doebele et al; journal of clinical oncology; 2019
Study type and design	comparative efficacy analysis between entrectinib trial and crizotinib real-world ROS1 fusion-positive (ROS1+) NSCLC patients.
Follow-up time	15.5 months for entrectinib
Population (inclusion and exclusion criteria)	Inclusion/exclusion: ● Patients treated with entrectinib or crizotinib as the first-line ROS1 TKI ● No previous TKI inhibitor allowed, but other prior therapy permitted ● Patients with CNS metastases at diagnosis/recruitment were allowed ● In the entrectinib arm, only patients with ECOG PS 0–2 were included ● In the entrectinib arm, only patients with ECOG PS 0–2 were included ● Patients tested and positive for concomitant oncogene mutations (e.g. KRAS or EGFR) were excluded. ● Index date was the date of treatment initiation.
Intervention	Entrectinib and Crizotinib
Baseline characteristics	See table 6.
Primary and secondary endpoints	Primary endpoints: ● Time to treatment discontinuation Secondary endpoints: ● Progression-free survival (PFS)(real-world PFS for the crizotinib arm, based on clinician documentation of tumor growth, and clinical trial PFS for the entrectinib arm) ● Overall survival (OS)
Method of analysis	Time-to-event analyses were performed on a propensity score matched population, using Kaplan-Meier analyses and Cox regression models to compare the effect of entrectinib versus crizotinib on TTD, PFS, and OS. Inverse probability of treatment weighting was applied to the propensity score to assign a weight to each patient
Subgroup analyses	None

Table 35. Main study characteristics of Matching Adjusted Indirect Treatment Comparison	
Trial name	*N/A*
NCT number	*N/A*
Objective	The principle objective of the systematic review (SR) was to provide a summary of clinical efficacy and effectiveness evidence for the currently available ROS proto-oncogene 1 (*ROS1)*-targeted agents in patients with non-small cell lung cancer (NSCLC). A meta-analysis feasibility was also conducted to assess whether a robust comparison of the relative efficacy and safety of entrectinib versus other *ROS1*-targeted agents was possible for outcomes of interest. Data from the current SR was used to update a previous matching adjusted indirect comparison (MAIC) conducted by Bresmed in June 2019 (1). Due to the limited evidence base in the *ROS1* population, data from a second previous SR and feasibility assessment (also conducted by Bresmed) was used to provide evidence for the anaplastic lymphoma kinase positive (*ALK*+) population (used as a proxy).
Publications – title, author, journal, year	Matching-adjusted indirect comparison: Entrectinib versus crizotinib in ROS1 fusion-positive non-small cell lung cancer, Chu et al; Journal of comparative effectiveness research, 2020
Study type and design	Matching adjusted indirect comparison
Follow-up time	Patients in entrectinib treatment had a median survival follow-up of 15.84 months compared to 62.6 months in PROFILE 1001 for Crizotinib.
Population (inclusion and exclusion criteria)	● See Table 6 and Table 8
Intervention	Entrectinib and Crizotinib
Baseline characteristics	See Table 6.
Primary and secondary endpoints	● Overall survival (OS), Progression-free survival (PFS), Objective response rate (ORR) and discontinuation due to adverse events (AE).

Method of analysis	Individual entrectinib patients were assigned statistical weights to adjust for the relative representation compared to PROFILE 1001. Propensity weights were assigned as per the methods proposed by Signorovitch [9,37,38]. After weighting, average baseline characterstics were balanced between the entrectinib cohort and the comparative evidence source. Weighted Kaplan-Meier curves were generated and hazard ratios were estimated using Cox proportional hazards models. Discontinuations due to AEs were calculated using the derived weights, CIs were estimated using bootstrap sampling.
Subgroup analyses	N/A

10.3 Results per study

Table 36. Results from the PROFILE 1001 study

Trial name:	**A Study Of Oral PF-02341066, A C-Met/Hepatocyte Growth Factor Tyrosine Kinase Inhibitor, In Patients With Advanced Cancer (PROFILE 1001)** Published in: 1. EPAR, Crizotinib 2. SPC, Crizotinib 3. Shaw et al., N Engl J Med, 2014 4. Shaw et al., Ann Oncol, 2019
NCT number:	00585195

Efficacy outcomes

Outcome	Study arm	N (patients with event)	Result (CI)	Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
				Difference	95% CI	*P* value	Hazard/Odds/ Risk ratio	95% CI	*P* value		
*Median Overall Survival (OS) (**Critical outcome**)*	Crizotinib	53 (26)	51.4 months (29.3-NR)								
*Median time to CNS Progression (**Important outcome**)*	N/A	N/A	N/A								
PFS for patients with CNS metastases	N/A	N/A	N/A								

Median Progression-Free Survival (PFS) (***Important outcome***)	Crizotinib	53 (36)	19.3 (15.2-39.1)								
Safety outcomes											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (n)	Difference	95% CI	*P* value	Hazard/Odds/ Risk ratio	95% CI	*P* value		
Proportion of patients with treatment discontinuation due to adverse events (***Critical outcome***)	Crizotinib	53	7.5% (4)								
Proportion of patients experiencing grade 3-4 adverse events, % (***Important outcome***)	Crizotinib	53	52.8% (28)								
Quality of life outcomes											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result, n	Difference	95% CI	*P* value	Hazard/Odds/ Risk ratio	95% CI	*P* value		

EORTC-QLQ-30 (**Important outcome**)	N/A	N/A	N/A					

Table 37. Results from the OX-ONC study

Trial name:	**Phase II Safety and Efficacy Study of Crizotinib in East Asian Patients With ROS1 Positive, ALK Negative Advanced NSCLC** Published in: 1. Wu et al., J Clin Oncol, 2018											
NCT number:	01945021											
Efficacy outcomes												
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References	
Outcome	Study arm	N (patients with event)	Result (CI)	Difference	95% CI	*P* value	Hazard/Odds/ Risk ratio	95% CI	*P* value			
*Median Overall Survival (OS) (**Critical outcome**)*	Crizotinib	127	32.5 (32.5-NR)									
*Median time to CNS Progression (**Important outcome**)*	N/A	N/A	N/A									
PFS for patients with CNS metastases	Crizotinib	23	10.2 (5.6-13.1)									

Median Progression-Free Survival (PFS) (***Important outcome***)	Crizotinib	127	15.9 (12.9-24.0)									
Safety outcomes												
				Estimated absolute difference in effect				Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (n)	Difference	95% CI	*P* value		Hazard/Odds/ Risk ratio	95% CI	*P* value		
Proportion of patients with treatment discontinuation due to adverse events (***Critical outcome***)	N/A	N/A	N/A									
Proportion of patients with treatment discontinuation due to treatment-related adverse events	Crizotinib	127	0.8% (1)									
Proportion of patients experiencing grade 3-4 adverse events, % (***Important outcome***)	N/A	N/A	N/A									

Proportion of patients experiencing grade 3-4 treatment-related adverse events, %	Crizotinib	127	25.2% (32)								
Quality of life outcomes											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Hazard/Odds/ Risk ratio	95% CI	*P* value		
EORTC-QLQ-30 Mean change from baseline (**Important outcome**)	Crizotinib	122	≈7.1 (highest change)								

Table 38. Results from the AcSé study											
Phase 2 Study Assessing Efficacy and Safety of Crizotinib in Patients Harboring an Alteration on ALK, MET or ROS1 (AcSé)											
Trial name:	Published in: 1. Moro-Sibilot, Ann Oncol, 2019										
NCT number:	02034981										
Efficacy outcomes											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N (patients with event)	Result (CI)	Difference	95% CI	*P* value	Hazard/Odds/ Risk ratio	95% CI	*P* value		
Median Overall Survival (OS) (***Critical outcome***)	Crizotinib (ROS1 cohort)	37	17.2 (6.8-32.8)								
Median time to CNS Progression (***Important outcome***)	N/A	N/A	N/A								
PFS for patients with CNS metastases	N/A	N/A	N/A								

Median Progression-Free Survival (PFS) (***Important outcome***)	Crizotinib (ROS1 cohort)	37	5.5 (4.2-9.1)									
Safety outcomes												
				Estimated absolute difference in effect				Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (n)	Difference	95% CI	*P* value		Hazard/Odds/ Risk ratio	95% CI	*P* value		
*Proportion of patients with treatment discontinuation due to adverse events (**Critical outcome**)*	Crizotinib (ROS1 cohort)	37	8.6% (3)								Reported as "Toxicity"	
Proportion of patients with treatment discontinuation due to treatment-related adverse events	N/A	N/A	N/A									
*Proportion of patients experiencing grade 3-4 adverse events, % (**Important outcome**)*	N/A	N/A	N/A									

Proportion of patients experiencing grade 3-4 treatment-related adverse events, %	N/A	N/A	N/A									
Quality of life outcomes												
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References	
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Hazard/Odds/ Risk ratio	95% CI	*P* value			
EORTC-QLQ-30 Mean change from baseline (**Important outcome**)	N/A	N/A	N/A									

Table 39. Results from the EUCROSS study											
Trial name:	**EUCROSS: European Trial on Crizotinib in ROS1 Translocated Lung Cancer (EUCROSS)** Published in: 1. Michels et al., J Thorac Oncol, 2019										
NCT number:	02183870										
Efficacy outcomes											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N (patients with event)	Result (CI)	Difference	95% CI	*P* value	Hazard/Odds/ Risk ratio	95% CI	*P* value		
Median Overall Survival (OS) (***Critical outcome***)	Crizotinib	34	NR (17.1-NR)								
Median time to CNS Progression (***Important outcome***)	N/A	N/A	N/A								
PFS for patients with CNS metastases	Crizotinib	34	9.4 (1.7-NR)							Reported as “Brain metastases”	

Median Progression-Free Survival (PFS) (***Important outcome***)	Crizotinib	34	20.0 (10.1-NR)									
Safety outcomes												
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References	
Outcome	Study arm	N	Result (n)	Difference	95% CI	*P* value	Hazard/Odds/ Risk ratio	95% CI	*P* value			
*Proportion of patients with treatment discontinuation due to adverse events (**Critical outcome**)*	Crizotinib	34	5.9% (2)									
Proportion of patients with treatment discontinuation due to treatment-related adverse events	N/A	N/A	N/A									
*Proportion of patients experiencing grade 3-4 adverse events, % (**Important outcome**)*	Crizotinib	34	56% (19)									

Proportion of patients experiencing grade 3-4 treatment-related adverse events, %	Crizotinib	34	24% (8)							reported as “grade 3”	
Quality of life outcomes											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Hazard/Odds/ Risk ratio	95% CI	*P* value		
EORTC-QLQ-30 Mean change from baseline (**Important outcome**)	Crizotinib	33	≈ 23 (highest change)								

Table 40. Results from the METROS study												
Trial name:	**Crizotinib in Pretreated Metastatic Non-small-cell Lung Cancer With MET Amplification or ROS1 Translocation (METROS) (METROS)** Published in: 1. Landi et al., Clin Cancer Res, 2019											
NCT number:	02499614											
Efficacy outcomes												
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References	
Outcome	Study arm	N (patients with event)	Result (CI)	Difference	95% CI	*P* value	Hazard/Odds/ Risk ratio	95% CI	*P* value			
Median Overall Survival (OS) ***(Critical outcome)***	Crizotinib (Cohort A – ROS1)	26	NR									
Median time to CNS Progression ***(Important outcome)***	N/A	N/A	N/A									
PFS for patients with CNS metastases	N/A	N/A	N/A									
Median Progression-Free Survival (PFS) ***(Important outcome)***	Crizotinib (Cohort A – ROS1)	26	22.8 (15.2-30.3)									

Safety outcomes											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (n)	Difference	95% CI	*P* value	Hazard/Odds/ Risk ratio	95% CI	*P* value		
*Proportion of patients with treatment discontinuation due to adverse events (**Critical outcome**)*	N/A	N/A	N/A								
Proportion of patients with treatment discontinuation due to treatment-related adverse events	Crizotinib (Cohort A – ROS1)	26	6% (3)								
*Proportion of patients experiencing grade 3-4 adverse events, % (**Important outcome**)*	N/A	N/A	N/A								
Proportion of patients experiencing grade 3-4 treatment-related	Crizotinib (Cohort A – ROS1)	26	11.5% (3)								

adverse events, %										
Quality of life outcomes										
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Hazard/Odds/ Risk ratio	95% CI	*P* value		
EORTC-QLQ-30 Mean change from baseline (**Important outcome**)	N/A	N/A	N/A								

