Medicinrådet

Bilag til Medicinrådets anbefaling vedrørende entrectinib til behandling af NTRK-fusion-positiv kræft

Vers. 1.0

Bilagsoversigt

1. Medicinrådets sundhedsøkonomiske afrapportering vedr. entrectinib, version 1.0
2. Forhandlingsnotat fra Amgros vedr. entrectinib
3. Høringssvar fra ansøger, inkl. eventuel efterfølgende dialog
4. Medicinrådets vurdering vedr. entrectinib til behandling af NTRK-fusion-positiv kræft, version 1.0
5. Ansøgers endelige ansøgning
6. Ansøgers tekniske dokument til den sundhedsøkonomiske ansøgning
7. Medicinrådets protokol for vurdering vedr. entrectinib til behandling af NTRK-fusion-positiv kræft, version 1.0

Medicinrådet

Medicinrådets sundheds-økonomiske afrapportering

Entrectinib

NTRK-fusion-positiv kræft

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 NRTK-fusion-positiv kræft 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 2.4 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
BSC	*Best supportive care*
DKK	Danske kroner
DRG	Diagnose Relaterede Grupper
GBP	British pound
KM	Kaplan-Meier
NTRK	Neurotrofisk tyrosinreceptorkinase
NGS	Next-generation sequencing
OS	Overlevelse
PD	Progredieret overlevelse
PFS	Progressionsfri overlevelse
TTD	*Time to Treatment Discontinuation*
SAIP	Sygehusapotekernes indkøbspris
SmPC	*Summary of Product Characteristics*

2. Opsummering

Baggrund

Entrectinib som monoterapi er indiceret til behandling af voksne og børn (≥ 12 år) med solide tumorer, der udtrykker en NTRK-genfusion, der har en sygdom, der er lokalt avanceret, metastatisk, eller hvor kirurgisk resektion sandsynligvis vil resultere i svær morbiditet, og der ikke tidligere er behandlet med en NTRK-inhibitor, og som ikke har nogen andre tilfredsstillende behandlingsmuligheder. 10-40 patienter vil årligt kandidere 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 30 år. Entrectinib sammenlignes med *best supportive care* (BSC) til patienter med solide tumorer, der udtrykker en NTRK-genfusion.

Inkrementelle omkostninger og budgetkonsekvenser

I det scenarie, sekretariatet mener, er mest sandsynligt, er de inkrementelle omkostninger for entrectinib ca. [redacted] DKK sammenlignet med BSC. Hvis analysen udføres med AIP, bliver de inkrementelle omkostninger til sammenligning ca. 789.000 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 budgetkonsekvenser ca. 15,7 mio. DKK i år 5.

Konklusion

De inkrementelle omkostninger er i høj grad drevet af lægemiddelomkostningerne for entrectinib, men omkostninger til test for NTRK-fusion udgør også en stor del af de inkrementelle omkostninger. Den sundhedsøkonomiske analyse indeholder en række parametre og elementer, som bidrager med usikkerhed. De væsentligste usikkerheder er størrelsen af omkostninger til test for NTRK-fusion, potentiel forskel mellem patientpopulationer, da patienterne behandlet med BSC i studiet har ukendt NTRK-status, samt at modellen er baseret på en naiv sammenligning med BSC. Desuden er der kun udført en sundhedsøkonomisk analyse af klinisk spørgsmål 1, da der ikke foreligger data til at gennemføre en analyse af klinisk spørgsmål 2.

3. Baggrund for den sundhedsøkonomiske analyse

Roche (herefter omtalt som ansøger) er markedsføringstilladelsesindehaver af entrectinib og har den 3. november 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

En solid tumor er en unormal vævsmasse (svulst). Solide tumorer kan være benigne (ikke kræft) eller maligne (kræft), hvor sidstnævnte kan gennemtrænge væv eller sprede sig til andre dele af kroppen. Kræft inddeles i forskellige typer, afhængig af hvilken celletype kræften udgår fra. Solidt voksende kræfttyper kan overordnet inddeles i f.eks. sarkomer (bløddels- og knoglekræft), karcinomer (epitel deriverede kræftformer), neurogen deriverede tumorer og melanomer (modermærkekræft). For hver af disse overordnede kræfttyper findes talrige undertyper, baseret på hvilken celletype de udgår fra, hvilke histopatologiske og eventuelle molekylærbiologiske forandringer der kendetegner kræften [1,2]. De forskellige kræfttyper rammer forskelligt i befolknings- og aldersgrupper og kræver forskellig diagnostik og behandling.

Forekomsten af kræft i Danmark er stigende, og ca. 1/3 af alle danskere vil få kræft i løbet af deres liv. Antallet af nye tilfælde pr. år er ca. 40.000, lidt flere mænd end kvinder. Den største andel af nye kræfttilfælde er i den ældre del af befolkningen. 2/3 af alle nye kræfttilfælde er hos personer over 60 år. Lidt over 280.000 nulevende danskere har på et tidspunkt fået konstateret kræft, og 6 ud af 10 kræftpatienter overlever deres sygdom i mindst 5 år [3].

Selvom kræft er sjældent hos børn (under 18 år), er det den næst hyppigste dødsårsag efter 1-årsalderen. Mindre end 1 % af alle kræfttilfælde forekommer hos børn, og ca. 200 børn får årligt konstateret kræft. Den 5-årige overlevelsesrate for børn med kræft er på ca. 80 %. Fordelingen af kræfttyperne hos børn er helt anderledes end hos voksne [3]. Voksne får således typisk karcinomer, mens børn hyppigst får blodkræft [4].

Neurotrofisk tyrosinkinase (NTRK) er navnet på en gruppe af tre gener, NTRK1, NTRK2 og NTRK3, der koder for tyrosinreceptorkinaser (Trk) A, B og C. Trk er afgørende for normale nervecellers udvikling og overlevelse. Genfusioner, der involverer NTRK1, NTRK2 eller NTRK3, koder for Trk-fusionsproteiner, som kan medføre ukontrolleret Trk-signalering og dermed tumorvækst [5,6]. NTRK-fusioner er sjældne og påvises med yderst varierende hyppighed på tværs af tumortyper hos både børn og voksne. Herudover er det uvist, om der er geografiske og epidemiologiske forskelle i forekomst af NTRK-fusioner. NTRK-fusioners hyppighed i forskellige kræftformer er angivet i tabellen nedenfor. Dette skal

dog tages med forbehold for de ovennævnte forskelle. Frekvenserne for NTRK-fusion for forskellige kræftformer er præsenteret i Tabel 1.

Tabel 1: Oversigt over frekvens for NTRK-fusion ved forskellige kræftformer.

Kræftform	Frekvens for NTRK-fusion
Infantil fibrosarkom	Omkring 100 % [7,8]
Sekretorisk karcinom i både spytkirtel og bryst	Omkring 100 % [7,8]
Kræfttyper i luftveje, fordøjelseskanal, bryst og hjerne	< 5 % [7,8]
Lungekræft, kolorektalkræft, modermærkekræft og brystkræft	0,1-1 % [9]

Samlet vurderer fagudvalget, at der årligt vil være 10-40 patienter (voksne og børn) med NTRK-fusioner som kandiderer til behandling med entrectinib.

3.1.1 Komparator

Medicinrådet har defineret placebo eller best supportive care som komparatorer til entrectinib, se Tabel 2.

Tabel 2: Definerede populationer og komparatorer.

Population	Komparator
Patienter ≥ 18 år med lokalfremskreden eller metastatisk kræft med NTRK-fusion, hvor alle øvrige tilfredsstillende behandlingsmuligheder er udtømte.	Placebo eller best supportive care
Patienter mellem 12 og 18 år med lokalfremskreden eller metastatisk kræft med NTRK-fusion, hvor alle øvrige tilfredsstillende behandlingsmuligheder er udtømte.	Placebo eller best supportive care

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 værdi af entrectinib som vedligeholdelsesbehandling og specificeret følgende kliniske spørgsmål:

Klinisk spørgsmål 1:
Hvad er den kliniske merværdi af entrectinib til behandling af voksne med NTRK-fusion-positiv kræft, hvor øvrige behandlingsmuligheder er udtømte, sammenlignet med placebo?

Klinisk spørgsmål 2:
Hvad er den kliniske merværdi af entrectinib til behandling af børn med NTRK-fusion-positiv kræft, hvor øvrige behandlingsmuligheder er udtømte, sammenlignet med placebo?

4. Vurdering af den sundhedsøkonomiske analyse

Ansøger har indsendt en sundhedsøkonomisk analyse, der estimerer de inkrementelle omkostninger pr. patient for entrectinib sammenlignet med best supportive care (BSC). I det nedenstående vil den sundhedsøkonomiske model, som ligger til grund for estimeringen af de inkrementelle omkostninger pr. patient, blive præsenteret. Ansøger har kun indleveret en sundhedsøkonomisk analyse af klinisk spørgsmål 1, da ansøger argumenterer for, at der ikke foreligger tilstrækkelige data til at udføre en sundhedsøkonomisk analyse af klinisk spørgsmål 2. På baggrund heraf omhandler resten af denne afrapportering udelukkende klinisk spørgsmål 1.