Table 41. Results from the integrated analysis of entrectinib												
Trial name:	**First-in-human, phase I study of entrectinib – an oral pan-trk, ROS1, and ALK inhibitor – in patients with advanced solid tumors with relevant molecular alterations (ALKA-372-001)** **A Phase 1, Multicenter, Open-Label Study of Oral Entrectinib (RXDX-101) in Adult Patients With Locally Advanced or Metastatic Cancer Confirmed to be Positive for NTRK1, NTRK2, NTRK3, ROS1, or ALK Molecular Alterations (STARTRK-1)** **An Open-Label, Multicenter, Global Phase 2 Basket Study of Entrectinib for the Treatment of Patients With Locally Advanced or Metastatic Solid Tumors That Harbor NTRK1/2/3, ROS1, or ALK Gene Rearrangements (STARTRK-2)** Published in: 1. EPAR, Entrectinib 2. SPC, Entrectinib 3. Drilon et al., Lancet Oncol, 2020											
NCT number:	NCT: 02097810 NCT: 02568267 EudraCT: 2012-000148-88											
Efficacy outcomes												
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References	
Outcome	Study arm	N (patients with event)	Result (CI)	Difference	95% CI	*P* value	Hazard/Odds/ Risk ratio	95% CI	*P* value			
Median Overall Survival (OS) ***(Critical outcome)***	Entrectinib (Integrated analysis)	94 (25)	NE (28.3-NE)									

	Entrectinib (Integrated analysis)	161 (38)	NE (28.3-NE)									
*Median time to CNS Progression (**Important outcome**)*	Entrectinib (Integrated analysis)	94	24.8 (16.1-NE)									
PFS for patients with CNS metastases	Entrectinib (Integrated analysis)	94 (22)	9.9 (4.6-17.4)									
*Median Progression-Free Survival (PFS) (**Important outcome**)*	Entrectinib (Integrated analysis)	94 (54)	16.8 (12.0-21.4)									
	Entrectinib (Integrated analysis)	161 (82)	15.7 (11.0-21.1)									
Safety outcomes												
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References	
Outcome	Study arm	N	Result (n)	Difference	95% CI	*P* value	Hazard/Odds/ Risk ratio	95% CI	*P* value			

*Proportion of patients with treatment discontinuation due to adverse events (**Critical outcome**)*	Entrectinib (Integrated analysis – Overall safety population)	504	9.1% (46)				
Proportion of patients with treatment discontinuation due to treatment-related adverse events	Entrectinib (Integrated analysis – Overall safety population)	504	4.4%				
*Proportion of patients experiencing grade 3-4 adverse events, % (**Important outcome**)*	Entrectinib (Integrated analysis – Overall safety population)	355	61.1% (217)			reported as "AE grade ≥3"	
Proportion of patients experiencing grade 3-4 adverse events, %	Entrectinib (Integrated analysis – Overall safety population)	504	61.1% (160)			Reported as "AE grade ≥3"	
Quality of life outcomes							
				Estimated absolute difference in effect	Estimated relative difference in effect	Description of methods used for estimation	References

Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Hazard/Odds/ Risk ratio	95% CI	*P* value		
EORTC-QLQ-30 Mean change from baseline (**Important outcome**)	Entrectinib	37	N/A								

Table 42. Results from the MAIC analysis of entrectinib and crizotinib												
	Matching-adjusted indirect comparison: entrectinib versus crizotinib in ROS1 fusion-positive non-small cell lung cancer											
Trial name:	Published in: 1. Chu et al., J Comp Eff Res, 2020											
NCT number:	N/A											
Efficacy outcomes												
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N (sum of weights)	Result (CI)	Difference	95% CI	*P* value	Hazard ratio	95% CI	*P* value		
Median Overall Survival (OS) ***(Critical outcome)***	Entrectinib (Original)	53							N/A	Individual entrectinib patients were assigned statistical weights to adjust for the relative representation compared to PROFILE 1001. Propensity weights were assigned as per the methods proposed by Signorovitch [9, 37-38]. After weighting, average baseline characterstics were balanced between the entrectinib cohort and the comparative evidence source. Weighted Kaplan-Meier curves were generated and hazard ratios were estimated using Cox	
	Entrectinib (Scenario 1)	(39.98)	NR (NR-NR)				0.471	0.112-1.034	N/A		
	Entrectinib (Scenario 2)	(42.57)	NR (NR-NR)				0.504	0.134-1.066	N/A		
	Entrectinib (Scenario 3)	(44.91)	NR (NR-NR)				0.609	0.164-1.273	N/A		
				N/A	N/A	N/A					
	Crizotinib (Original)	53	51.4 (29.3-NR)								

											proportional hazards models. Discontinuations due to AEs were calculated using the derived weights, CIs were estimated using bootstrap sampling.	
*Median time to CNS Progression (**Important outcome**)*	N/A	N/A	N/A									
PFS for patients with CNS metastases	N/A	N/A	N/A									
*Median Progression-Free Survival (PFS) (**Important outcome**) – Investigator Assessed (IA)*	Entrectinib (Original)	53		N/A	N/A	N/A				Individual entrectinib patients were assigned statistical weights to adjust for the relative representation compared to PROFILE 1001. Propensity weights were assigned as per the methods proposed by Signorovitch [9, 37-38]. After weighting, average baseline characterstics were balanced between the entrectinib cohort and the comparative evidence source. Weighted Kaplan-Meier curves were generated	
	Entrectinib (Scenario 1)	(39.98)	17.708 (15.507-NR)	-1.622	N/A	N/A	1.286	0.840-1.819	N/A		
	Entrectinib (Scenario 2)	(42.57)	17.511 (14.489-NR)	-1.819	N/A	N/A	1.346	0.902-1.863)	N/A		
	Entrectinib (Scenario 3)	(44.91)	15.507 (12.222-NR)	-3.823	N/A	N/A	1.535	1.063-2.107)	N/A		
	Crizotinib (Original)	53	19.33 (15.27-33.15)								
*Median Progression-Free Survival (PFS) (**Important outcome**) –*	Entrectinib (Original)	53	19.0 (12.2-36.6)	-0.33	N/A	N/A					
	Entrectinib (Scenario 1)	(39.98)	26.326 (19.023-NR)	6.996	N/A	N/A	0.939	0.528-1.427	N/A		
	Entrectinib (Scenario 2)	(42.57)	26.316 (15.737-NR)	6.986	N/A	N/A	0.960	0.561-1.448	N/A		

Blinded Independent Central Review (BICR)	Entrectinib (Scenario 3)	(44.91)	19.023 (15.737-NR)	-0.307	N/A	N/A	1.046	0.640-1.603	N/A	and hazard ratios were estimated using Cox proportional hazards models. Discontinuations due to AEs were calculated using the derived weights, CIs were estimated using bootstrap sampling.	
	Crizotinib (Original)	53	19.33 (15.27-33.15)								
Safety outcomes											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N (sum of weights)	Result (n)	Difference	95% CI	*P* value	Odds ratio	95% CI	*P* value		
*Proportion of patients with treatment discontinuation due to adverse events (**Critical outcome**)*	Entrectinib (Original)	53			N/A	N/A			N/A	Individual entrectinib patients were assigned statistical weights to adjust for the relative representation compared to PROFILE 1001. Propensity weights were assigned as per the methods proposed by Signorovitch [9, 37-38]. After weighting, average baseline characterstics were balanced between the entrectinib cohort and the comparative evidence source. Weighted Kaplan-Meier curves were generated and hazard ratios were	
	Entrectinib (Scenario 1)	(93.38)	6.81% (6.36)	-0.73%	N/A	N/A	0.896	0.231-1.910	N/A		
	Entrectinib (Scenario 2)	(101.63)	6.66% (6.77)	-0.88%	N/A	N/A	0.874	0.250-1.826	N/A		
	Entrectinib (Scenario 3)	(115.85)	6.08% (7.04)	-1.46%	N/A	N/A	0.793	0.290-1.444	N/A		
	Crizotinib (Original)	53	7.54% (4)								

					estimated using Cox proportional hazards models. Discontinuations due to AEs were calculated using the derived weights, CIs were estimated using bootstrap sampling.	
Proportion of patients with treatment discontinuation due to treatment-related adverse events	N/A	N/A	N/A			
*Proportion of patients experiencing grade 3-4 adverse events, % (**Important outcome**)*	N/A	N/A	N/A			
Proportion of patients experiencing grade 3-4 treatment-related adverse events, %	N/A	N/A	N/A			
Quality of life outcomes						

				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Hazard/Odds/ Risk ratio	95% CI	*P* value		
EORTC-QLQ-30 Mean change from baseline (**Important outcome**)	N/A	N/A	N/A								

Table 43. Results from the Flatiron analysis											
Trial name:	**Time-to-treatment discontinuation (TTD) and real-world progression-free survival (rwPFS) as endpoints for comparative efficacy analysis between entrectinib trial and crizotinib real-world ROS1 fusion-positive (ROS1+) NSCLC patients** Published in: 1. Doebele et al., ASCO 2019 #9070, 2019									
NCT number:	N/A									
Efficacy outcomes										
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N (patients with event)	Result (CI)	Difference	95% CI	*P* value	Hazard ratio	95% CI	*P* value		
Median Overall Survival (OS) (***Critical outcome***)	Entrectinib	53	NE	N/A	N/A	N/A	N/A	N/A	N/A	Analysis carried out on propensity score matched population based on crizotinib-treated patients. Time-to-event analyses carried out using Kaplan-Meier analyses and Cox regression models.	
	Crizotinib (Unweighted)	69	19.9 (15.1-NE)								
	Crizotinib (Weighted)	54	18.5 (15.1-19.9)								
Median time to CNS Progression (***Important outcome***)	N/A	N/A	N/A								
PFS for patients with CNS metastases	N/A	N/A	N/A								

Median Progression-Free Survival (PFS) ***(Important outcome)***	Entrectinib	53	19.0 (12.2-NE)	10.5	N/A	N/A	0.49 (Unadjusted)	0.30-0.80	N/A	Analysis carried out on propensity score matched population based on crizotinib-treated patients. Time-to-event analyses carried out using Kaplan-Meier analyses and Cox regression models.		
	Crizotinib (Unweighted)	69	8.5 (6.2-10.1)				0.43 (Covariate adjusted)	0.25-0.74	N/A			
	Crizotinib (Weighted)	54	8.8 (8.2-9.9)	10.2	N/A	N/A	0.44 (Propensity score inverse probability of treatment weight)	0.26-0.74	N/A			
Safety outcomes												
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References	
Outcome	Study arm	N	Result (n)	Difference	95% CI	*P* value	Hazard/Odds/ Risk ratio	95% CI	*P* value			
*Proportion of patients with treatment discontinuation due to adverse events (**Critical outcome**)*	N/A	N/A	N/A									
Proportion of patients with treatment discontinuation due to treatment-related adverse events	N/A	N/A	N/A									
Proportion of patients experiencing grade 3-4	N/A	N/A	N/A									

*adverse events, % (**Important outcome**)*											
Proportion of patients experiencing grade 3-4 treatment-related adverse events, %	N/A	N/A	N/A								
Quality of life outcomes											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Hazard/Odds/ Risk ratio	95% CI	*P* value		
EORTC-QLQ-30 Mean change from baseline (**Important outcome**)	N/A	N/A	N/A								

Cost- and budget impact analysis of Rozlytrek (Entrectinib) for ROS1+ Non-Small Cell Lung Cancer patients

On the 11th of June 2020, Roche received the protocol for evaluating the clinical added value of Rozlytrek® (entrectinib for first-line treatment of incurable ROS1-positive non-small cell lung cancer) by the Danish Medicine Council. The protocol included one clinical question, which sets the scope of this economic analysis.

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

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EXECUTIVE SUMMARY

Baggrund

Den 11. juni 2020 offentliggjordes Medicinrådets protokol for vurdering af entrectinib til førstelinjebehandling af uhelbredelig ROS1-positiv ikke-småcellet lungekræft. Protokollen omfattede følgende kliniske spørgsmål:

1. Hvilken værdi har entrectinib sammenlignet med crizotinib som førstelinjebehandling af patienter med uhelbredelig ROS1-positiv NSCLC?

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

Metode

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

Modellen er primært baseret på resultaterne fra ALKA-372-001, STARTRK-1 og STARTRK2, to fase 1 studier og et fase 2 studie. ALKA-372-001 og STARTRK-1 inkluderede ROS1-patienter i forsøgspopulation, og data fra disse patienter er inkluderet i modellen. STARTRK-2 er et igangværende single-arm, klinisk forsøg, der undersøger effekten af entrectinib hos ROS1-positive NSCLC patienter. Patientdata fra det foreløbige data cut fra en integreret analyse af de tre studier var tilgængelige og er anvendt som input til den økonomiske model.

For at estimere effekten af entrectinib sammenlignet med crizotinib til ROS1-postive patienter anvendes indirekte analyser med det kliniske studie, PROFILE1001, som reference. PROFILE1001 er et fase 1 studie, der undersøger effekten af crizotinib i ROS1-positive NCSLC patienter.

Modellen anvender en livstidshorisont (20 år). Omkostninger diskonteres med 4% per år i overensstemmelse med Medicinrådets metodevejledning. Modellen har et begrænset samfundsperspektiv og inkluderer lægemiddelomkostninger, administrationsomkostninger, monitoreringsomkostninger, omkostninger til uønskede hændelser, patientomkostninger, transportomkostninger samt omkostninger til terminal pleje.

Resultater

Base casen for analysen viser en inkrementel diskonteret meromkostning på [redacted] for entrectinib sammenlignet med crizotinib.

Budgetkonsekvenserne estimeres i år 5 (steady state) til at være [redacted] ved anbefaling af entrectinib som førstelinjebehandling af patienter med uhelbredelig ROS1-positiv NSCLC.

Hvis effekten imellem entrectinib og crizotinib antages at være den samme, estimeres den inkrementel diskonteret omkostning til at være [redacted] for entrectinib sammenlignet med crizotinib.

Table of contents

List of tables

List of figures

1 Introduction

1.1 Background

Lung cancer is one of the most frequently diagnosed cancers in Denmark. In the year of 2016, 11.151 patients were living with lung cancer, and approximately 3.700 patients die of lung cancer each year in Denmark. Each year approximately 4.600 patients are diagnosed with lung cancer in Denmark. (1,2)

About 85-90% of the diagnosed cases are non-small cell lung cancers (NSCLC) (3). In 0,9-2% of the NSCLC cases, a chromosomal translocation of the gen, ROS proto-oncogene 1 receptor tyrosine kinase (ROS1) is observed in the tumor (4). These cases are classified as ROS1-positive NSCLC cases. The ROS1 translocation is observed in a younger patient population compared to the average lung cancer patient population, and often in non-smokers (4).

At the moment, the Danish Medicine Council (DMC) has not recommended any drugs for ROS1-positive patients, and the ROS1-positive NSCLC indication is not included in the current treatment guidelines for first-line treatment of incurable NSCLC (5,6).

According to the DMC protocol, approx. 10 patients are diagnosed with a ROS1-positive NSCLC every year (5).

1.2 Standard treatment

In patients with incurable NSCLC with a targetable mutation, the first-line treatment is a targeted treatment regimen for the majority of the patients. No standard treatment for ROS1-positive NSCLC has been determined by the DMC, however, it is stated in the current treatment guidelines for incurable NSCLC that patients, who are non-smokers, should be allocated to a targeted treatment with a tyrosine kinase inhibitor (TKI) (6).

In the current Danish clinical setting, the treatment of ROS1-positive NSCLC is decided for each individual patient based on a clinical assessment by the physicians. Some TKIs have demonstrated an effect on ROS1-positive tumors. Until now, Crizotinib has been the only drug with an EMA indication for incurable ROS1-positive NSCLC. The DMC (Fagudvalget) expects the majority of the ROS1-positive patient will currently be treated with crizotinib in the Danish clinical setting.

1.3 Intervention treatment

Rozlytrek (entrectinib) is a tyrosine kinase inhibitor, which inhibits the activity of the neurotrophin receptor tyrosine kinases (NTRK), anaplastic lymphoma kinase (ALK) and ROS1. Entrectinib was designed to specifically cross the blood-brain barrier and remain in the central nervous system, thereby having an effect on CNS metastases(7). The ALK and ROS1 molecules have a crucial role in tumor cell growth and differentiation. Through inhibition of ROS1, the activity of the signal cascade responsible for the tumor's survival and proliferation is reduced. In ROS1-

positive NSCLC, the ROS1 molecules are more active compared to tumors without the translocation. By inhibition of the ROS1 molecules, entrectinib can limit the tumor's growth and the spreading of the tumor.

2 Purpose

The economic model was developed to estimate the incremental costs per patient as well as the budget impact of entrectinib for treating incurable ROS1-positive non-small cell lung cancer compared to crizotinib. The model will utilize a restricted societal perspective.

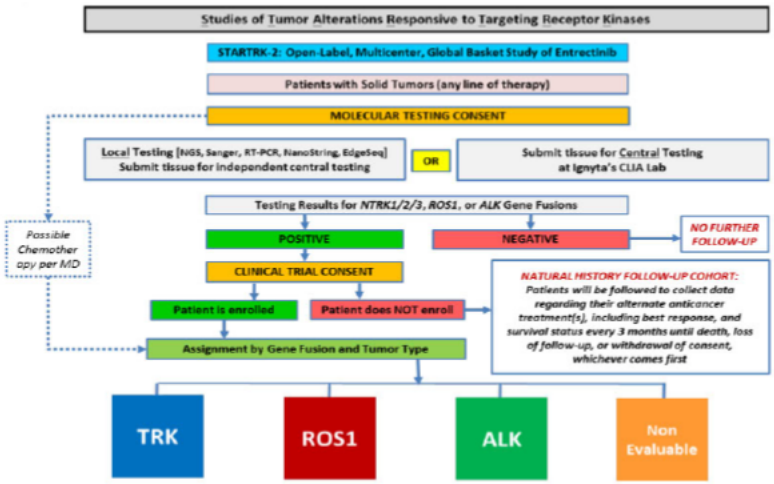
3 Direct clinical evidence

3.1 Description of the pooled Entrectinib trials

In the two phase 1 clinical studies - ALKA-372-001 (8) and STARTRK-1 (9) - that were conducted to determine the recommended Phase 2 dose (RP2D) of entrectinib, patients with locally advanced or metastatic solid tumors were enrolled irrespective of tumor type. Within the two Phase 1 trials, ROS1-positive patients were treated.

STARTRK-2 is an open-label, multicenter, global Phase 2 basket study of entrectinib for the treatment of patients with solid tumors that harbor an NTRK1/2/3, ROS1, or ALK gene rearrangement (fusion).

Figure 1: Design of STARTRK-2 Basket study



3.2 Overview of the pooled trial analysis

ROS-1-positive locally advanced or metastatic NSCLC

[redacted]

Table 1. Cohort overview of pooled analysis on entrectinib

	ROS1 NSCLC Efficacy (n)
ALKA-372-001 (adults Ph1)	9
STARTRK-1 (adults Ph1)	7
STARTRK-2 (adults Ph2)	145
TOTAL	**161**
Last patient enrolled	31 Oct 2018
Data cutoff date	1 May 2019
Database lock	18 Sep 2019

3.3 Pooled Clinical trial results

3.3.1 ROS1 result overview

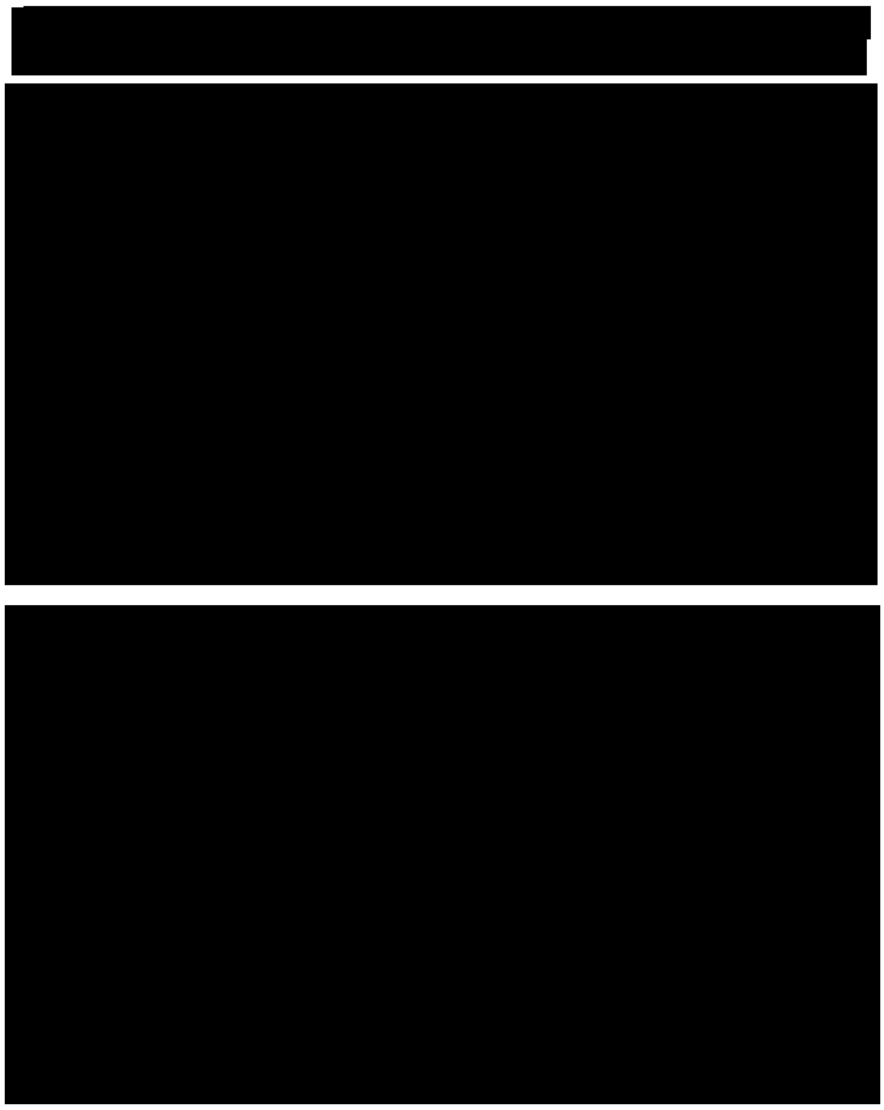
The following tables demonstrate the OS and PFS benefit of entrectinib in the ROS1 NSCLC pooled population. The ROS1 OS data are immature at this point in time. The following section, the data are assessed and implemented in the model. The progression-free survival based on a blinded independent central review (BICR) is presented in [redacted] and the overall survival curve is presented in [redacted]

[redacted]

[redacted]

[redacted]

[redacted]



4 Indirect Clinical Evidence

Since entrectinib was assessed in single-arm trials, indirect evidence is necessary in order to allow comparison of entrectinib with crizotinib.

Four different data sources for the efficacy of crizotinib were available. Two of the data sources were for different indications i.e. ALK+ patients, one was an observational study, and one was a phase 1 trial. The available data sources are illustrated in Table 4.

Table 4. Included indirect evidence for Crizotinib

	Crizotinib				
Study type	**RWD**	**Trial**	**MAIC**	**Trial**	**Trial**
Study name	Flatiron	PRO-FILE1001	MAIC vs. PRO-FILE1001	PRO-FILE1014	ALEX
Study type, location	Observational, USA	Phase I, United States	Phase I, United States	Phase III, Global	Phase III, Global
Patient population	ROS1+	ROS1+	ROS1+	ALK+	ALK+
Reference	Roche, Interim analyses Nov. 2018	NICE-TA529(10)	Chu et al. 2020 (updated with later entrectinib datacut)	Mok et al. 2017	Peters et al. 2017
No of Patients	93	53	53	172	151
Outcomes	PFS, OS	PFS	PFS, OS	OS	PFS

PROFILE1001 is an ongoing phase 1 trial on crizotinib, where ALK+, c-Met and ROS1+ patient have been included in the patient population. The patients received crizotinib at a starting dose of 250 mg twice daily. 53 patients had the ROS1-mutation and were followed up for 46.2 months on PFS and OS.(10,11)

As discussed in the clinical application, the reported median PFS and OS for crizotinib in ROS1-positive NSCLC has varied depending on the specific trial. Results have differed both within the ROS1 indication but also when comparing to data from the ALK-positive indication. For this reason, the model also allows for other options regarding crizotinib PFS and OS.

The data available for crizotinib in the remaining trials are for the ALK+ NSCLC population, i.e. ALEX for PFS and PROFILE1014 for OS as well as the Flatiron Real World Study in ROS1-positive NSCLC for both parameters.

The Flatiron RWD is an observational study with a cohort comprised of patients diagnosed with advanced or metastatic lung cancer between January 1, 2011 and 30th June 2018, with stage IIIB or IV NSCLC at initial diagnosis and those who presented with earlier stage NSCLC but subsequently developed advanced disease on or after January 1, 2011, as identified by Flatiron unstructured data. In the cohort, 150 ROS1+ patients were enrolled. Of the 150 patients with ROS1+ NSCLC, 93 patients were treated with crizotinib. All patients from the Flatiron database retained after application of inclusion and exclusion criteria derived from the STARTRK-2 pivotal study (used also for the integrated efficacy analysis set of entrectinib) were considered (n=69), from whom a matched crizotinib arm (n=54) was derived for the comparative analysis. Time-to-event analyses were carried out on a propensity score matched population to align patient characteristics. Kaplan-Meier analyses and Cox regression models were used to compare the effect of entrectinib and crizotinib on the included outcomes.