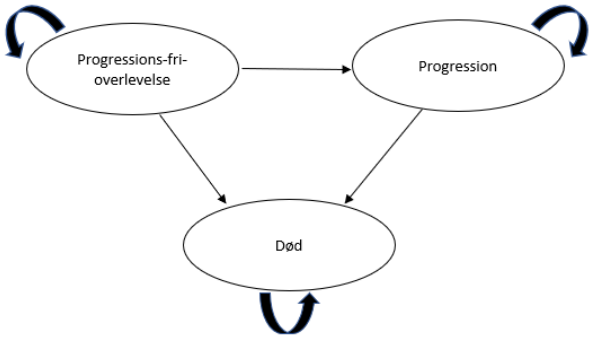
4.1 Antagelser og forudsætninger for model

Den sundhedsøkonomiske model har til formål at estimere de inkrementelle omkostninger ved behandling af patienter med entrectinib til NTRK-fusion-positiv kræft. 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 BSC, har ansøger valgt at foretage en naiv sammenligning med BSC. Til denne sammenligning anvender ansøger data fra BSC-armen fra en række studier med andre lægemidler, som ligger inden for entrectinibs indikation, se Tabel 3. Disse studier er identificeret baseret på en søgestreng, som Medicinrådet har angivet i protokollen.

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 kan være i PFS-stadiet, indtil de progredierer, hvorefter de er i PD-stadiet, indtil de dør. Der vil dog også være nogle patienter, der går direkte fra PFS-stadiet til død af andre årsager. I løbet af PFS-stadiet bliver patienter behandlet med enten entrectinib eller BSC.

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 for entrectinib-armen ud fra estimerede og ekstrapolerede data baseret på Kaplan-Meier (KM)-data for TTD (Time to Treatment Discontinuation), PFS og OS. Disse KM-data kommer fra et kombineret datasæt bestående af data fra ALKA-372-001, STARTRK-1 og STARTRK-2 og er kun tilgængelige for entrectinib [10,11]. Ansøger har estimeret og ekstrapoleret TTD, PFS og OS-kurverne individuelt med en [redacted]. Dette er valgt, da den [redacted] funktion udviser det bedste statistiske fit for alle 3 kurver. Kurverne for TTD, PFS og OS er præsenteret i Figur 2, Figur 3 og Figur 4.

[redacted]

Figur 2. TTD for entrectinib for patienter med NTRK-fusion-positiv kræft.

Figur 3. PFS for entrectinib for patienter med NTRK-fusion-positiv kræft.

Figur 4. OS for entrectinib for patienter med NTRK-fusion-positiv kræft.

For BSC anvender ansøger den mediane PFS og OS fra BSC-armen fra en række studier med andre lægemidler til at approksimere den gennemsnitlige PFS og OS ved at antage, at PFS- og OS-kurverne følger en eksponentiel funktion. Disse studier er identificeret baseret på en søgestreng, som er stillet til rådighed af Medicinrådet. I disse studier er ikke oplyst NTRK-status men alle senstadier af kræft, som ligger inden for entrectinibs indikation. I alt indgår 10 studier for kolorektalkræft, 10 studier for ikke-småcellet lungekræft og 8 studier med andre relevante kræftformer, som ansøger anvender til at approksimere PFS og OS for de specifikke sygdomme. Disse er præsenteret i Tabel 3. For de øvrige relevante kræftformer, hvor entrectinib potentielt er en relevant behandling, men hvor ansøger ikke har identificeret et studie, som kan anvendes til at approksimere PFS og OS, anvender ansøger den gennemsnitlige PFS og OS fra alle studierne præsenteret i Tabel 3.

Tabel 3: Mediane PFS og OS anvendt til udregning af den gennemsnitlige PFS og OS for patienter i behandling med BSC.

Sygdom	Median PFS [måneder]	Median OS [måneder]	Antal studier [antal]
Kolorektalkræft	1,90	5,19	10
Ikke-småcellet lungekræft	2,39	5,52	10
Gastrointestinale stromale tumorer	2,59	12,9	2
Bugspytkirtelkræft	1,41	2,59	3
Sarkomer	1,40	10,80	1
Hjernetumor	3,68	6,9	1
Melanom	N/A	4,5	1
Gennemsnit	**2,06**	**5,54**	

Sekretariatets vurdering

Fagudvalget vurderer, at de estimerede og ekstrapolerede TTD-, PFS- og OS-kurver er klinisk plausible, men pointerer, at der er stor usikkerhed ved ekstrapoleringen. Desuden bemærker fagudvalget, at der er stor usikkerhed omkring de antagne PFS og OS for BSC, da NTRK-status i de anvendte studier er ukendt, samt at fagudvalget i udarbejdelsen af vurderingsrapporten har fundet, at de repræsenterede tumortyper varierer væsentligt fra sammensætningen i entrectinibpopulationen. Fagudvalget vurderer, at de samlede effektestimater på tværs af alle tumortyper ikke kan anvendes som sammenligningsgrundlag i den kliniske vurdering, men at kun OS- og PFS-data fra de individuelle tumortyper i placeboanalysen kan anvendes som supplerende sammenligningsgrundlag for entrectinib, hvor data er opgivet på enkelttumorniveau. I sundhedsøkonomiske analyser er kvantitative estimater dog nødvendige, og derfor er de accepteret her, men sekretariatet pointerer, at estimaterne er hæftet med betydelig usikkerhed.

Sekretariatet accepterer ansøgers tilgang vedr. ekstrapolering og data men pointerer, at disse data og ekstrapoleringer er forbundet med betydelig usikkerhed.

4.1.2 Analyseperspektiv

Ansøgers omkostningsanalyse har et begrænset samfundsperspektiv. Analysen har en tidshorisont på 30 år. Dette er valgt, da ansøger argumenterer for, at den gennemsnitlige behandlingslængde med entrectinib og komparatorer ligger inden for denne tidshorisont. Omkostninger, der ligger efter det første år, er diskonteret med en rate på 4 %.

Sekretariatets vurdering
Sekretariatet accepterer ansøgers tilgang vedr. analyseperspektiv, tidshorisont og diskontering.

4.2 Omkostninger

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

4.2.1 Lægemiddelomkostninger

Ansøger antager, at 25 % af patienter, som modtager BSC, vil modtage carboplatin, mens de resterende patienter ikke vil modtage behandling. Ansøger argumenter dog for, at de resterende patienter i dansk klinisk praksis sandsynligvis vil modtage en form for behandling, men dette er ikke inkluderet. Ansøger antager, at patienter får behandling med carboplatin indtil progression, mens ansøger anvender TTD som behandlingslængde for patienter i behandling med entrectinib. Ansøger har hentet doser fra de respektive produkters produktresuméer (SmPC'er).

Behandling med entrectinib:
600 mg entrectinib én gang dagligt.

Best supportive care:
400 mg/m2 carboplatin IV hver 4. uge for 25 % af patienterne.
Ingen behandling for 75 % af patienterne.

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 (marts 2021).

Lægemiddel	Styrke	Pakningsstørrelse	Pris [DKK]	Betingede pris* [DKK]	Kilde
Entrectinib	100 mg	30 stk.	[redacted]	[redacted]	Amgros
Entrectinib	200 mg	90 stk.	[redacted]	[redacted]	Amgros
Carboplatin	10 mg/ml	15 ml	[redacted]		Amgros
Carboplatin	10 mg/ml	45 ml	[redacted]		Amgros

[redacted]

Ansøger anvender det gennemsnitlige overfladeareal (1,82 m2) og gennemsnitlige dosis intensitet ([redacted]) fra STARTRK-2-studiet til at udregne lægemiddelomkostningerne ved carboplatin og entrectinib.
Ansøger antager, at det ikke er muligt at dele hætteglas ved behandling med carboplatin, og der vil derfor opstå spild. Ansøger antager derimod ikke, at der vil opstå spild ved behandling med entrectinib. Det er dog muligt manuelt at inkludere omkostninger til spild i analysen, og her antager ansøger, at patienter vil få udleveret én pakke af entrectinib, og hvis patienten dør, så vil resten af pakken gå til spilde. Ansøger antager, at denne spildte pakke udgør et gennemsnit af de to pakningsstørrelser.

Sekretariatets vurdering
Fagudvalget vurderer, at meget få eller ingen af patienterne i BSC vil modtage platinbaseret kemoterapi, men derimod at patienterne sandsynligvis vil modtage symptomlindrende behandling. Symptomlindrende behandling er ikke inkluderet i modellen, hvilket bidrager til usikkerhed omkring resultatet. Usikkerheden peger dog i retning af underestimerede omkostninger for BSC og dermed overestimering af de inkrementelle omkostninger. Fagudvalget vurderer desuden, at der vil opstå lægemiddelspild, men også at der potentielt vil være større spild ved entrectinib end antaget af ansøger. Dette skyldes, at patienter sandsynligvis vil få udleveret mere end én pakke medicin ad gangen, men dette er svært at kvantificere og vil variere mellem behandlingsstederne. Der er ligeledes usikkerhed omkring, hvilken pakningstørrelse som udleveres ved behandling med entrectinib. Ansøger antager, hvis spild inkluderes, at der udleveres den lille pakning (100 mg og 30 stk.) til halvdelen af patienterne og den store pakning (200 mg og 90 stk.) til den anden halvdel. 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. Der er således usikkerhed på to parametre vedr. lægemiddelspild for entrectinib: pakningsstørrelsen og mængden af udleverede pakninger.