PROFILE1014 is a phase 3 trial comparing crizotinib to chemotherapy in ALK+ NSCLC patients. The trial enrolled 343 patients (172 patients in the crizotinib arm), who were followed up for OS. The patients in the crizotinib arm received a dose of 250 mg twice a day.

ALEX is an ongoing phase 3 trials comparing alectinib to crizotinib in ALK+ NSCLC patients. The trial enrolled 303 patients (151 patients in the crizotinib arm), who are followed up for PFS. The patients in the crizotinib arm receive a dose of 250 mg twice a day.

4.1 Comparative analyses vs. crizotinib

4.1.1 Matching Adjusted Indirect Comparison (MAIC) vs. crizotinib

Methodology

Both PROFILE1001 and Flatiron included PFS and OS outcomes and allowed for performing indirect treatment comparisons (ITCs). Due to the single-arm designs of the trials and heterogeneity between the patient populations, standard ITCs were not possible. Instead matching adjusted indirect comparisons (MAICs) were performed.

Individual patient data (IPD) were not available for the identified comparative evidence sources. Instead, KM graphs were digitized using GetData Graph Digitizer to create pseudo-IPD using the algorithm of Guyot (12). These pseudo-IPD data were be considered alongside the IPD from the entrectinib trial in one dataset and analyzed as described below.

To make an adjusted comparison between entrectinib patients and the comparative evidence source, individual entrectinib-treated patients were assigned statistical weights that adjust for their over- or under-representation relative to that observed in each comparative evidence source. After weighting, average baseline characteristics (mean and variance) are balanced between the selected entrectinib cohort(s) and the comparative evidence source. All analyses were performed in line with NICE DSU Technical Support Document 18 (13).

Weights were derived using a MAIC – a form of propensity score weighting (14,15). A propensity score logistic regression model estimated the odds of being enrolled in the entrectinib cohort or the comparative evidence source.

The patient characteristics to be used in matching were selected based on the assessment of clinical heterogeneity. Variables proposed for inclusion in the propensity score logistic regression model were prioritized based on the degree of imbalance between study populations. Variables included for each comparison are encoded as listed below:

- Age (continuous)
- Sex (Male, Female)
- Smoking status (Never versus current or former)
- Race (Asian, Non-Asian)
- Eastern Cooperative Oncology Group (ECOG) performance status (0 or 1 versus 2)
- Histology (Adenocarcinoma versus Non-adenocarcinoma)
- Number of prior anti-cancer therapies (0 [treatment naive] versus ≥1 [treatment experienced]).
- Percentage of CNS metastasis
  - No data was available for this was available for PROFILE1001
  - 24,64% was reported in the Flatiron RWD comparison, the largest study in ROS1-positive patients
    - This have been assumed for the PROFILE1001 population in the base-case MAIC analysis.
  - 3 scenarios are available in the model

The patient characteristics have been adjusted for CNS metastasis, due to the prognosis of CNS metastasis compared to different metastasis. CNS metastasis are associated with a higher mortality and faster disease progression. Crizotinib is a substrate for a key efflux transporter of the blood-brain barrier, which means it is not able to achieve clinically relevant exposures in the CNS, compared to entrectinib, which was designed to cross the blood-brain barrier, thus having an effect on present CNS metastases(7).After the matching procedure has been conducted and the weights derived, efficacy outcomes were compared between balanced treatment groups using statistical tests that incorporate the derived weights. For OS and PFS, weighted KM curves were generated. Hazard ratios (HRs) comparing entrectinib cohort(s) and the comparative evidence source were estimated using weighted Cox proportional hazards models.

4.1.2 Results of MAIC vs. PROFILE1001

The following tables summarize the OS and PFS HR that are incorporated into the model. The MAIC analysis used in the model is based on the efficacy population of 161 patients. Progression-free survival (PFS) can be reported as investigator-assessed (PFS IA) or assessed by the blinded independent review committee (PFS BICR) with some studies reporting both endpoints. Table 8 shows the patient characteristics adjustment from the entrectinib trials to those from PROFILE1001.

It was unclear whether PFS reported in PROFILE1001 was investigator-assessed (IA) or by BICR, therefore analyses were conducted with both the IA and BICR of entrectinib. The data of PROFILE1001, as reported by the manufacturer on NICE in TA529, were used (10).

The results presented in the following tables and graphs are for scenario 2 of the MAIC analysis.

[redacted]

[redacted]

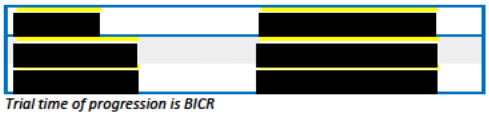
[redacted]

[redacted]

4.1.3 Flatiron Real World Data

The following tables are showing the initial results of this comparative analysis for the OS and PFS endpoint. The PFS HR of entrectinib vs. crizotinib was estimated to be [redacted] and the OS HR of entrectinib vs. crizotinib was estimated to be [redacted] The HR are incorporated into the model for the Flatiron option.

Table 9. Estimated HR for entrectinib vs. crizotinib, Flatiron RWD (adjusted and IPTW weighted)



Trial time of progression is BICR
IPWT: inverse probability of treatment weight

4.2 Naïve Comparisons vs Crizotinib

The PFS data from the ALEX trial and PROFILE1001 have been included as option for naïve fits in the model. For OS, PROFILE1014 data have been included in the model. The PFS data from the PROFILE1001 have been included for validation of the MAIC analysis vs. PROFILE1001.

The Naïve comparison vs PROFILE1001 were not deemed an appropriate approach for estimating the relative efficacy of entrectinib and crizotinib on PFS and OS due to the differences in baseline characteristics. Instead, the MAIC was deemed a more appropriate analysis for the comparison with crizotinib in PROFILE1001 than a naïve comparison. The data have been included for transparency, however, due to the vast differences in patient characteristics, we do not consider this as an appropriate approach for modelling PFS and OS for crizotinib for ROS1-positive patients.

As mentioned, the model also allows for the user to select other scenarios for crizotinib OS and PFS: The ALK+ NSCLC population, i.e. ALEX for PFS and PROFILE1014 for OS. Due to the limitations in naïve treatment comparisons in general due to both different patient characteristics and indications, none of these have been selected as the base-case.

Extrapolation curves for both the PFS and OS data have been included in the appendix, section 11.

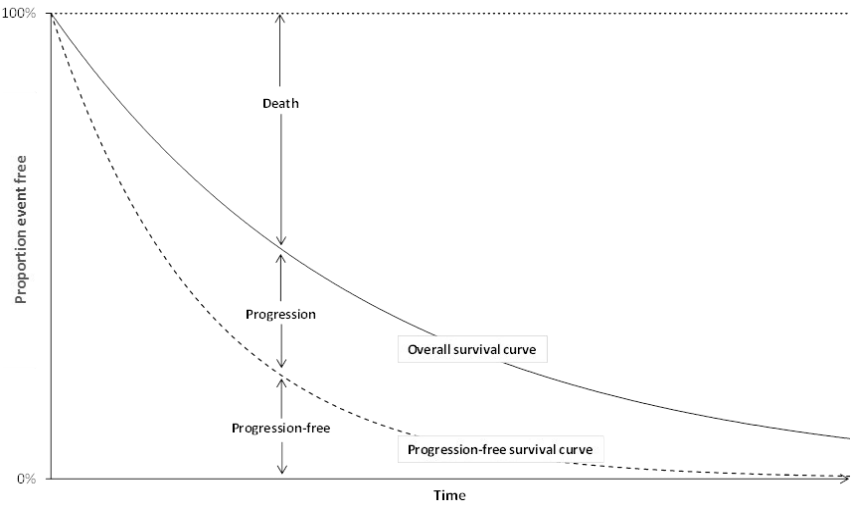
5 Health economic model structure

5.1 Model Description

The health economic model used in the analysis is a 3-health state partitioned survival model with health states consisting of progression-free, post-progression, and death. Within a partitioned survival model, health states are based on the partitioning of the proportion of patients alive into on PFS and PPS at discrete time points. The proportion of patients in the PPS health state at a given point in time is calculated as the difference in the proportion of patients who are alive and the proportions of progression-free patients. This type of model allows for usage of the available clinical study data whilst also relying on the most commonly used health stages in previous oncology models, i.e. the mutually exclusive healing states of progression-free, post-progression, and death.

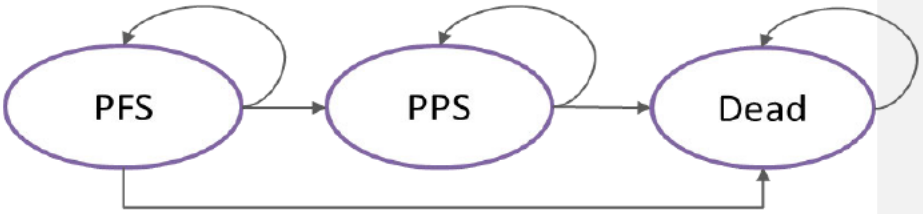
The model inputs were based on the results of the pooled entrectinib trials, as described in section **3**. Crizotinib was not assessed in the pooled entrectinib trials, and are included using hazard ratios (HRs) from the MAIC or naïve fits, as described in section **4**.

Figure 7 Example of a partitioned survival model



Patients enter the model in the progression-free state. In each cycle, patients can either remain in the progression-free health state or transition to the post-progression or death health state (Figure 7). Patients who have progressed can remain in the post-progression state or transition to the death state but never go back to the progression-free state. All patients eventually enter the death state.

Figure 8 Diagram of the model for a partitioned survival model



5.1.1 Progression-free state

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

5.1.2 Post-progression state

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

5.1.3 Death state

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

5.2 The rationale for model structure

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

However, there are limitations to these models as they cannot model the underlying disease or account for recurrent events. The assumption that PFS and OS are independent is very strong and violated in the case of three-state oncology models. PFS and OS are related because they both include death as an event, progression can never occur after death, and progression can

be predictive of the time to death. Generally, the validity and robustness of partitioned survival models beyond the observed trial duration are dependent on the maturity of the used survival data. However, due to the maturity of the survival data, in this case, we believe this to be less influential

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

5.3 Model cycle duration

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

Half-cycle corrections are applied to the model to account for mid-cycle transitions. This assumes that state transitions occur, on average, half-way through the cycle. Due to the short cycle length of 1 week the half-cycle correction does not have a large impact on the results, but it is included in the model for completeness.

6 Model inputs

6.1 Clinical inputs

6.1.1 Parametric Fit overview

Extrapolation beyond the pooled entrectinib trials clinical follow-up period was performed by fitting parametric distributions to the observed time to event data from the pooled entrectinib trials on the ITT population. For the MAIC, the HRs were applied to the PFS and OS curves of the entrectinib arm to generate curves for the crizotinib armFor the naïve comparison parametric distributions were fitted independently per treatment arm.

6.1.2 PFS: Probability of remaining in PFS

Patients remain in the PFS health state as long as they remain progression-free (as defined by RECIST v.1.1) or have not died.

Since the entrectinib trials are single-arm, diagnostic plots of the log cumulative hazard for PFS over the log of time to test the PH assumption for PFS are not required.

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

- The Akaike Information Criterion (AIC). Low values for AIC indicate a better statistical fit of the parametric function to the actual data.
- The Bayesian Information Criterion (BIC). Low values for BIC indicate a better statistical fit of the parametric function to the actual data.
- Visual assessment of each parametric function.

Table 10 provides the AIC and BIC goodness of fit results for the functions used to model PFS. Based on the AIC and BIC statistics, the best fit overall would be obtained with an exponential function. However, most of the functions fit the data reasonably well. It has to be considered that this assessment only looks at the fit to the existing data and does not allow any conclusion about the appropriateness of the tail of the distribution. Based on the visual inspection, the exponential function appears to fit the KM data well and provides conservative long-term projections for the tail. Only the Log-normal and the Log-logistic functions seem to have a poor visual fit and provide more optimistic long-term projections. The remaining functions provide similar long-term projections. Based on the overall assessment, the exponential function is therefore used in the base case for modelling PFS.

Table 10: AIC, BIC and Hazard Trend for PFS in ROS1

Parametric distribution	AIC ROS1	BIC ROS1
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

[redacted]

6.1.3 OS: Probability of remaining in OS

Table 11 provides the AIC and BIC goodness of fit results for the functions used to model OS in ROS1. [redacted]

6.1.4 Clinical comparison in the base-case analysis

For the base case, the MAICs have been chosen, as these analyses adjusts for differences in the baseline patient characteristics to generate a more appropriate indirect comparison compared to a naïve treatment comparison. The MAIC vs PROFILE1001 has been chosen for both PFS and OS. The MAIC vs PROFILE1001 has been chosen over the Flatiron analysis due to the study design of PROFILE1001, a controlled clinical trial, whereas the Flatiron RWD study is a retrospective observational study. For PFS, the BICR MAIC have been chosen over the IA MAIC, as the use of the blinded independent review eliminates the potential for investigator bias.

6.2 Time horizon

It is recommended that the selected time horizon should be long enough to reflect all the important differences in costs between the technologies being compared (16).

For the base-case analysis, a time horizon of 20 years has been selected. [redacted]

6.3 Perspective

The perspective of the economic model is a restricted societal perspective, which includes cost related to drug acquisition, drug administration, monitoring, adverse events, routine care, patient time, and transportation. Indirect costs are not included following the DMC's guidelines (16).

6.4 Discounting rate

In the base-case, the annual discount rate for future costs were 4% in alignment with DMC's guidelines, where the use of the Danish Ministry of Finance's discount rate is recommended (17).

6.5 Adverse events

In the cost-per-patient model, all grade 3 to 5 or serious AEs in pooled entrectinib trials and PROFILE1001 have been included. The number of occurrences and the number of patients with at least one occurrence are included on the sheet "AE Cost". The frequencies for enetrectinib were obtained from the entrectinib trials at the 1st of May 2019 data cut off for the first patients randomized (primary population) who had received at least one dose of the trial drug. If a comparator did not report on an AE, the frequency was assumed to be equal to the frequency of the other comparator.

6.6 Cost inputs

6.6.1 Drug dosing and acquisition costs

Entrectinib and crizotinib follow a fixed-dose regimen (Table 12). Patients are assumed to be treated until progression in line with the labels. Consequently, the expected drug costs per patient were calculated using the PFS parametric curves.

The dose per administration was based on average dose intensity as recorded in the STARTRK-2 entrectinib trial. [redacted] is observed in the STARTRK-2 trial. Due to the absence of data for crizotinib in ROS1 patients, the dose intensity was assumed to be equal to the intensity applied to entrectinib, [redacted]

For entrectinib and crizotinib, wastage is assumed in the base case. In this scenario it is assumed that 1 pack is provided to the patient, and if the patient dies before using up the entire pack, the remaining drug quantity is assumed wasted.

At the time of submission of this analysis the entrectinib list price is not yet available. Therefore, the analysis uses a dummy price for both packages. The model allows for the user to change the price accordingly when entrectinib is listed in "Taksten" and an official list price is available.

Table 12. Drug cost and dosing used in the model

Treatment	Package size	Composition	Cost per pack (DKK)	Cost per tab (DKK)	Dosing Regimen
Entrectinib	30 pc	100 mg/tablet	[redacted]	[redacted]	600 mg administered orally once-daily from day 1 in repeated 4-week cycles
Entrectinib	90 pc	200 mg/tablet	[redacted]	[redacted]	600 mg administered orally once-daily from day 1 in repeated 4-week cycles
Crizotinib	60 pc	250 mg/tablet	[redacted]	[redacted]	500 mg administered orally once-daily from day 1

*Source: Roche preliminary price
**Source: Medicinpriser.dk – Accessed 21-07-2020

6.6.2 Drug administration costs

For the assessment of drug administration cost, a one-off cost has been applied to the first administration. As both entrectinib and crizotinib are oral drugs, it is assumed that the patients receive training on how to administer the drugs at the first visit. The following visits will be visits related to dispensing the drug, and therefore no administration costs has been assumed for these visits. For the first visit, administration cost has been estimated using Interactive DRG 2020, with the diagnosis code "Kræft I lungens øverste lap" and the procedure code "Indøvning af administration af egen medicin". Interactive DRG 2020 identified 04MA98, "MDC04 1-dagsgruppe, pat. mindst 7 år". The tariff was applied to both entrectinib and crizotinib in the first cycle of the model. The administration cost has been presented in Table 13.

Table 13 Drug administration costs of entrectinib and crizotinib

Treatment	Cost (DKK)	Source
Entrectinib	1.799	DRG 2020, 04MA98: MDC04 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DC341: Kræft i lungens øverste lap Procedure: BTPD5 Indøvning af administration af egen medicin
Crizotinib	1.799	DRG 2020, 04MA98: MDC04 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DC341: Kræft i lungens øverste lap Procedure: BTPD5 Indøvning af administration af egen medicin

6.6.3 Supportive care cost

The details of the health state costs are described in table 14-17. Costs were stratified based on patients' disease status (first cycle progression-free, subsequent cycles progression-free and post-progression). A micro-costing approach was applied for specialist and nurse resource use based on the average duration of each visit. The resource use and frequency for the two health states has been estimated in collaboration with a Danish clinical expert within NSCLC (18). A micro-costing approach was chosen for supportive care to reflect the costs as precisely as possible and to avoid double counting of resource use. The clinical expert estimates allowed a detailed estimation of the expected resource use associated with different health states.

Table 14 Cost of blood sample package

Activity	Unit cost (DKK)	Reference
ALAT	DKK 24	Rigshospitalets Labportal
Haemoglobin + thrombocytes	DKK 31	Rigshospitalets Labportal
LDH	DKK 24	Rigshospitalets Labportal
Ionized calcium	DKK 26	Rigshospitalets Labportal
Renal function	DKK 79	Rigshospitalets Labportal
Alkaline phophatase	DKK 24	Rigshospitalets Labportal
Bilirubin	DKK 24	Rigshospitalets Labportal
Leucocytes	DKK 15	Rigshospitalets Labportal
Creatinine	DKK 24	Rigshospitalets Labportal
Sodium	DKK 14	Rigshospitalets Labportal
Potassium	DKK 14	Rigshospitalets Labportal
Albumin	DKK 53	Rigshospitalets Labportal
Total cost of blood sample package:	**DKK 352**	

Table 15 Progression-free state cost, first cycle

Activity	Proportion of patients	Unit cost (DKK)	Reference
Oncologist	100%	DKK 1.316	Danish Medicine Council's "Estimating unit costs", Clinical expert validation: Oncologist, 90 mins at start
Nurse	100%	DKK 554	Danish Medicine Council's "Estimating unit costs", Clinical expert validation: Nurse, 90 mins at start
Blood sample package	100%	DKK 352	Blood sample package
CT-scan	100%	DKK 2.470	DRG 2020, 36PR07: Klinisk fysiologi/nuklearmedicin grp. G, Diagnosis: DC349: Kræft i lunge UNS Procedure: WMBCSXYXX CT Thorax på SPECT/CT
Total cost for first cycle:		**DKK 5.627**	

Table 16 Progression-free state, subsequent cycles

Activity	Proportion of patients	Monthly frequency	Unit cost (DKK)	Reference
Oncologist	100%	0,33 x	DKK 1.316	Danish Medicine Council's "Estimating unit costs", Clinical expert validation: Oncologist, 30 mins at subsequent follow-ups
Nurse	100%	0,33 x	DKK 554	Danish Medicine Council's "Estimating unit costs", Clinical expert validation: Nurse, 60 mins at subsequent follow-ups
CT-scan	100%	0,33 x	DKK 2.470	DRG 2020, 36PR07: Klinisk fysiologi/nuklearmedicin grp. G, Diagnosis: DC349: Kræft i lunge UNS Procedure: WMBCSXYXX CT Thorax på SPECT/CT
MR-scan	5%	0,33 x	DKK 2.470	DRG 2020, 36PR07: Klinisk fysiologi/nuklearmedicin grp. G, Diagnosis: DC349: Kræft i lunge UNS Procedure: WMAMPXYXX MR WB på PET/MR
Totals	**Monthly cost:**	**DKK 1.269**	**Per cycle cost:**	**DKK 293**

Table 17 Post-progression state, all cycles

Activity	Proportion of patients	Monthly frequency	Unit cost (DKK)	Reference
Oncologist	100%	0,33 x	DKK 1.316	Danish Medicine Council's "Estimating unit costs", Clinical expert validation: Oncologist, 90 mins at start
Nurse	100%	0,33 x	DKK 554	Danish Medicine Council's "Estimating unit costs", Clinical expert validation: Nurse, 90 mins at start
CT-scan	100%	0,33 x	DKK 2.470	DRG 2020, 36PR07: Klinisk fysiologi/nuklearmedicin grp. G, Diagnosis: DC349: Kræft i lunge UNS Procedure: WMBCSXYXX CT Thorax på SPECT/CT
MR-scan	5%	0,33 x	DKK 2.470	DRG 2020, 36PR07: Klinisk fysiologi/nuklearmedicin grp. G, Diagnosis: DC349: Kræft i lunge UNS Procedure: WMAMPXYXX MR WB på PET/MR
Totals	**Monthly cost:**	**DKK 1.269**	**Per cycle cost:**	**DKK 293**

6.6.4 Adverse event costs

For the analysis, only grade 3+ AEs were considered. AEs were only included if they lead to a hospital visit or prolonged and ongoing hospitalization. The cost of adverse event management is calculated as a one-off cost based on the relevant DRG tariffs and the frequencies observed in the entrectinib trials and the PROFILE1001. The costs of the AEs for entrectinib are estimated to be DKK 7.433 and for crizotinib, the costs are estimated to DKK 10.815. The costs have been added in the first cycle for both the entrectinib and crizotinib in the model.

The AE rates from the entrectinib trial and the PROFILE1001 trial and the DRG tariffs with diagnosis codes are presented in Table 18.

Table 18 Adverse event costs

AEs	% AE Entrectinib	% AE Crizotinib	Unit cost (DKK)	Reference
ACUTE KIDNEY INJURY	1,2%	1,2%	DKK 43.160	DRG 2020, 11MA01: Akutte medicinske nyresygdomme uden dialyse og uden plasmaferese, Diagnosis: DN179: Akut nyreinsufficiens UNS
ALANINE AMINOTRANSFERASE INCREASED	2,5%	2,5%	DKK 1.748	DRG 2020, 23MA98: MDC23 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DR740: Transaminase- og laktatdehydrogenaseforhøjelse
ARTHRALGIA	1,9%	1,9%	DKK 1.796	DRG 2020, 08MA17: Øvrige sygdomme i knogler og led, Diagnosis: DM255: Ledsmerter
ASPARTATE AMINOTRANSFERASE INCREASED	1,9%	1,9%	DKK 1.748	DRG 2020, 23MA98: MDC23 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DR740: Transaminase- og laktatdehydrogenaseforhøjelse
BLOOD CREATINE PHOSPHOKINASE MB INCREASED	1,2%	1,2%	DKK 2.734	DRG 2020, 07MA98: MDC07 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DR748: Anden abnorm serumenzymkoncentration
BLOOD CREATININE INCREASED	1,2%	1,2%	DKK 4.082	DRG 2020, 23MA03: Symptomer og fund, u. kompl. bidiag., Diagnosis: DR798: Anden abnorm blodprøve
COGNITIVE DISORDER	1,2%	1,2%	DKK 30.628	DRG 2020, 01MA06: Degenerative sygdomme i nervesystemet, Diagnosis: DG318: Anden degenerativ sygdom i nervesystemet
DEHYDRATION	1,2%	1,2%	DKK 1.540	DRG 2020, 10MA98: MDC10 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DE869A: Dehydrering
DIARRHOEA	2,5%	2,5%	DKK 5.297	DRG 2020, 06MA11: Malabsorption og betændelse i spiserør, mave og tarm, pat. mindst 18 år, u. kompl. bidiag., Diagnosis: DK529B: Ikke-infektiøs diaré UNS

ELECTROCARDIOGRAM QT PROLONGED	1,2%	3,8%	DKK 1.162	DRG 2020, 05MA98: MDC05 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DI458: Anden ledningsforstyrrelse i hjertet
HYPERTRIGLYCERIDAEMIA	2,5%	2,5%	DKK 1.540	DRG 2020, 10MA98: MDC10 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DE781: Hyperglyceridæmi
HYPERURICAEMIA	5,6%	5,6%	DKK 4.082	DRG 2020, 23MA03: Symptomer og fund, u. kompl. bidiag., Diagnosis: DE790: Asymptomatisk hyperurikæmi
HYPOTENSION	1,2%	1,2%	DKK 1.847	DRG 2020, 05MA08: Andre hjertesygdomme, Diagnosis: DI952: Hypotension forårsaget af lægemiddel
MUSCULAR WEAKNESS	1,2%	1,2%	DKK 1.676	DRG 2020, 08MA15: Reumatologiske sygdomme i bløddele, Diagnosis: DM628: Anden muskelsygdom
MYALGIA	2,5%	2,5%	DKK 1.676	DRG 2020, 08MA15: Reumatologiske sygdomme i bløddele, Diagnosis: DM791: Myalgi
NEUTROPENIA	3,1%	9,4%	DKK 20.376	DRG 2020, 16MA98 + 16MA03: Granulo- og trombocytopeni, Diagnosis: DD709A: Neutropeni og agranulocytose forårsaget af lægemiddel
NEUTROPHIL COUNT DECREASED	5,0%	15,1%	DKK 20.376	DRG 2020, 16MA98 + 16MA03: Granulo- og trombocytopeni, Diagnosis: DD709A: Neutropeni og agranulocytose forårsaget af lægemiddel
PULMONARY EMBOLISM	11,3%	11,3%	DKK 31.882	DRG 2020, 04MA04: Lungeemboli, Diagnosis: DI269A: Lungeemboli UNS
PYREXIA	2,5%	2,5%	DKK 2.711	DRG 2020, 18MA98: MDC18 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DR509: Feber UNS
SYNCOPE	5,7%	5,7%	DKK 8.544	DRG 2020, 05MA98: MDC05 1-dagsgruppe, pat. Mindst 7 år & 05MA07: Hjertearytmi og synkope, Diagnosis: DR559: Besvimelse eller kollaps
VOMITING	1,2%	5,7%	DKK 0	
WEIGHT INCREASED	9,3%	9,3%	DKK 0	
Total cost for entrectinib:	DKK 7.433		Total cost for crizotinib:	DKK 10.815

6.6.5 Patient costs

Patient costs are included in the model in line as per the DMC's method guidelines. The unit cost per hour is assumed to be DKK 179,00 in line with the DMC guidelines. Time usage for the supportive care has been assumed for the progression-free state and the post-progression state based on the clinical expert testimony for the routine care resource use.