Sekretariatet accepterer ansøgers antagelser vedr. lægemiddelomkostninger, men vælger at anvende muligheden for at inkludere omkostninger til lægemiddelspild. Desuden bemærker sekretariatet, at denne metode er forbundet med usikkerhed omkring lægemiddelspildet, og at det sandsynligvis er underestimeret. Sekretariatet vælger yderligere at ekskludere omkostninger til platinbaseret kemoterapi for patienter i BSC, da fagudvalget vurderer, at ingen eller meget få patienter vil modtage platinbaseret kemoterapi.

4.2.2 Hospitalsomkostninger

Da entrectinib administreres oralt, har ansøger ikke inkluderet nogen faste administrationsomkostninger, men har dog inkluderet ét besøg på hospitalet i første cyklus til oplæring i egen administration. For kemoterapien i BSC, carboplatin, har ansøger inkluderet hospitalsomkostninger til administration. Ansøger har anvendt DRG-takster til at estimere hospitalsomkostninger, se Tabel 5.

Tabel 5: Omkostninger til lægemiddeladministration.

	Enhedsomkostning [DKK]	Frekvens	Kilde
Oplæring i administration af entrectinib	1.799	Engangsomkostning	DRG 2020: 04MA98
Administration af carboplatin	1.949	Hver 3. uge	DRG 2020: 04MA98

Ansøger inkluderer desuden omkostninger til monitorering af både patienter i behandling med entrectinib og BSC. Ansøger antager, at monitoreringsfrekvensen er ens for begge behandlinger, men varierer indholdet og frekvensen af monitorering afhængig af sygdomsstadiet, se Tabel 6.

Tabel 6: Omkostninger til monitorering.

	Andel	Frekvens	Tidsforbrug	Enhedsomkost-ning [DKK]	Kilde
PFS – Første cyklus					
Onkolog konsultation	100 %	Én gang	90 min	1.316 DKK/pr. time	Medicinrådets værdisætning af enhedsomkostninger
Sygeplejerske	100 %	Én gang	90 min	554 DKK/pr. time	Medicinrådets værdisætning af enhedsomkostninger
Blodprøver	100 %	Én gang	30 min	352 DKK	Mikrobaseret tilgang med udgang i Rigshospitalets labportal
CT-scanning	100 %	Én gang	60 min	2.470 DKK	DRG 2020: 36PR07

	Andel	Frekvens	Tidsforbrug	Enhedsomkost-ning [DKK]	Kilde
PFS – Efterfølgende cyklus					
Onkolog konsultation	100 %	Hver 3. måned	30 min	1.316 DKK/pr. time	Medicinrådets værdisætning af enhedsomkostninger
Sygeplejerske	100 %	Hver 3. måned	60 min	554 DKK/pr. time	Medicinrådets værdisætning af enhedsomkostninger
MR-scanning	5 %	Hver 3. måned	60 min	2.470 DKK	DRG 2020: 36PR07
Blodprøver	100 %	Hver 3. måned	30 min	352 DKK	Mikrobaseret tilgang med udgang i Rigshospitalets labportal
CT-scanning	100 %	Hver 3. måned	60 min	2.470 DKK	DRG 2020: 36PR07
Efter progression					
Onkolog konsultation	100 %	Hver 3. måned	30 min	1.316 DKK/pr. time	Medicinrådets værdisætning af enhedsomkostninger
Sygeplejerske	100 %	Hver 3. måned	60 min	554 DKK/pr. time	Medicinrådets værdisætning af enhedsomkostninger
MR-scanning	5 %	Hver 3. måned	60 min	2.470 DKK	DRG 2020: 36PR07
Blodprøver	100 %	Hver 3. måned	30 min	352 DKK	Mikrobaseret tilgang med udgang i Rigshospitalets labportal
CT-scanning	100 %	Hver 3. måned	60 min	2.470 DKK	DRG 2020: 36PR07

Ansøger antager, at omkostninger til test for NRTK-fusion kan approksimeres med en DRG-takst. DRG-taksten dækker over "Genetisk risikovurdering og rådgivning" og udgør en omkostning på 3.444 DKK. Desuden antager ansøger, at der på nuværende tidspunkt anvendes NGS-test rutinemæssigt i 3 af landets 5 regioner, og derfor antager ansøger, at de resterende 40 % af patienterne vil modtage NGS-test, hvis entrectinib anbefales. Omkostningerne er præsenteret i Tabel 7.

Tabel 7: Omkostninger til test for NTRK.

	Andel	Frekvens	Enhedsomkostning [DKK]	Kilde
NGS-test	40 %	Én gang	3.444	DRG 2020: 31PR03

Ansøger har desuden inkluderet terminalomkostninger. Her anvender ansøger et engelsk studie [12] fra 2014, der estimerer de totale omkostninger til håndtering af terminale

kræftpatienter. I studiet deles patienter op i omkostninger 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 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 engelske pund, hvilket ansøger omregner til 2020-priser i danske kroner. Dette gøres ved at anvende valutakursen mellem DKK og GBP fra en ukendt dato, den relative købekræftsparitet mellem England og Danmark fra 2013 samt nettoprisindekset fra 2013 til 2020.

Sekretariatets vurdering

Fagudvalget vurderer, at frekvensen hvormed patienter i PFS skal monitoreres eller have udleveret medicin vil være én gang om måneden. Desuden vurderer fagudvalget, at patienter ikke vil monitoreres efter progression.

Fagudvalget vurderer ikke, at 60 % af patienterne bliver testet rutinemæssigt på nuværende tidspunkt, og vurderer, at ansøgers estimat af testomkostninger er undervurderet, da det ikke inkluderer omkostninger til test af patienter, som ikke har NTRK-fusioner. Fagvalget vurderer, at der årligt er ca. 10.000 danske patienter, som har uhelbredelig kræft [4], og at ca. 1/3 af disse vil udtømme øvrige behandlingsmuligheder, men stadig være i tilstrækkelig performancestatus til at modtage yderligere behandling. Det er således i ovenstående population, at man skal identificere de patienter, som kan være kandidater til behandling med entrectinib. Af disse vurderer fagudvalget, at mellem 1.000 og 1.500 patienter vil have modtaget en test i tidligere behandlingsforløb, og derfor vurderer fagudvalget, at der skal testes mellem 1.500 og 2.000 patienter årligt for at finde de 10-40 patienter, som vil være kandidater til entrectinib.

Fagudvalget vurderer derfor ikke, at ansøgers anvendte testomkostning repræsenterer de faktiske testomkostninger. Fagudvalget vurderer, at patienter indledningsvist skal testes med immunohistokemi (IHC) til en omkostning på ca. 600 DKK. Påvises NTRK-fusion ved IHC følges op med en NGS-test. IHC vil føre til nogle falsk positive prøver, hvilket betyder, at ca. 40 patienter vil skulle testes ved NGS til en omkostning på ca. 5.000 DKK for at finde de 20 patienter, som ansøger antager. Fagudvalget vurderer derfor, at de samlede årlige testomkostninger bliver mellem 1,1 mio. DKK og 1,4 mio. DKK (1.500-2.000 x 600 + 40 x 5.000), hvilket betyder, at den gennemsnitlige testomkostning per patienter bliver 55.000-70.000 DKK. Dette scenarie anvendes i hovedanalysen.

Et alternativt scenarie er bred testning med NGS. I dette scenarie vil samtlige 1.500-2.000 patienter testes med NGS, men vil ikke kræve yderligere test efterfølgende. I det scenarie vil de gennemsnitlige testomkostninger per patienter bliver 375.000-500.000 DKK (1.500-2.000 x 5.000). Denne teststrategi udforskes i en følsomhedsanalyse. Desuden bliver de gennemsnitlige testomkostninger påvirket af patientantallet, således at et højere patientantal reducerer de gennemsnitlige testomkostninger, og et lavere patientantal øger de gennemsnitlige testomkostninger. Sekretariatet vælger derfor også at foretage en følsomhedsanalyse, hvor patientantallet justeres, og en følsomhedsanalyse helt uden testomkostninger.

Sekretariatet vælger desuden at omregne terminalomkostninger fra GBP til DKK baseret på den gennemsnitlige valutakurs fra 2013 fremfor en specifik valutakurs fra en ikke-angivet dato for at undgå volatilitet i valutakursen.

Sekretariatet accepterer ansøgers tilgang vedr. hospitalsomkostninger, men vælger at justere en række parametre. Den månedlige frekvens, hvormed patienter monitoreres, justeres til én gang om måneden for patienter i PFS, hvorimod den månedlige frekvens, hvormed patienter monitoreres efter progression, justeres til 0. Den gennemsnitlige testomkostning justeres til 55.000 DKK per patient, men der udføres en følsomhedsanalyse, hvor testomkostningerne sættes til 70.000 DKK per patient samt en følsomhedsanalyse, hvor patientantallet justeres inden for fagudvalgets forventede patientantal. Desuden foretages en følsomhedsanalyse af teststrategien, hvor det antages, at der benyttes bred NGS-testning. I denne følsomhedsanalyse justeres testomkostninger til 375.000 kr. per patient. Desuden foretages en følsomhedsanalyse uden testomkostninger. Slutteligt justeres valutakursen, hvormed terminalomkostninger omskrives fra GBP til DKK til den gennemsnitlige valutakurs i 2013.

4.2.3 Bivirkningsomkostninger

Ansøger har inkluderet bivirkningsomkostninger ved behandlingsstart, da ansøger argumenterer for, at bivirkninger forekommer oftere ved behandlingsstart, se Tabel 8. Ansøgers model inkluderer omkostninger til bivirkninger af grad 3 eller mere, som samtidig kræver behandling på hospitalet. Bivirkningsfrekvenserne kommer fra det kombinerede datasæt fra STARTRK-studierne. Ansøger har estimeret bivirkningsomkostningerne ved at anvende DRG-takster fra 2020, se Tabel 8. Ansøger har ikke inkluderet bivirkningsomkostninger for patienter i behandling med BSC.

Tabel 8: Rapporterede bivirkningsfrekvenser ved behandling med entrectinib og placebo.

	Entrectinib [%]	Omkostning [DKK]	Kilde [DRG-takst]
Forhøjet Alanin-aminotransferase	[redacted]	1.748	DRG 2020:23MA98
Anæmi	[redacted]	22.212	DRG 2020: 16MA98
Anafylaktisk reaktion	[redacted]	4.564	DRG 2020: 21MA01
Forhøjet aspartat-aminotransferase	[redacted]	1.748	DRG 2020: 23MA98
Forhøjet kreatinin-værdi i blodet	[redacted]	4.082	DRG 2020: 23MA03
Hjertestop	[redacted]	15.926	DRG 2020: 05MA07
Hjertesvigt	[redacted]	17.750	DRG 2020: 05MA98
Kognitiv svækkelse	[redacted]	30.628	DRG 2020: 01MA06

Diarré	[redacted]	5.297	DRG 2020: 06MA11
Dyspnø	[redacted]	1.799	DRG 2020: 04MA98
Træthed	[redacted]	2.711	DRG 2020: 18MA98
Hypermagnesiæmi	[redacted]	1.540	DRG 2020: 10MA98
Hyperurikæmi	[redacted]	4.082	DRG 2020: 23MA03
Hypokaliæmi	[redacted]	13.048	DRG 2020: 10MA06
Hyponatriæmi	[redacted]	13.048	DRG 2020: 10MA06
Hypofosfatæmi	[redacted]	1.540	DRG 2020: 10MA98
Hypotension	[redacted]	1.847	DRG 2020: 05MA08
Lokaliseret ødem	[redacted]	4.082	DRG 2020: 23MA03
Lymfopeni	[redacted]	3.149	DRG 2020: 16MA98
Muskelsvaghed	[redacted]	1.676	DRG 2020: 08MA15
Neutropeni	[redacted]	20.376	DRG 2020: 16MA98
Ødem	[redacted]	4.082	DRG 2020: 23MA03
Perifert ødem	[redacted]	4.082	DRG 2020: 23MA03
Ortostatisk hypotension	[redacted]	8.544	DRG 2020: 05MA98
Osteoartrose	[redacted]	1.796	DRG 2020: 08MA17
Synkope	[redacted]	8.544	DRG 2020: 05MA07
Thalamisk infarkt	[redacted]	36.280	DRG 2020: 01MA05

Sekretariatets vurdering
Idet bivirkningsomkostninger ikke er inkluderet for BSC, vurderer sekretariatet, at de inkrementelle bivirkningsomkostninger er overestimeret.

Sekretariatet accepterer ansøgers tilgang vedr. bivirkningsomkostninger men pointerer, at de inkrementelle bivirkningsomkostninger potentielt er overestimeret.

4.2.4 Patientomkostninger og transportomkostninger

Patientomkostninger er estimeret på baggrund af lægemiddeladministration og monitoreringsbesøg på hospitalet, og her antager ansøger, at patienttid er identisk med ressourceforbruget på hospitalet præsenteret i Tabel 5 og Tabel 6. Ansøgers estimerede patienttid kan ses i Tabel 9. Ansøger anvender en patientomkostning på 179 DKK/time.

Tabel 9: Patientomkostninger.

	Andel	Frekvens	Tidsforbrug	Enhedsomkostning [DKK]	Kilde
			PFS		
Onkolog konsultation	100 %	Hver 3. måned	30 min	179	Klinisk vurdering*
Sygeplejerske	100 %	Hver 3. måned	60 min	179	Klinisk vurdering*
MR-scanning	5 %	Hver 3. måned	60 min	179	Antagelse
Blodprøver	100 %	Hver 3. måned	30 min	179	Antagelse
CT-scanning	100 %	Hver 3. måned	60 min	179	Antagelse
			Efter progression		
Onkolog konsultation	100 %	Hver 3. måned	30 min	179	Klinisk vurdering*
Sygeplejerske	100 %	Hver 3. måned	60 min	179	Klinisk vurdering*
MR-scanning	5 %	Hver 3. måned	60 min	179	Antagelse
Blodprøver	100 %	Hver 3. måned	30 min	179	Antagelse
CT-scanning	100 %	Hver 3. måned	60 min	179	Antagelse

* [redacted].

Ansøger tillægger alle ovenstående besøg på hospitalet en transportomkostning. Denne omkostning udgør 3,52 DKK/km, og ansøger antager, at alle patienter i gennemsnit har 28 km til hospitalet.

Sekretariatets vurdering

Sekretariatet accepterer ansøgers tilgang vedr. patientomkostninger, dog vil patientomkostningerne følge ændringerne beskrevet i 4.2.2, dvs. frekvensen øges for patienter i PFS og sænkes for patienter med 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:

- Varierende parametrisk ekstrapolering af PFS, OS og TTD
- Andel af patienter i BSC, som modtager carboplatin
- Varierende tidshorisont

- Inkludering af spild
- Inkludering af vial sharing (dvs. deling af hætteglas mellem patienter)
- Anvendelse af den ikke-betingede pris

Sekretariatets vurdering
Ansøgers følsomhedsanalyser belyser i høj grad modellens usikkerheder. Sekretariatet vælger dog at udføre en ekstra følsomhedsanalyse, hvor usikkerheden ved testomkostningerne belyses. Dette gøres ved at justere antallet af patienter, som skal testes for NTRK-fusion samt ved at variere patientantallet og teststrategi.
Slutteligt udføres en følsomhedsanalyse af sekretariatets hovedanalyse, hvor den ikke-betingede pris anvendes.

Sekretariatet accepterer ansøgers tilgang vedr. patientomkostninger, men vælger kun at præsentere et udsnit af ansøgers følsomhedsanalyser samt at udføre en ekstra følsomhedsanalyse, hvor antallet af patienter, som testes for NTRK-fusion, justeres samt en følsomhedsanalyse, hvor patientantallet justeres. Desuden foretages en følsomhedsanalyse, hvor der anvendes en bred testning med en NGS for samtlige 1.500-2.000 patienter samt en følsomhedsanalyse af sekretariatets hovedanalyse, hvor den ikke-betingede pris anvendes.

4.4 Opsummering af basisantagelser

I Tabel 10 opsummeres basisantagelserne for ansøgers hovedanalyse sammenlignet med de ændringer, som sekretariatet har lavet i egen hovedanalyse.

Tabel 10: Basisantagelser for ansøgers og sekretariatets hovedanalyse.

Basisantagelser	Ansøger	Sekretariatet
Tidshorisont	30 år	30 år
Diskonteringsrate	4 %	4 %
Inkluderede omkostninger	Lægemiddelomkostninger	Lægemiddelomkostninger
	Hospitalsomkostning	Hospitalsomkostning
	Monitoreringsomkostninger	Monitoreringsomkostninger
	Patient- og transportomkostninger	Patient- og transportomkostninger
	Bivirkningsomkostninger	Bivirkningsomkostninger
	Terminalomkostninger	Terminalomkostninger

Basisantagelser	Ansøger	Sekretariatet
Dosering	Entrectinib: 600 mg én gang dagligt BSC: 25 % carboplatin 400 mg/m2 hver 4. uge 75 % ingen behandling	Entrectinib: 600 mg én gang dagligt BSC: 100 % ingen behandling
Behandlingslængder		
Intervention:	[redacted]	[redacted]
Komparator:	[redacted]	[redacted]
Parametriske kurver for PFS:		
Intervention:	[redacted]	[redacted]
Komparator:	[redacted]	[redacted]
Parametriske kurver for OS:		
Intervention:	[redacted]	[redacted]
Komparator:	[redacted]	[redacted]
Inkludering af spild	Nej	Ja
Andre væsentlige antagelser	Testomkostning for 40 % af patienterne Gennemsnitlig dosis intensitet på [redacted] for entrectinib	Gennemsnitlige testomkostning på 55.000 per patient. Gennemsnitlig dosis intensitet på [redacted] for entrectinib

5. Resultater

5.1 Resultatet af sekretariatets hovedanalyse

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

- Ekskludering af platinbaseret kemoterapi for patienter i BSC
- Antal patienter, som skal testes for NRTK-fusion samt prisen for testen
- Den månedlige frekvens hvormed patienter monitoreres både før og efter progression
- Inkludering af lægemiddelspild

Den inkrementelle omkostning pr. patient bliver ca. [redacted] DKK over en tidshorisont på 30 år i sekretariatets hovedanalyse. Udføres analysen med AIP bliver den inkrementelle omkostning pr. patient ca. 789.000 DKK.

Resultaterne fra sekretariatets hovedanalyse præsenteres i Tabel 11.

Tabel 11: Resultatet af sekretariatets hovedanalyse ved sammenligning med BSC, DKK, diskonterede tal, betingede pris.