Table 19 Progression-free state, patient cost of entrectinib and crizotinib

Activity	Proportion of patients	Monthly frequency	Time usage	Reference
Oncologist	100%	0,33 x	½ hour	Clinical expert validation: Oncologist, 30 mins per session
Nurse	100%	0,33 x	1 hour	Clinical expert validation: Nurse, 60 mins per session
CT-scan	100%	0,33 x	1 hour	Assumption of 1 hour
MR-scan	5%	0,33 x	1 hour	Assumption of 1 hour
	Weighted weekly time usage:		0,27 hours	
	Weekly patient cost:		DKK 48	

Table 20 Post-progression state, patient cost of entrectinib and crizotinib

Activity	Proportion of patients	Monthly frequency	Time usage	Reference
Oncologist	100%	0,33 x	½ hour	Clinical expert validation: Oncologist, 30 mins per session
Nurse	100%	0,33 x	1 hour	Clinical expert validation: Nurse, 60 mins per session
CT-scan	100%	0,33 x	1 hour	Assumption of 1 hour
MR-scan	5%	0,33 x	1 hour	Assumption of 1 hour
	Weighted weekly time usage:		0,27 hours	
	Weekly patient cost:		DKK 48	

6.6.6 Transportation cost

Transportation costs are included in the model. An average rate of DKK 3,52 per km is assumed with an average distance of 28 km per hospital visit in line with DMC's methods guidelines. In the model, the number of visits are calculated based on the number of visits assumed for administration and routine care. Transportation costs are illustrated in Table 21.

Table 21 Transportation costs per health state

Disease state	Frequency per model cycle	Cost per cycle (DKK)
Progression-free state	0,31	30,33
Post-progression state	0,08	7,58

6.6.7 End-of-life costs

To reflect the fact that individuals incur additional resources shortly before death, a one-off end-of-life cost was applied to patients at the point of death to reflect the cost of terminal care. This cost will surely be present and very relevant to include. It is however hard to accurately

calculate as there are no relevant tariffs in Denmark that can be used to assess this cost. However, an article by Round et al. has calculated the mean cost of end-of-life care (19). The calculation is based on English tariffs for four cancer types. The cost includes hospital care, hospice care, and social municipal care. Due to the similarities between the health care systems in the UK and Denmark, the estimates are expected to be somewhat representative of the costs in Denmark.

The estimate has been used and was accepted by NICE in the assessment of avelumab for metastatic Merkel-cell carcinoma and has furthermore been used and accepted in previous assessments in the DMC. The estimate has also been accepted by Amgros in previous assessments. The cost has been converted from GPD to DKK using the Danish National bank's exchange rates, 3rd September 2020 (20), inflated to July 2020 costsusing Statistics Denmark 2020 (PRIS114) (21), and adjusted for price level indices between UK and DK in 2013 using the EUROSTAT's price level indices list(22). The end-of-life cost applied in the model is illustrated in Table 22.

Table 22 End of life care costs

Reported cost (DKK)	Cost inflated to 2020	Reference
54.6815	69.855	Round et al., 2015(19). Mean cost of health care over all cancer types (table 5)

6.7 Base case settings

Element	Base-case
Discount rate (per annum)	4%
Time horizon	20 years
Comparator	Crizotinib
Assume equal efficacy and safety between comparators?	No
Wastage	Wastage assumed
Dosing option	Mean observed dose
MAIC analysis – CNS metastasis scenario	Scenario 2 (Flatiron RWD assumption)
Progression-free survival (PFS)	
[redacted]	[redacted]
PFS Crizotinib option	MAIC vs entrectinib BICR
Overall Survival (OS)	
[redacted]	[redacted]
OS Crizotinib option	MAIC vs entrectinib

7 Results

7.1 Base-case

In the base-case, the cost per patient analysis results in a cost of [redacted]

7.1.1 Incremental cost per patient

The cost analysis results in an average incremental cost per patient of [redacted] for entrectinib compared to crizotinib. The results of the base-case are presented below in Table 23.

The total cost for both entrectinib and crizotinib are primarily driven by the drug costs. More supportive care- and patient cost are accrued in the entrectinib arm, due to the longer mean OS for entrectinib compared to crizotinib.

Table 23 Incremental cost per patient

	Entrectinib (DKK)	Crizotinib (DKK)	Incremental costs (DKK)
[redacted]	[redacted]	[redacted]	[redacted]
Administration costs	1.799	1.799	0
AE costs	7.433	10.815	-3.382
Supportive care	71.835	60.723	11.112
Patient costs	10.953	9.122	1.830
Transportation costs	3.790	3.996	-206
End of life costs	58.552	60.962	-2.401
[redacted]	[redacted]	[redacted]	[redacted]

7.2 Scenario analyses

Scenario analyses were undertaken to assess the impact of varying structural and methodological assumptions implemented in the model. The results of the scenario analyses can be seen in Table 24.

In the scenario where the efficacy and safety of entrectinib and crizotinib is assumed to be equal, the incremental cost of entrectinib increases to [redacted]

Table 24, Results of scenario analysis

Number	Parameter	Value	Incremental costs
Base-case			[redacted]
1	Distribution Entrectinib ROS1 PFS	Weibull	
2	Distribution Entrectinib ROS1 PFS	Log-normal	
3	Distribution Entrectinib ROS1 PFS	Gamma	
4	Distribution Entrectinib ROS1 PFS	Log-logistic	
5	Distribution Entrectinib ROS1 PFS	Gompertz	
6	Assume equal efficacy and safety between comparators	Yes	
7	PFS option Crizotinib ROS1	ALEX PFS	
8	PFS option Crizotinib ROS1	PROFILE1001 Naïve fit	
9	PFS option Crizotinib ROS1	MAIC vs. entrectinib IA	
10	PFS option Crizotinib ROS1	Flatiron vs. entrectinib	
11	Distribution Entrectinib ROS1 OS	Weibull	
12	Distribution Entrectinib ROS1 OS	Log-normal	
13	Distribution Entrectinib ROS1 OS	Gamma	
14	Distribution Entrectinib ROS1 OS	Log-logistic	
15	Distribution Entrectinib ROS1 OS	Gompertz	
16	OS option Crizotinib ROS1	PROFILE 1014 - ITT	
17	OS option Crizotinib ROS1	PROFILE 1014 - nonTKI	
18	OS option Crizotinib ROS1	Flatiron vs. entrectinib	
19	Apply HR from the clinical application to PFS and OS	Yes	
20	Time horizon	5	
21	Time horizon	17,5	
22	Time horizon	30	
23	OS HR – MAIC vs. Entrectinib	0,90	
24	OS HR – MAIC vs. Entrectinib	1,00	

8 Budget impact analysis

8.1 Methods

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

The cost per patient model was partially nested within the budget impact model, and therefore any changes in the settings of the cost per patient model would affect the results of the budget impact model. The budget impact result is representative of the population in the cost per patient model.

The analysis was developed by comparing the costs for the Danish regions per year over five years in the scenario where entrectinib is recommended as possible standard treatment and the scenario where entrectinib is not recommended as possible standard treatment. The total budget impact per year is the difference between the two scenarios.

8.1.1 Incidence of ROS1-positive NSCLC

The Danish Medicine Council (Fagudvalget) estimates the patient population of ROS1-positive NSCLC to be approx. 10 patients in Denmark every year.

8.1.2 Current treatment of ROS1-positive NSCLC in Denmark

A budget impact model must be based on the current treatment landscape. At the moment, no treatment guidelines have been made for ROS1-positive NSCLC. The DMC assesses that the majority of the patients are treated with Crizotinib at the moment. Crizotinib has therefore been included as the only treatment in the current scenario in the budget impact model.

8.1.3 Market Share

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

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

The market shares used in the budget impact analysis can be seen in Table 25.

Table 25. Market shares for adjuvant treatment of ROS1-positive NSCLC

	No recommendation for Entrectinib					Recommendation for Entrectinib				
Treatment	Year 1	Year 2	Year 3	Year 4	Year 5	Year 1	Year 2	Year 3	Year 4	Year 5
Entrectinib	5%	0%	0%	0%	0%	100%	100%	100%	100%	100%
Crizotinib	95%	100%	100%	100%	100%	0%	0%	0%	0%	0%

	No recommendation for Entrectinib					Recommendation for Entrectinib				
Total	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%

The expected market shares are based on the following:

- In the scenario without a recommendation, it is expected that some patients will receive entrectinib within the first year. This translates into a market share of 5% in the model. In the subsequent years, the market share will drop to 0%, as we believe no patient will receive entrectinib in the scenario of no recommendation.
- In the scenario with a recommendation, it is expected that entrectinib will be the standard of care for ROS1-positive NSCLC cases, and therefore will gain the market share of crizotinib in this therapy regiment.

8.1.4 Costs

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

8.1.5 Scenario analyses

Alternative scenarios were tested to assess the result of different assumptions for market shares. The scenarios tested for the budget impact model are described in Table 26.

Table 26 Scenarios for budget impact model

Scenario	Assumptions made for scenario analyses
Base case	100 % of patients receive entrectinib in year 5
Lower	40 % of patients receive entrectinib in year 5
Upper	80 % of patients receive entrectinib in year 5

8.2 Results

8.2.1 Base case results

Based on the base case assumptions, the estimated budget impact of recommending entrectinib as a possible standard treatment in Denmark was [redacted] in year 1, and [redacted] in year 5 as shown in Table 27.

The budget impact analysis is indicating, a recommendation of entrectinib is resulting in added costs at AIP-level. The yearly added costs are rising for the first 2 years before stabilizing from year 3 and forward at approximately [redacted]

Table 27. Budget impact for base case scenario

	Year 1	Year 2	Year 3	Year 4	Year 5
Not recommended	[redacted]				
Recommended					
Total budget impact					

8.2.2 Scenario analysis results

For the lower scenario, the budget impact of recommending entrectinib as a possible standard treatment in Denmark was estimated to be [redacted] in year 1, and [redacted] in year 5 as shown in Table 28.

For the upper scenario, the budget impact of recommending entrectinib as a possible standard treatment in Denmark was estimated to be [redacted] in year 1, and [redacted] in year 5 as shown in Table 29.

Table 28. Budget impact analysis results, lower scenario

	Year 1	Year 2	Year 3	Year 4	Year 5
Not recommended	[redacted]				
Recommended					
Total budget impact					

Table 29. Budget impact analysis results, upper scenario

	Year 1	Year 2	Year 3	Year 4	Year 5
Not recommended	[redacted]				
Recommended					
Total budget impact					

9 Discussion

The analysis of the model estimated that treatment of ROS1+ NSCLC with entrectinib results in additional costs when compared to crizotinib in the base case. The cost for both arms of the model are primarily driven by the drug acquisition cost. In the entrectinib arm, higher supportive care and patient cost are estimated, due to the longer time spend in the PP state compared to crizotinib. A sensitivity analysis showed that the incremental cost was not sensitivity to changes in the HR for the “MAIC vs. entrectinib” option for the crizotinib OS extrapolation.