	Entrectinib	BSC	Inkrementelle omkostninger
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Hospitalsomkostninger	140.412	84.613	55.799
Bivirkningsomkostninger	8.883	0	8.883
Patientomkostninger	14.807	2.563	12.244
Testomkostninger	55.000	0	55.000
Totale omkostninger	[redacted]	[redacted]	[redacted]

5.1.1 Resultatet af sekretariatets følsomhedsanalyser

Ved samme antagelser som i sekretariatets hovedanalyse for meromkostninger udfører sekretariatet følsomhedsanalyser præsenteret i Tabel 12.

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

Scenarie	Inkrementelle omkostninger [DKK]
Resultatet af hovedanalysen	[redacted]
Alternativ teststrategi (bred testning med NGS)	[redacted]
2000 patienter skal testes og dermed vil der være en gennemsnitlig testomkostning på 70.000 per patient	[redacted]
Ingen testomkostninger	[redacted]
Patientantal på 10	[redacted]
Patientantal på 40	[redacted]
25 % af BSC-patienterne modtager platinbaseret kemoterapi	[redacted]
Ekskludering af spild	[redacted]

Scenarie	Inkrementelle omkostninger [DKK]
Tidshorisont på 5 år	[redacted]
Tidshorisont på 17,5 år	[redacted]
Resultat af hovedanalysen med ikke-betingede priser	[redacted]

6. Budgetkonsekvenser

Budgetkonsekvenserne pr. år er baseret på antagelsen om, at entrectinib vil blive anbefalet som standardbehandling. 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.

6.1 Ansøgers estimat af patientantal og markedsandel

Ansøger antager, at der årligt vil være 20 patienter, og at entrectinib vil opnå et markedsoptag på 100 % allerede fra år 1.

Tabel 13 viser estimatet af antal patienter årligt i budgetkonsekvenserne.

Tabel 13: Ansøgers estimat af antal nye patienter pr. år.

	År 1	År 2	År 3	År 4	År 5
Anbefales					
Entrectinib	20	20	20	20	20
BSC	0	0	0	0	0
Anbefales ikke					
Entrectinib	0	0	0	0	0
BSC	20	20	20	20	20

Sekretariatets vurdering

Sekretariatet accepterer ansøgers tilgang vedr. patientantal og markedsoptag, men vælger at udføre en følsomhedsanalyse af budgetkonsekvenserne, hvor patientantallet justeres til hhv. 10 og 40 patienter.

6.2 Sekretariatets budgetkonsekvensanalyse

Ansøger har valgt at ekskludere test- og terminalomkostninger fra budgetkonsekvensanalysen. I sekretariatets budgetkonsekvensanalyse inkluderes både test- og terminalomkostninger.

Sekretariatet estimerer, at anvendelse af entrectinib vil resultere i budgetkonsekvenser på ca. [redacted] DKK i år 5. Resultatet er præsenteret i Tabel 14.

Hvis analysen udføres med AIP, bliver budgetkonsekvenserne ca. 15,7 mio. DKK i år 5.

Tabel 14: 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 hvor det årlige patientantal justeres til 10 og 40 patienter, vil de årlige budgetkonsekvenser være hhv. ca. [redacted] DKK og ca. [redacted] DKK i år 5, se Tabel 15.

Tabel 15: Sekretariatets analyse af totale budgetkonsekvenser ved et patientantal på 10 og 40 nye patienter om året, mio. DKK, ikke-diskonterede tal, betingede pris for entrectinib ved anbefaling.

	År 1	År 2	År 3	År 4	År 5
	10 nye patienter om året				
Anbefales	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anbefales ikke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Totale budgetkonsekvenser	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	År 1	År 2	År 3	År 4	År 5
			40 nye patienter om året		
Anbefales	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anbefales ikke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Totale budgetkonsekvenser	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Ved samme antagelser som i sekretariatets hovedanalyse, men med ikke-betingede priser bliver budgetkonsekvenserne ca. [redacted] DKK i år 5, se Tabel 16.

Tabel 16: Sekretariatets analyse af totale budgetkonsekvenser med den ikke-betingede priser, mio. DKK, ikke-diskonterede tal.

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

7. Diskussion

Behandling med entrectinib er forbundet med betydelige inkrementelle omkostninger sammenlignet med behandling med BSC. De inkrementelle omkostninger er i høj grad drevet af lægemiddelomkostningerne for entrectinib, men omkostninger til test for NTRK-fusion udgør også en stor del af de inkrementelle omkostninger.

7.1 Usikkerheder

Test

Der er usikkerhed omkring den gennemsnitlige omkostning til test for NTRK-fusion. Fagudvalget vurderer, at mellem 1.500 og 2.000 patienter skal testes for at finde de 20 patienter, som vil være kandidater til behandling med entrectinib. I sekretariatets hovedanalyse er antaget, at 1.500 patienter skal testes, mens hvis 2.000 patienter benyttes, så vil de inkrementelle omkostninger stige med 15.000 DKK per patient. Det er ikke muligt for fagudvalget at give et mere præcist estimat, og der er betydelig usikkerhed vedr. testomkostningerne. Derfor vælger sekretariatet at anvende et konservativt estimat på 1.500 årlige test, hvilket giver en gennemsnitlig testomkostning på 55.000 per patient.

Ekstrapolering og sammenligning med komparator
Fagudvalget vurderer, at de anvendte kurver er klinisk plausible, men de bemærker, at de ekstrapolerede kurver er usikre, da fagudvalget ikke har tilstrækkeligt kendskab til behandlingsforløbet.

Der er desuden usikkerhed omkring sammenligningen mellem entrectinib og BSC, da der ikke foreligger en direkte sammenligning af entrectinib og BSC. I modellen er anvendt en naiv sammenligning med BSC-armene fra andre studier, hvor NTRK-status er ukendt. Det er usikkert, hvor repræsentative disse BSC-arme er for de patienter, hvor entrectinib er indiceret, og fagudvalget har i udarbejdelsen af vurderingsrapporten vurderet, at de repræsenterede tumortyper fra disse studier varierer væsentligt fra sammensætningen i entrectinibpopulationen. Dette er dog en pragmatisk løsning og har mindre økonomisk betydning, da BSC udgør relativt få omkostninger.

Fagudvalget har i udarbejdelsen af vurderingsrapporten fundet, at de repræsenterede tumortyper varierer væsentligt fra sammensætningen i entrectinibpopulationen. Fagudvalget vurderer, at de samlede effektestimater på tværs af alle tumortyper ikke kan anvendes som sammenligningsgrundlag i den kliniske vurdering, men kun at OS- og PFS-data fra de individuelle tumortyper i placeboanalysen kan anvendes som supplerende sammenligningsgrundlag for entrectinib, hvor data er opgivet på enkelttumorniveau. I sundhedsøkonomiske analyser er kvantitative estimater dog nødvendige, og derfor er de accepteret her, men sekretariatet pointerer, at dette bidrager med betydelig usikkerhed.

BSC
Der er i modellen ikke inkluderet omkostninger udover monitorering og terminalomkostninger for patienter i behandling med BSC. Dette kan potentielt være en underestimering af omkostningerne ved behandling med BSC, da patienter sandsynligvis vil modtage symptomlindrende behandling, og derved vil de inkrementelle omkostninger være overestimerede. Denne usikkerhed er dog svær at kvantificere.

Spild
Der er i modellen usikkerhed vedr. spild i to dimensioner, størrelsen på de udleverede pakninger og antallet af udleverede pakninger. Både størrelsen og antallet af udleverede pakninger vil variere fra klinik til klinik og er derfor svær at kvantificere, men som tidligere beskrevet peger usikkerheden i retning af, at de inkrementelle omkostninger er underestimeret for entrectinib, idet fagudvalget vurderer, at der vil udleveres mere end én pakke ad gangen, og dermed vil der være et større lægemiddelspild.

Klinisk spørgsmål 2
Ansøger har valgt, grundet et begrænset datagrundlag, ikke at udføre en sundhedsøkonomisk analyse af klinisk spørgsmål 2. Derfor er de økonomiske konsekvenser ved behandling med entrectinib for patienter mellem 12 og 18 år ikke belyst og meget usikkert. Fagudvalgets skøn på 10-40 patienter årligt inkluderer både voksne og børn, og der ligger derfor ikke en stor ekstra udgift til flere patienter ved kun at fokusere på den voksne population.

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9. Bilag

9.1 Resultatet af ansøgers hovedanalyse

I ansøgers hovedanalyse bliver den inkrementelle omkostning pr. patient ca. [redacted] over en tidshorisont på 20 år. Resultaterne fra ansøgers hovedanalyse er præsenteret i Tabel 17.

Tabel 17: Resultatet af ansøgers hovedanalyse, DKK, diskonterede tal.

	Entrectinib	BSC	Inkrementelle omkostninger
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Hospitalsomkostninger	118.267	83.413	34.853
Bivirkningsomkostninger	8.883	0	8.883
Patientomkostninger	10.987	2.765	8.222
Testomkostninger	1.378	0	1.378
Totale omkostninger	[redacted]	[redacted]	[redacted]

9.2 Ansøgers budgetkonsekvensanalyse

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

Med de ovenstående antagelser om patientantal og markedsandel estimerer ansøger, at anvendelse af entrectinib vil resultere i budgetkonsekvenser på ca. [redacted] DKK i år 5.
Ansøgers estimat af budgetkonsekvenserne fremgår af Tabel 18.

Tabel 18: Ansøgers hovedanalyse for totale budgetkonsekvenser, mio. DKK, ikke-diskonterede tal, betingede priser 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 36 måneder startende d. 25.03.2021 til d. 31.03.2024.

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 03-02-2021

Høringssvar fra Roche Danmark vedrørende Medicinrådets vurdering af Rozlytrek (entrectinib) til behandling af patienter med NTRK-fusions positiv kræft

Roche takker for Medicinrådets vurdering af entrectinib til behandling af NTRK fusions-positiv kræft og har ingen yderligere kommentarer til kategoriseringen.

Roche stiller sig dog kritisk over for specifikke dele af Medicinrådets sundhedsøkonomiske afrapportering. I nedenstående afsnit forholder Roche sig til følgende emner enkeltvis:

- Omkostninger til tests af NTRK-fusioner
- Omkostninger til komparator-armen
- Omkostninger ved spild

Omkostninger til tests af NTRK-fusioner

I Medicinrådets sundhedsøkonomiske afrapportering påregnes entrectinib-armen testomkostninger svarende til omkostningerne for IHC-testning af 1500-2000 patienter, herunder evt. opfølgende NGS-test. Denne tilgang tilskriver således entrectinib-armen alle omkostninger for både NTRK-fusions negative og positive patienter, hvorimod ingen testningsomkostninger tildeles komparator-armen

Roche anerkender, at det er relevant at undersøge testningsomkostninger ved implementering af nye lægemidler. I Medicinrådets tilgang inddrages der dog både omkostninger for positive og negative testsvar, og samtidigt pålægges entrectinib-armen alle omkostninger for testning. Denne tilgang er problematisk og kan potentielt hæmme fremtidig implementering af personlig medicin, hvor man forsøger at skræddersy behandlingen ud fra sjældne diagnostiske markører.
Medicinrådets tilgang er desuden forbundet med meget stor usikkerhed, der kan medføre en overestimering af omkostningerne for implementering af en ny behandling. Denne beregning antager således, at Medicinrådets anbefaling i sig selv vil medføre testning af alle patienter med uhelbredelig kræft i Danmark på tværs af onkologiske specialer. Dette er en meget usikker antagelse, da testningen inden for onkologi i Danmark også drives af en lang række andre faktorer. Her bør det eksempelvis nævnes, at bredere testning såsom NGS-tests bliver mere og mere udbredt inden for onkologien.

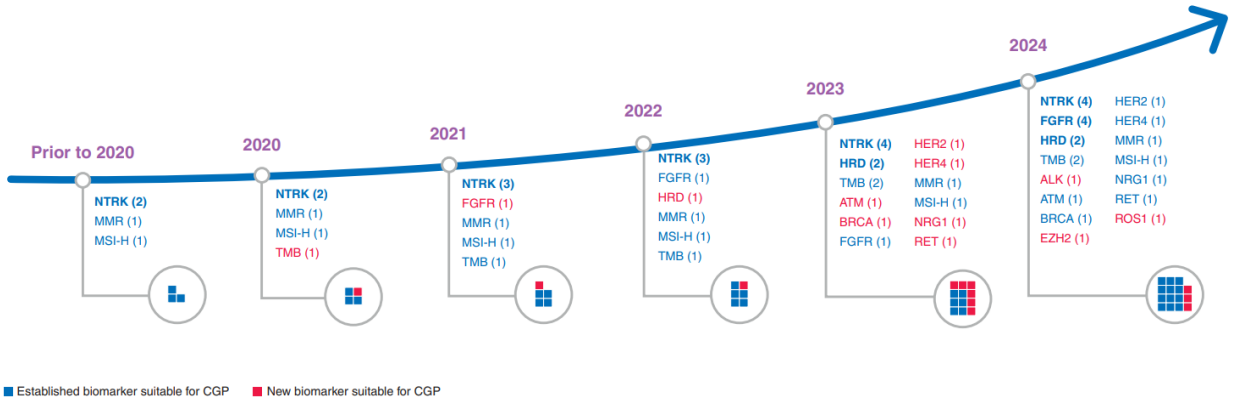
Fordele ved en bred NGS testning er, at den tillader, at man kan belyse tilstedeværelsen af flere markører via et samlet panel frem for at teste for markører enkeltvis som ved f.eks. IHC. NGS-testen kan derfor give et mere komplet overblik over relevante behandlingsmuligheder og evt. eksperimentelle behandlinger via kliniske studier.
Implementering af den brede testning er en gradvis proces, som drives af flere initiativer og en lang række faktorer både nationalt og internationalt. Internationalt ses det således nævnt i guidelines såsom ESMO, som løbende udgiver og opdaterer guidelines vedrørende implementering af NGS-testning inden for onkologien. Disse guidelines anbefaler for nuværende også NGS-testning til metastatisk ikke-småcellet

lungekræft, cholangiocarcinomer, prostatakræft og ovariekræft, og det anbefales, at universitetshospitaler udfører NGS-tests for at give adgang til innovative behandlinger [1].

I Danmark pågår der også flere initiativer, som kan bidrage til at udbrede NGS-testning. Herunder eksempelvis det Nationale Genomcenter, hvor der snart forventes klarhed omkring hvilke patientgrupper, der kan tilbydes helgenomsekventering. Gennem dialog med danske onkologer er Roche bekendt med, at der en ansøgt om, at netop uhelbredelige kræftpatienter kan blive en af disse patientgrupper. Skulle uhelbredelig kræftpatienter blive en af de udvalgte grupper, vil en donation fra Novo Nordisk fonden på 1 mia. således dække udgifter til testning de næste 4,5 år.

Implementeringen af NGS-tests internationalt såvel som i Danmark drives således af flere forskellige faktorer, og omkostningen for tests af uhelbredelige kræftpatienter vil ikke nødvendigvis ligge hos de danske regioner.
På det grundlag er det meget usikkert, at Medicinrådet i sit primære scenarie for omkostningsanalysen og budgetkonsekvensanalysen tilskriver implementering af testning som værende udelukkende afhængig af Medicinrådets anbefaling af et enkelt lægemiddel. Dette skyldes, at den løbende implementering af bredere testning inden for onkologi foregår uafhængigt af entrectinibs implementering. Dermed kan der såvel også forekomme testningsomkostninger i komparator-armen, og en del af omkostningen for at teste de resterende patienter kan også ligge uden for regionernes budgetter. Med den nuværende tilgang er der en markant risiko for at overestimere omkostningerne ved implementering af entrectinib og ved andre targeterede behandlinger, der afhænger af testning.

Som beskrevet i den endelige ansøgning, vil der løbende udvikles flere targeterede behandlinger og tumor-agnostiske behandlinger. Behovet for bredere testning vil således stige, og man bør derfor være varsom ved at tilskrive alle testningsomkostninger til de første tumor-agnostiske behandlinger på markedet. Nedenstående figur viser forventede tumor-agnostiske lægemidler, der targeterer driver-mutationer baseret på igangværende kliniske studier [2].



Figur 1: forventet godkendelse af tumor agnostiske lægemidler der targetere driver-mutationer fra nuværende kliniske studier.
Dette er baseret på fase II og III studier, der var påbegyndt inden 1. februar 2020 og havde information tilgængelig fra d. 1. juni 2020. Det forventes, at alle studierne vil føre til godkendelse.

Omkostninger i komparatorarmen

I den sundhedsøkonomiske afrapportering har Medicinrådet valgt at se bort fra omkostninger til behandling for komparator, og har således fjernet omkostninger til kemoterapi.

Roche mener, at tilgangen i omkostningsanalysen i forvejen var konservativ, og at omkostninger til komparator-armen sandsynligvis underestimeres. Dette skyldes, at Medicinrådet i sin tolkning af den relevante komparator har valgt pallierende behandling (*best supportive care)* eller placebo.

Da der er tale om en behandlingsmulighed på tværs af flere onkologiske specialer i Danmark kan der forventeligt være flere tolkninger af indikationen, hvor tilfredsstillende behandlingsmuligheder skal være udtømte.

Generelt set bliver targeterede behandlinger løbende rykket frem i behandlingslinjerne, og i de onkologiske specialer, hvor NGS-testning er mere udbredt ved diagnose eller progression, vil man kunne finde avanceret eller metastatiske NTRK-fusions positive patienter, som er behandlingsnaive eller kun har modtaget en enkelt behandlingslinje. I disse tilfælde vil kemoterapi i flere specialer være den normale 2. linjebehandling. Roche mener derfor ikke, at det er usandsynligt, at nogle patienter rent faktisk modtager behandling med entrectinib i stedet for kemoterapi. Den nuværende tilgang medfører derfor en risiko for at overestimere den inkrementelle omkostninger ved implementering af entrectinib.

Omkostninger ved spild

I den sundhedsøkonomiske afrapportering angives en usikkerhed omkring spild på grund af de to pakningsstørrelser samt hvor mange pakninger patienter får udleveret på hospitalet. Den samme usikkerhed gør sig også gældende i afrapporteringen for ROS1-indikationen for entrectinib. Her beskrives det 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 [3].

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

Den lille pakningsstørrelsen er tiltænkt patienter med en overfladevolumen under 1,51 m^2, men begge gruppe vil med fordel kunne benytte den større pakning med 90 kapsler med 200 mg, som vil passe til hhv. 45 og 30 dages behandling. Derved skal patienterne kun møde op med en til halvanden måneds mellemrum. Vi forventer ikke, at der med de to pakningsstørrelser skulle være større eller anderledes spild ved entrectinib end det der ses ved andre targeterede behandlinger. Det vil være op til den enkelte afdeling, hvordan lægemidlet administreres i praksis. I nogle afdelinger er det således praksis kun at give en enkelt blisterpakning med hjem af gangen.