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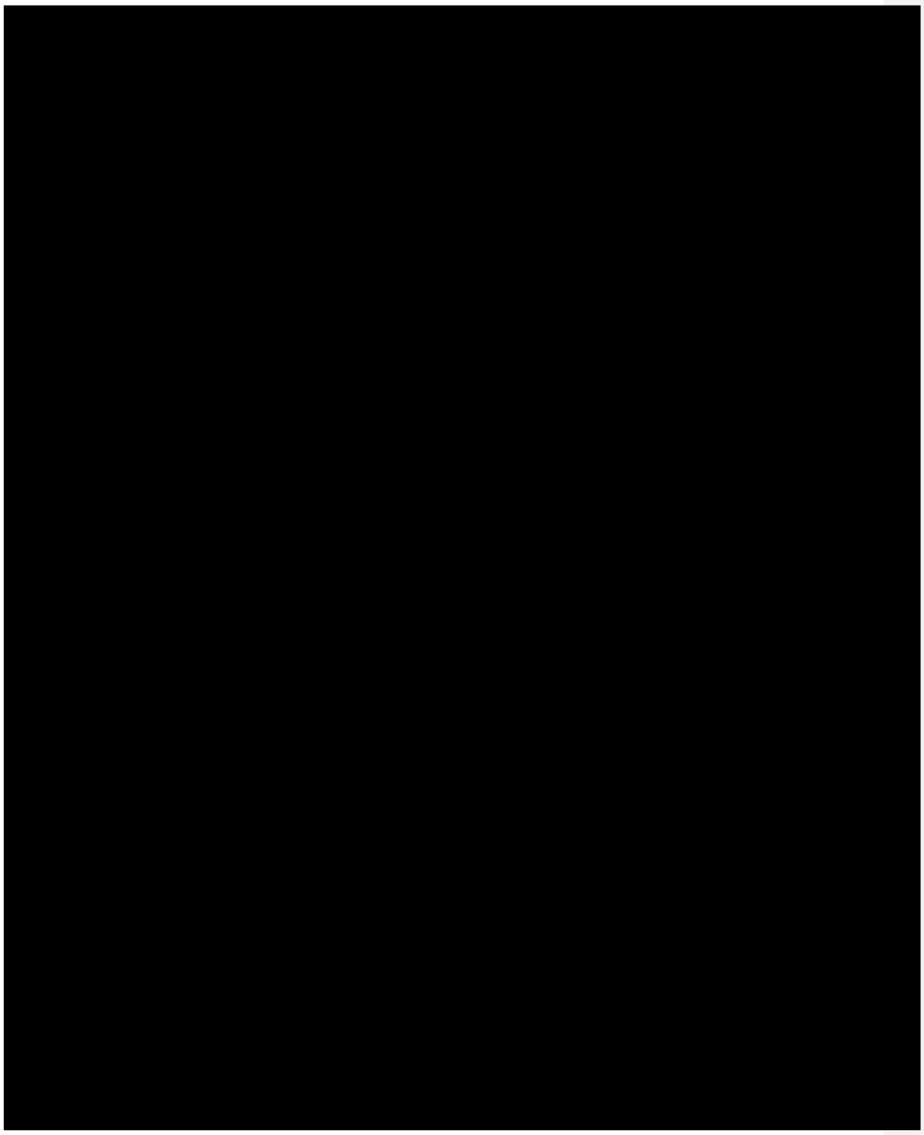
11 Appendix



Medicinrådet

Medicinrådets protokol for vurdering af entrectinib til førstelinjebehandling af uhelbredelig ROS1-positiv ikke-småcellet lungekræft

Versionsnr.: 1.0

Medicinrådet

Om Medicinrådet

Medicinrådet er et uafhængigt råd etableret af Danske Regioner.

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

Om protokollen

Protokollen beskriver, hvordan Medicinrådet vil foretage vurderingen af lægemidlets værdi for patienterne. Den indeholder et eller flere kliniske spørgsmål, som den ansøgende virksomhed skal besvare i deres endelige ansøgning. Til hvert spørgsmål knytter sig en definition af patientgruppen, det lægemiddel vi undersøger, den behandling vi sammenligner med og effektmålene. Udover de(t) kliniske spørgsmål indeholder protokollen også en beskrivelse af, hvordan litteratursøgning, -selektion og databehandling skal foregå.

Protokollen er udarbejdet med udgangspunkt i Håndbog for Medicinrådets proces og metode, som du kan finde på Medicinrådets hjemmeside under siden Metoder, og den ansøgende virksomheds foreløbige ansøgning, der fortæller, hvilke data der findes for lægemidlet.

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

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Indhold

1 Begreber og forkortelser

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

2 Introduktion

Protokollen er udarbejdet, fordi Medicinrådet har modtaget en foreløbig ansøgning fra Roche, som ønsker, at Medicinrådet vurderer entrectinib som førstelinjebehandling af ROS proto-onkogene 1 receptor tyrosin kinase (ROS1)-positiv uhelbredelig ikke-småcellet lungekræft.

Entrectinib har indikation til solide tumorer med neurotrophin receptor tyrosin kinase (NTRK)-fusion (vævsagnostisk indikation) samt ROS1-positiv lungekræft. Denne protokol specificerer, hvordan Medicinrådet vil foretage vurderingen af lægemidlets værdi for patienter med ROS1-positiv lungekræft.

Vi modtog den foreløbige ansøgning den 30. marts 2020.

2.1 Ikke-småcellet lungekræft

Omtrent 4.600 danskere diagnosticeres årligt med lungekræft, og dermed er lungekræft en af de hyppigst forekommende kræftsygdomme i Danmark [1,2]. Af de diagnosticerede har ca. 85-90 % ikke-småcellet lungekræft (NSCLC) [3]. Ikke-småcellet lungekræft inddeles i planocellulære og ikke-planocellulær tumorer. Fagudvalget estimerer, at ca. 25 % af patienterne har planocellulære tumorer, og ca. 75 % har ikke-planocellulære tumorer. Langt de fleste ikke-planocellulære tumorer er såkaldte adenokarcinomer.

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

Lungekræft er inddelt i stadier afhængigt af udbredelsesgrad, jævnfør International Association for the Study of Lung Cancer (IASCL) Tumor, Node, Metastasis (TNM)-klassifikation for lungekræft. De epidemiologiske data i protokollen er relateret til TNM version 7[4], mens man i dansk klinisk praksis i dag anvender version 8 [5]. I henhold til version 7 har patienter med spredning til lymfeknuder svarende til N3-sygdom i stadium IIIB, mens stadium IV betegner metastatisk sygdom. Disse stadier betragtes som udgangspunkt som uhelbredelig NSCLC.

I slutningen af 2016 levede knap 11.151 personer med lungekræft, mens cirka 3.700 personer årligt dør af lungekræft [2]. Den seneste årsrapport fra Dansk Lunge Cancer Register viser, at 1-årsoverlevelsesraten for patienter med lungekræft udredt i 2017 uanset stadie var 51,4 %, mens 5-årsoverlevelsen for patienter udredt i 2013 var 15,9 %[6]. Der er altså tale om en sygdom med en dårlig prognose og kort overlevelse efter diagnosetidspunkt for størstedelen af patienterne.

Behandlingsmålet for patienter med uhelbredelig NSCLC er symptomlindring og levetidsforlængelse. Patienter med uhelbredelig NSCLC kan få forskellige typer behandling afhængig af tumorkarakteristika. Hvis en undersøgelse viser mutationer, som en behandling kan målrettes mod, vil en såkaldt targeteret behandling være første valg. I dansk klinisk praksis drejer det sig på nuværende tidspunkt om aktiverende epidermal growth factor receptor (EGFR)-mutationer samt anaplastisk lymfom kinase (ALK)-translokationer [7]. Targeteret behandling er kun relevant for patienter med uhelbredelig NSCLC og ikke for patienter med NSCLC i tidligere stadier.

En tredje mutation, som er fundet hos nogle patienter med lungekræft, er translokationer som involverer genet ROS proto-onkogene 1 receptor tyrosin kinase (ROS1). Hvis en tumor har en kromosomal translokation, som involverer ROS1 (ROS1-rearrangement), kaldes den ROS1-positiv. ROS1-rearrangementer giver ophav til fusionproteiner, som aktiverer signaleringskaskader involveret i udvikling og spredning af kræft. ROS1-rearrangementer er sjældne i lungekræft og ses i omkring 0,9-2 % af alle undersøgte tilfælde af NSCLC [8]. ROS1-positive patienter ligner patienter med ALK-translokation ved at være yngre end gennemsnitlige patienter med lungekræft, der er flere, som aldrig har røget, og de fleste har

tumor af den histologiske type, adenokarcinom [8]. Med de tilgængelige behandlinger har ROS1-positive patienter ligesom patienter med ALK-translokation eller aktiverende EGFR-mutation en bedre prognose end patienter uden mutationer.

Rearrangementer i ROS1-genet kan detekteres ved hjælp af forskellige teknikker, enten *fluorescence in situ hybridization* (FISH), immunhistokemi eller gensekventering. I dansk klinisk praksis benyttes både FISH, immunhistokemi og sekventering til at undersøge for ROS1-rearrangement som et led i udredningen af patienter med ikke-planocellulær NSCLC. Fagudvalget understreger, at i Danmark bør alle patienter med ikke-planocellulær NSCLC testes for ROS1-rearrangement. Undersøgelsen er en forudsætning for, at relevante patienter kan tilbydes targeteret behandling. Opgørelser for test for ROS1-rearrangement indgår endnu ikke i Dansk Lunge Cancer Gruppes årsrapporter, hvilket gør estimatet af antal patienter usikkert.

Medicinrådet har endnu ikke anbefalet nye lægemidler til ROS1-positive patienter, og indikationen indgik ikke i Medicinrådets behandlingsvejledning for førstelinjebehandling af uhelbredelig NSCLC [7].

Fagudvalget vurderer, at antallet af ROS1-positive patienter med NSCLC i Danmark er ca. 10 om året.

2.2 Entrectinib

Entrectinib er en tyrosin kinase inhibitor (TKI), der virker gennem hæmning af neurotrophin receptor tyrosin kinaser (NTRK), ALK og ROS1. Molekylerne ALK og ROS1 spiller en afgørende rolle for cellevækst og differentiering. Ved at hæmme ROS1 reduceres aktiviteten af de signaleringskaskader, der har betydning for cellernes overlevelse og proliferation [9], og som er særligt aktive i ROS1-positiv NSCLC. På den måde mindsker entrectinib tumors vækst samt spredning.

Der er ansøgt markedsføringstilladelse for entrectinib hos *European Medicines Agency* (EMA). Den forventede indikation er:

Entrectinib som monoterapi er indiceret til behandling af voksne patienter med ROS1-positiv, fremskreden ikke-småcellet lungecancer (NSCLC), der ikke tidligere er behandlet med ROS1-hæmmere.

Der er også ansøgt om markedsføringstilladelse for en tumoragnostisk indikation, nemlig 'sidstelinjebehandling' af patienter med solide tumorer med NTRK-fusion. Denne indikation behandles sideløbende i Medicinrådet af fagudvalget vedr. tværgående kræftlægemidler.

Entrectinib administreres peroralt. Standarddosis er 600 mg én gang dagligt. Entrectinib findes som kapsler på 100 og 200 mg. Behandlingen gives indtil sygdomsprogression eller intolerable bivirkninger.

2.3 Nuværende behandling

For patienter med uhelbredelig NSCLC med en mutation, hvor der er en målrettet (targeteret) behandling til, vil den targeterede behandling være førstevalg for hovedparten af patienterne. Medicinrådets behandlingsvejledning for førstelinjebehandling af uhelbredelig NSCLC beskriver behandlingen af patienter med ALK-translokation og aktiverende EGFR-mutation [7].

Der findes ikke en standardbehandling i Danmark for patienter med uhelbredelig ROS1-positiv NSCLC. I Medicinrådets behandlingsvejledning for førstelinjebehandling af uhelbredelig NSCLC har fagudvalget anført, at "For patienter, som aldrig har røget, kan sjældnere markører (eksempelvis ROS proto-onkogen 1) i nogle tilfælde selektere patienter til targeteret behandling med TKI."

I nuværende dansk klinisk praksis har behandling af patienter med uhelbredelig NSCLC som er ROS1-positive altså været op til en klinisk vurdering. Nogle TKI'er med effekt på ALK-translokationer kan også have effekt på ROS1-positive tumorer. ALK-TKI'en crizotinib har som det hidtil eneste lægemiddel EMA-

indikation til uhelbredelig ROS1-positiv NSCLC. Fagudvalget vurderer, at størstedelen af de ROS1-positive patienter i dansk klinisk praksis behandles med crizotinib.

3 Kliniske spørgsmål

Medicinrådet bruger kliniske spørgsmål til vores vurderinger af lægemidlers værdi for patienterne. Til hvert spørgsmål knytter sig en definition af patientgruppen (population) af det lægemiddel, vi undersøger (interventionen), af den behandling vi sammenligner med (komparator(er)) og af effektmålene.

3.1 Klinisk spørgsmål 1

Hvilken værdi har entrectinib sammenlignet med crizotinib som førstelinjebehandling af patienter med uhelbredelig ROS1-positiv NSCLC?

Population
Patienter med uhelbredelig NSCLC som er ROS1-positiv og ikke tidligere er behandlet med ROS1-hæmmere.

Intervention
Entrectinib 600 mg oralt en gang dagligt.