I Medicinrådets sundhedsøkonomiske model 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 forventer vi, 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 uddeles til patienten. Muligheden for at anvende flere pakningsstørrelser burde således udelukkende give afdelingerne mere fleksibilitet og ikke i sig selv være årsag til øget spild.

Med venlig hilsen

Niels Juul Brogaard
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Andreas Fanø
Scientific Partner
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Referencer

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Sekretariatets svar på ansøgers høringssvar

Fra: Hans Christian Cederberg Helms
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Til: Brogaard, Niels <niels.brogaard@roche.com>
Cc: Fanoe, Andreas <andreas.fanoe@roche.com>; Christian Graves Beck <CGB@medicinraadet.dk>
Emne: SV: Høringssvar til Medicinrådets vurdering af Rozlytrek (NTRK)

Kære Niels og Andreas

Tak for jeres høringssvar angående den sundhedsøkonomiske afrapportering, som vi har gennemgået og forelagt fagudvalgsformanden.

Afrapporteringen følger fagudvalgets vurderinger af de sundhedsøkonomiske antagelser og følger Medicinrådets metodevejledning for omkostningsanalyser ift. at omkostninger til diagnostiske tests medtages i de økonomiske analyser (Metodevejledning for omkostningsanalyser af nye lægemidler og indikationer i hospitalssektoren (medicinraadet.dk)). Vi finder således ikke, at jeres kommentarer giver anledning til ændringer i afrapporteringen.
Jeres høringssvar vil indgå i den videre sagsbehandling af entrectinib, og vil blive offentliggjort sammen med den endelige anbefaling.

Mvh

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Emne: Entrectinib (NTRK) - Clock-stop og info vedr. høringssvar

Hej Hans Christian,

For også at følge op på høringssvaret, så nævnte vi, at der var blevet ansøgt om, at patienter med uhelbredelig kræft skulle tilbydes genom-test via de nationale genomcenter. Der er nu kommet en nyhedsmeddelelse fra det nationale genomcenter om hvilke grupper, der de næste 4 år skal tilbydes helgenomsekventering. To af disse grupper er børn med kræft (op til 18 år) og uhelbredelige kræftpatienter. Disse vil altså nu kunne tilbydes helgenomsekventering. Dette burde altså have betydningen for andelen af patienter, som i dag ikke rutinemæssigt screenes for bl.a. NTRK, og man må kunne forvente lavere testningsomkostninger ved implementering.

Link til nyheden findes her: https://ngc.dk/nyheder/2021/februar/12-patientgrupper-valgt-til-helgenomsekventering

Vh
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Emne: SV: Entrectinib (NTRK) - Clock-stop og info vedr. høringssvar

Kære Niels

Vi har vendt din henvendelse ang. Nationalt genomcenter og planerne for hel-genomsekventering af patienter med uhelbredelig kræft og børn med kræft med fagudvalgsformanden for tværgående kræftlægemidler. Vi finder ikke anledning til at ændre i den sundhedsøkonomiske afrapportering for entrectinib til NTRK-fusion-positiv kræft, som I har fået tilsendt på baggrund af dette.

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Cc: Fanoe, Andreas <andreas.fanoe@roche.com>
Emne: Re: Entrectinib (NTRK) - Clock-stop og info vedr. høringssvar

Hej Hans Christian,

Skal beklage, at jeg ikke har fået kvitteret for din mail. Tak for info vedrørende tilgangen i den sundhedsøkonomiske analyse, som vi selvfølgelig tager til efterretning.

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Medicinrådet

Medicinrådets vurdering vedrørende entrectinib til behandling af NTRK-fusion-positiv kræft

Version 1.0

Om Medicinrådet

Medicinrådet er et uafhængigt råd etableret af Danske Regioner.

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

Om vurderingsrapporten

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

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

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

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Udgivet af Medicinrådet, 27. januar 2021

1. Medicinrådets konklusion

Medicinrådet finder, at den samlede værdi af entrectinib overfor placebo til behandling af voksne og børn (>12 år) med NTRK-fusion-positiv kræft **ikke kan kategoriseres**. Vurderingen er baseret på enkeltarmede studier med en lille patientgruppe med forskellige kræftformer og deraf forskellige prognoser, der sammenstilles med observationelle data for patienter med NTRK-fusion-positiv kræft.

Medicinrådet følger fagudvalgets vurdering af, at datagrundlaget, om end meget usikkert, indikerer, at entrectinib har klinisk relevant effekt hos patienter, der ikke har anden tilfredsstillende behandlingsmulighed.

Til trods for at datagrundlaget for børn er yderst sparsomt, finder Medicinrådet ligesom fagudvalget ikke grund til at antage, at effekten af entrectinib i børn mellem 12 og 18 år afviger betydeligt fra effekten hos voksne.

Evidensens kvalitet er meget lav. Medicinrådet vurderer ligesom fagudvalget, at sjældenheden af NTRK-fusion og entrectinibs vævsagnostiske indikation gør det vanskeligt at foretage en nøjagtig vurdering af entrectinibs kliniske værdi.

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

BSC: *Best supportive care*

CI: Konfidensinterval

CNS: Centralnervesystemet

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

EPAR: *European Public Assessment Report*

FISH: *Fluorescence in situ hybridization*

GMI: *Growth modulation index*

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

HR: *Hazard ratio*

IHC: Immunhistokemi (*immunohistochemistry)*

ITT: *Intention to treat*

NGS: *Next generation sequencing*

NSCLC: Ikke-småcellet lungekræft (*non small-cell lung cancer*)

NTRKJ: Neurotrofisk tyrosinkinase

ORR: Objektiv responsrate

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*

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

ROS1 *ROS proto-oncogene 1 receptor tyrosine kinase*

RR: Relativ risiko

SMD *Standardized Mean Difference*

SmPC: Produktresumé (*summary of product characteristics)*

Trk: Tyrosinkinasereceptor

3. Introduktion

Formålet med Medicinrådets vurdering af entrectinib til behandling af kræft med NTRK-fusion 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 3. november 2020.

De kliniske spørgsmål er:

1. *Hvad er den kliniske merværdi af entrectinib til behandling af voksne med NTRK-fusion-positiv kræft, hvor øvrige behandlingsmuligheder er udtømte, sammenlignet med placebo?*
2. *Hvad er den kliniske merværdi af entrectinib til behandling af børn (≥ 12 år) med NTRK-fusion-positiv kræft, hvor øvrige behandlingsmuligheder er udtømte, sammenlignet med placebo?*

3.1 NTRK-fusion-positiv kræft

En solid tumor er en unormal vævsmasse (svulst). Solide tumorer kan være benigne (ikke kræft) eller maligne (kræft), hvor sidstnævnte kan gennemtrænge væv eller sprede sig til andre dele af kroppen. Kræft inddeles i forskellige typer, afhængig af hvilken celletype kræften udgår fra. Solidt voksende kræfttyper kan overordnet inddeles i f.eks. sarkomer (bløddels- og knoglekræft), karcinomer (epitel deriverede kræftformer), neurogen deriverede tumorer og melanomer (modermærkekræft). For hver af disse overordnede kræfttyper findes talrige undertyper, baseret på hvilken celletype de udgår fra, hvilke histopatologiske og eventuelle molekylærbiologiske forandringer der kendetegner kræften [1,2]. De forskellige kræfttyper rammer forskelligt i befolknings- og aldersgrupper og kræver forskellig diagnostik og behandling.

Forekomsten af kræft i Danmark er stigende, og ca. 1/3 af alle danskere vil få kræft i løbet af deres liv. Antallet af nye tilfælde pr. år er ca. 40.000, lidt flere mænd end kvinder. Den største andel af nye kræfttilfælde er i den ældre del af befolkningen. 2/3 af alle nye kræfttilfælde er hos personer over 60 år. Lidt over 280.000 nulevende danskere har på et tidspunkt fået konstateret kræft, og 6 ud af 10 kræftpatienter overlever deres sygdom i mindst 5 år [3].

Selvom kræft er sjældent hos børn (under 18 år), er det den næst hyppigste dødsårsag efter 1-årsalderen. Mindre end 1 % af alle kræfttilfælde forekommer hos børn, og ca. 200 børn får årligt konstateret kræft. Den 5-årige overlevelsesrate for børn med kræft er på ca. 80 %. Fordelingen af kræfttyperne hos børn er helt anderledes end hos voksne [3]. Voksne får således typisk karcinomer, mens børn hyppigst får blodkræft [4].

Neurotrofisk tyrosinkinase (NTRK) er navnet på en gruppe af tre gener, NTRK1, NTRK2 og NTRK3, der koder for tyrosinreceptorkinaser (Trk) A, B og C. Trk er afgørende for normale

nervecellers udvikling og overlevelse. Genfusioner, der involverer NTRK1, NTRK2 eller NTRK3, koder for Trk-fusionsproteiner, som kan medføre ukontrolleret Trk-signalering og dermed tumorvækst [5,6]. NTRK-fusioner er sjældne og påvises med yderst varierende hyppighed på tværs af tumortyper hos både børn og voksne. Herudover er det uvist, om der er geografiske og epidemiologiske forskelle i forekomst af NTRK-fusioner. NTRK-fusioners hyppighed i forskellige kræftformer er angivet i tabellen nedenfor. Dette skal dog tages med forbehold for de ovennævnte forskelle.