Komparator
Crizotinib 250 mg oralt to gange dagligt.

Effektmål
De valgte effektmål står i tabel 1.

3.2 Effektmål

Medicinrådet mener, at vurderingen af lægemidlets værdi bliver bedst understøttet af de effektmål, vi har nævnt i tabel 1. For hvert effektmål har Medicinrådet fastsat en mindste klinisk relevant forskel (MKRF). I det følgende afsnit argumenterer vi for valget af effektmål og de mindste klinisk relevante forskelle. Af hensyn til intern konsistens har fagudvalget valgt at benytte tilsvarende effektmål og MKRF, som blev benyttet for targeterede behandlinger i behandlingsvejledningen for førstelinjebehandling af uhelbredelig NSCLC. Fagudvalget har valgt ikke at vurdere rater for overlevelse, PFS og CNS-progression, da det er uvist, på hvilket tidspunkt (12 måneder, 18 måneder eller flere år) en rate vil være mest informativ.

Tabel 1. Effektmål.

Effektmål	Vigtighed	Effektmålsgruppe	Måleenhed	Mindste klinisk relevante forskel
OS (overall survival)	Kritisk	Overlevelse	Median, mdr.	3 måneder
Behandlingsophør grundet uønskede hændelser	Kritisk	Alvorlige symptomer og bivirkninger	Forskel i andel patienter som ophører behandling	5 %-point
CNS-progression	Vigtig	Alvorlige symptomer og bivirkninger	Median, mdr.	3 måneder

PFS	Vigtig	Alvorlige symptomer og bivirkninger	Median, mdr.	3 måneder
Uønskede hændelser	Vigtig	Alvorlige symptomer og bivirkninger	Andel patienter der oplever mindst en grad 3-4 uønsket hændelse	5 %-point
			Gennemgang af bivirkningsprofil	Kvalitativ vurdering
Livskvalitet	Vigtig	Livskvalitet	Gennemsnitlig ændring over tid i EORTC-QLQ-C30	10 point

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

3.2.1 Kritiske effektmål

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

Patienter med targetérbare mutationer overlever generelt længere end patienter uden, men det er svært at finde præcise tal på, hvor længe ROS1-positive patienter lever, når de får førstelinjebehandling med crizotinib. Mange patienter i kliniske studier udvikler resistens for targeteret behandling og har modtaget måske flere behandlingslinjer før og efter, både med kemoterapi og targeteret behandling. Derfor er det svært at estimere, hvor længe patienterne forventes at overleve.

Fagudvalget kan derfor heller ikke udpege en relevant overlevelsesrate (12, 18 eller 24 måneder) til at supplere vurderingen af medianoverlevelse.

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

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

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

3.2.2 Vigtige effektmål

CNS-progression
Patienter med ROS1-positiv NSCLC har ofte spredning til hjernen [8], hvilket medfører betydelig morbiditet. Derfor anser fagudvalget udvikling af sygdom i centralnervesystemet (CNS)-progression som et vigtigt effektmål.

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

Progressionsfri overlevelse (PFS)
Progressionsfri overlevelse (PFS) bliver anvendt til at vurdere, hvor lang tid der går, inden sygdommen udvikler sig. PFS er defineret som tiden fra randomisering til første dokumentation af progression i henhold til Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 [10] eller dødsfald.

Patienter tåler generelt behandling med en TKI godt i sammenligning med andre typer behandling, såsom kemoterapi. Fagudvalget vurderer derfor, at det har stor betydning for patienterne at forblive i behandling med en TKI længst muligt, pga. den favorable bivirkningsprofil. I senere behandlingslinjer vil patienterne blive tilbudt platinbaseret kemoterapi, der betragtes som mere bivirkningstungt. Derfor vurderer fagudvalget, at PFS kan være et vigtigt effektmål, som afspejler symptombyrde.

I studier af crizotinib til ROS1-positive patienter har median PFS varieret mellem ca. 10 og 19 måneder, hvilket kan afspejle, at patienterne i disse studier har modtaget et forskelligt antal behandlingslinjer før crizotinib [8]. Fagudvalget vurderer, at 3 måneder er den mindste klinisk relevante forskel. Dette svarer til den mindste klinisk relevante forskel defineret i tidligere vurderinger af targeteret behandling til uhelbredelig NSCLC.

Uønskede hændelser
Forekomst af uønskede hændelser grad 3-4 er et udtryk for alvorlig toksicitet af lægemidlet [11]. På den baggrund vurderer fagudvalget, at uønskede hændelser er et vigtigt effektmål. Fagudvalget ønsker data på nedenstående måleenheder.

- Uønskede hændelser grad 3-4
  Fagudvalget finder, at forskellen i andelen af patienter, som i løbet af opfølgningstiden oplever én eller flere hændelser af grad 3 eller 4, er relevant for vurderingen. Hændelser af grad 3-4 er defineret i henhold til National Cancer Institute CTCAE version 4.03 [11].

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

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

Livskvalitet
Livskvalitet kan for NSCLC-patienter måles med flere forskellige instrumenter. I dette tilfælde vil vurdering af livskvalitet blive baseret på følgende: European Organisation for Research and Treatment of Cancer Quality-of-life Questionnaire-Core 30 (EORTC QLQ-C30) [12,13].

EORTC QLQ-C30 består af 30 spørgsmål omhandlende funktionsniveau, symptomer samt selvevalueret globalt helbred og livskvalitet. Data fra hvert domæne konverteres til en scoringsskala fra 0-100 [12]. Fagudvalget vil i deres vurdering tage udgangspunkt i resultater for global livskvalitet. Den mindste klinisk relevante forskel baserer sig på en lille ændring, defineret som 5-10 point på den globale skala [14]. En moderat ændring er 10-20 point, og en stor ændring er > 20 point. Fagudvalget har defineret den mindste klinisk relevante forskel som ≥ 10 point, da dette vil overstige mindstegrænsen for en lille ændring. Dette svarer til den mindste klinisk relevante forskel defineret i tidligere vurderinger af targeteret behandling til uhelbredelig NSCLC.

4 Litteratursøgning

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

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

Søgestreng til PubMed og CENTRAL:

#	Query	Hits
	PUBMED	
1	**entrectinib**[nm] OR entrectinib[tiab] OR Rozlytrek*[tiab] OR NMS-E628[tiab] OR RXDX-101[tiab]	99
2	**crizotinib**[mh] OR crizotinib*[tiab] OR Xalkori*[tiab]	2309
3	NSCLC[tiab]	42025
4	carcinoma, non-small-cell lung[mh]	52122
5	adenocarcinoma of lung[mh]	8170
6	(nonsmall cell[tiab] or non-small cell[tiab] or squamous cell[tiab] or large cell[tiab]) AND (cancer[tiab] or carcinoma[tiab] or carcinomas[tiab] OR adenocarcinoma*[tiab])	166666
7	ROS1[tiab] OR ROS-1[tiab] OR ROS proto-oncogene 1[tiab]	1345
8	((#1 OR #2) AND (#3 OR #4 OR #5 OR #6) AND #7)	280
9	(case report[ti] OR review of the literature[tiab] OR retrospective[ti] OR observational[ti])	423117

10	(Case Reports[pt] OR Comment[pt] OR Editorial[pt] OR Guideline[pt] OR Letter[pt] OR Review[pt])	6217649
11	**(#8 NOT (#9 OR #10))**	**143**
	CENTRAL	
1	(entrectinib or Rozlytrek* or "NMS E628" or "R2XDX 101"):ti,ab,kw	10
2	(crizotinib or Xalkori*):ti,ab,kw	300
3	(ROS1 or ROS-1 or "ROS next proto next oncogene 1"):ti,ab,kw	102
4	(#1 OR #2) AND #3	**33**
5	"conference abstract":pt	153136
6	**#4 not #5**	**7**

Kriterier for litteratursøgning

Ansøger skal søge relevant litteratur i databaserne PubMed og CENTRAL (via Cochrane Library). Ansøger skal dokumentere søgningen for hver af de to databaser, f.eks. i form af et skærmklip eller en downloadet søgestrategi. Eventuelle ændringer/tilføjelser til søgestrategien skal fremgå af dokumentationen.

Kriterier for udvælgelse af litteratur

Ansøger skal screene de artikler, der identificeres ved databasesøgningerne, for overensstemmelse med de i protokollen definerede kliniske spørgsmål samt kriterier for studie- og publikationstype(r). Det vil sige, at ansøger skal ekskludere artikler med andre populationer end de i protokollen specificerede. Dette gælder ligeledes for artikler, som ikke rapporterer mindst ét af de kritiske eller vigtige effektmål.

Den ansøgende virksomhed skal ved screening af artikler ekskludere først på titel- og abstractniveau, dernæst ved gennemlæsning af fuldtekstartikler. Artikler, der ekskluderes ved fuldtekstlæsning, skal fremgå af en eksklusionsliste, hvor eksklusionen begrundes kort. Den samlede udvælgelsesproces skal afrapporteres ved brug af et flowdiagram som beskrevet i PRISMA-Statement (http://prisma-statement.org/PRISMAStatement/FlowDiagram.aspx).

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

5 Databehandling og -analyse

Ansøger skal bruge Medicinrådets ansøgningsskema til sin endelige ansøgning. Vær opmærksom på følgende:

Studier og resultater

- Beskriv de inkluderede studier og baselinekarakteristikken af studiepopulationerne.
- Angiv hvilke studier/referencer, der er benyttet til at besvare hvilke kliniske spørgsmål.
- Brug som udgangspunkt ansøgningsskemaet til ekstraktion af al relevant data.

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

Statistiske analyser

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

Metaanalyser

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

Narrative analyser

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

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

6 Evidensens kvalitet

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

7 Andre overvejelser

Fagudvalget ønsker informationer, der kan belyse en vurdering af, hvorvidt og hvordan indførelsen af den ansøgte intervention i dansk klinisk praksis vil påvirke behandlinger i efterfølgende behandlingslinjer, hvad angår type, varighed og forventet effekt.

Fagudvalget ønsker ikke at benytte objektiv respons rate (ORR) som et effektmål, der indgår i kategoriseringen af lægemidlet, men beder ansøger om at redegøre for ORR for ROS1-positive patienter behandlet med entrectinib og crizotinib i ”andre overvejelser”. Resultaterne kan evt. indgå i en perspektivering af kategoriseringen.

Fagudvalget gør opmærksom på, crizotinib ikke har været behandlet af Medicinrådet til ROS1-positive patienter, og at erfaringen med behandling på denne indikation er sparsom i Danmark.

Derudover understreger fagudvalget, at der er begrænset erfaring i dansk klinisk praksis med hensyn til eventuel dosisreduktion af crizotinib hos ROS1-positive patienter.

8 Relation til behandlingsvejledning

Medicinrådets gældende behandlingsvejledning vedr. førstelinjebehandling af uhelbredelig NSCLC omfatter ikke patienter med ROS1-positiv NSCLC, og fagudvalget vil derfor ikke tage stilling til en foreløbig placering af lægemidlet. Fagudvalget vil efter behandling af entrectinib tage stilling til, om populationen af ROS1-positive patienter skal indgå i fremtidige behandlingsvejledninger og lægemiddelrekommandationer for uhelbredelig NSCLC.

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10 Sammensætning af fagudvalg og kontaktinformation til Medicinrådet

Medicinrådets fagudvalg vedrørende lungekræft

Formand	**Indstillet af**
Halla Skuladottir Overlæge, dr.med.	Lægevidenskabelige Selskaber
Medlemmer	**Udpeget af**
Kan ikke opfylde Medicinrådets habilitetskrav	Region Nordjylland
Udpegning i gang	Region Midtjylland
Stefan Starup Jeppesen Overlæge, ph.d.	Region Syddanmark
Jeanette Haar Ehlers Overlæge	Region Sjælland
Lotte Engell-Nørregård Overlæge, ph.d.	Region Hovedstaden
Nille Behrendt Overlæge	Dansk Patologiselskab
Peder Fabricius Ledende overlæge	Dansk Selskab for Lungemedicin
Nina Hannover Bjarnason Overlæge, dr.med.	Dansk Selskab for Klinisk Farmakologi
Annie Lorenzen Klinisk farmaceut	Dansk Selskab for Sygehusapoteksledelse
Morten Hiul Suppli Afdelingslæge, ph.d.	Dansk Selskab for Klinisk Onkologi
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Ønsker ikke at udpege yderligere medlemmer	Dansk Lunge Cancer Gruppe
Finn Klausen Patient/patientrepræsentant	Danske Patienter
Lisbeth Søbæk Hansen Patient/patientrepræsentant	Danske Patienter

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Jan Odgaard Jensen (biostatistiker) Tenna Bekker (teamleder)

11 Versionslog

Version	Dato	Ændring
1.0	11.06.2020	Godkendt af Medicinrådet.