Tabel 3-1. Oversigt over frekvens for NTRK-fusion ved forskellige kræftformer.

Kræftform	Frekvens for NTRK-fusion
Infantil fibrosarkom	Omkring 100 % [7,8]
Sekretorisk karcinom i både spytkirtel og bryst	Omkring 100 % [7,8]
Kræfttyper i luftveje, fordøjelseskanal, bryst og hjerne	< 5 % [7,8]
Lungekræft, kolorektalkræft, modermærkekræft og brystkræft	0,1-1 % [9]

3.2 Entrectinib

Trk-fusionsproteiner virker som 'onkogene drivere' der fremmer celledeling og overlevelse af tumorceller. Entrectinib (Rozlytrek) er en Trk-hæmmer, som hindrer neurotrophin-Trk-interaktion og dermed Trk-aktivering. Dette fører til celledød og hæmning af tumorer, som overudtrykker Trk [8,10]. Entrectinib hæmmer desuden *ROS proto-oncogene 1 receptor tyrosine kinase* (ROS1), der ved fusion med andre gener kan resultere i aktiverede proteiner. ROS1-fusionerede gener er en 'onkogen driver' ved blandt andet ikke-småcellet lungekræft (NSCLC) [11].

Patienter kan behandles med entrectinib, hvis de har en NTRK-fusion i en tumorprøve. Der testes i dag ikke rutinemæssigt for NTRK-fusion i tumorprøver, og der er ingen klinisk validerede tests eller 'companion diagnostics' tilgængelige til at udføre testen. Man kan både anvende *next-generation sequencing* (NGS), immunhistokemi (IHC) og *fluorescence in situ hydridization* (FISH) for at påvise fusioner (se afsnit 6.2).

Entrectinib er som enkeltstofbehandling indiceret til behandling af voksne og børn (≥ 12 år) med solide tumorer, der udtrykker en NTRK genfusion. Derudover skal følgende være opfyldt:

- Sygdommen er lokalt avanceret, metastatisk, eller kirurgisk resektion vil sandsynligvis resultere i svær morbiditet.
- Patienten er ikke tidligere behandlet med en NTRK-inhibitor.
- Der er ikke nogen andre tilfredsstillende behandlingsmuligheder.

Entrectinib har desuden indikation til voksne patienter med uhelbredelig ROS1-positiv NSCLC, der sideløbende bliver vurderet af fagudvalget vedrørende lungekræft.

Den anbefalede dosis af entrectinib for voksne er 600 mg oralt en gang dagligt. Dosis for børn (≥ 12 år) er 300 mg/m2 oralt en gang dagligt, hvilket i praksis betyder 400 mg dagligt, hvis overfladearealet er 1,11 – 1,5 m^2 og 600 mg dagligt, hvis overfladearealet er større end 1,5 m^2.

Behandlingen fortsættes indtil sygdomsprogression, uacceptabel toksicitet eller opnåelse af komplet patologisk respons, som betyder, at patienten har fået bortopereret resttumor og derefter fået påvist fravær af sygdom ved en histologisk undersøgelse af det bortopererede væv.

Entrectinib fik betinget markedsføringstilladelse af Europakommissionen den 31. juli 2020. Ansøger er forpligtet til at indlevere opfølgningsstudier senest 2027, hvori effekten i NTRK-positive tumorer skal undersøges i flere patienter, både samlet og på enkelttumorniveau. Manglende effekt i en given tumortype er i den forbindelse defineret som mindre end fire objektive respons i 13 sekventielt inkluderede patienter.

Estimat for antal patienter i Danmark
Antallet af patienter, der årligt er kandidater til behandling med entrectinib i Danmark, er usikkert. Dels findes der ikke tilstrækkelige data for hyppigheden af NTRK-fusion hos danske kræftpatienter, og derudover er entrectinib først indiceret, når øvrige muligheder for behandling er udtømte. Derfor skal et estimat af patientantal tage højde for frafald imellem behandlingslinjer på tværs af mange forskellige kræftformer.

En af forudsætningerne for behandling med entrectinib er, at alle øvrige behandlingsmuligheder er udtømte. I denne sammenhæng henviser fagudvalget til gældende nationale retningslinjer og Medicinrådets behandlingsvejledninger inden for de forskellige relevante kræftområder.

Fagudvalget skønner, at der årligt er ca. 10.000 danske patienter, som har uhelbredelig kræft [4], og at ca. 1/3 af disse vil udtømme øvrige behandlingsmuligheder, men stadig være i tilstrækkelig almen tilstand til at modtage yderligere behandling. Det er således blandt disse ca. 3.000 patienter, at man skal identificere de patienter, som kan være kandidater til behandling med entrectinib.

Fagudvalget tager i sit skøn højde for, at der vil være ganske få patienter med meget sjældne kræftformer, hvor NTRK-fusionen er hyppig (f.eks. infantil fibrosarkom) samt mange patienter med hyppigere kræfttyper (f.eks. tyk- og endetarmskræft, lungekræft og modermærkekræft), hvoraf kun ganske få (ca. 0,3 %) vil have en NTRK-fusion. Derudover skønner fagudvalget, at der blandt de 1.400 årlige tilfælde af hjernetumorer i Danmark [4] vil være maksimalt 10 patienter, som kan være kandidater til behandlingen. Fagudvalget skønner således samlet, at mellem 10 og 40 patienter (voksne og børn) årligt er kandidater til behandlingen i Danmark.

Fagudvalget understreger, at der ikke foreligger tilstrækkelige data til at foretage en valid vurdering af antallet af patienter, hvorfor ovenstående skøn er forbundet med væsentlig usikkerhed. Estimatet afhænger tilmed i vid udstrækning af, hvordan screening efter NTRK-fusion implementeres, samt hvordan indikationen fortolkes, særligt udsagnet vedr. at øvrige behandlingsmuligheder skal være udtømte.

Fase 1-enheden på Rigshospitalet deltager i klinisk afprøvning af NTRK-inhibitoren larotrectinib. Fagudvalget oplyser kendskab til tre danske patienter med NTRK-fusion-positiv kræft, som siden forsøgsstart i 2016 har modtaget behandling med larotrectinib. Fagudvalget gør opmærksom på, at ovenstående estimat for antallet af patienter alene omhandler den del af entrectinibs indikation, som vedrører NTRK-fusion.

3.3 Nuværende behandling

Hovedparten af patienter med kræft modtager standardbehandling, som primært afhænger af, hvilket væv kræften er opstået i, samt hvor udbredt kræften er. For en række kræfttyper er operation med henblik på helbredelse oftest førstevalg. Når kirurgisk behandling ikke er mulig eller ikke er tilstrækkelig, tilbydes patienterne enten strålebehandling og/eller medicinsk behandling (kemoterapi, targeteret behandling eller immunterapi).

Den valgte medicinske behandling afhænger af mange faktorer, herunder kræfttype, hvor udbredt sygdommen er, samt om kræfttypen eventuelt udtrykker særlige molekylærgenetiske forandringer, hvortil der er udviklet specifikke (targeterede) lægemidler. Herudover skal patienterne være i tilstrækkelig almen tilstand til at kunne tåle yderligere behandling. I studier måles almen tilstand ofte med ECOG-performance status [12].

For flere pædiatriske kræftformer er kemoterapi ofte førstevalg. For en lille andel af patienterne med meget sjældne kræftformer findes der ingen etableret standardbehandling. Derudover er der patienter med hyppigere kræftformer, som i løbet af deres behandlingsforløb udtømmer alle standardbehandlingsmuligheder. Disse patienter kan indgå i forsøg med eksperimentel behandling eller få tilbudt lindrende behandling (*best supportive care* (BSC)).

I modsætning til den traditionelle fremgangsmåde for kræftbehandling, kendetegnet ved i vid udstrækning at være histologi (vævstype)-afhængig, er entrectinib ikke indiceret til én bestemt kræfttype, men til alle tilfælde af solide tumorer med NTRK-fusion (ofte benævnt som 'vævs-/tumor-agnostisk'). Af denne årsag, og fordi entrectinib er indiceret, når øvrige muligheder for behandling er udtømte, findes der ikke standardbehandling for de patienter, som kandiderer til behandling med entrectinib. Derfor kan der heller ikke fastslås et enkelt eller nogle få medicinske behandlingsalternativer til entrectinib. Dog vurderes larotrectinib, som er en NTRK-hæmmer med lignende indikation, også aktuelt af Medicinrådet.

4. Metode

Medicinrådets protokol for vurdering vedrørende entrectinib beskriver sammen med *Håndbog for Medicinrådets proces og metode vedr. nye lægemidler og indikationsudvidelser*, hvordan Medicinrådet vil vurdere lægemidlets værdi for patienterne.

5. Resultater

5.1 Klinisk spørgsmål 1

5.1.1 Litteratur

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

Studier af entrectinib
Ansøger har søgt litteratur med søgestrengen fra protokollen og har udvalgt én fuldtekstartikel, der beskriver entrectinibs effekt og sikkerhed til behandling af NTRK-fusion-positiv kræft [13]. Studiet er en integreret analyse af tre enkeltarmede kliniske studier (Tabel 5-1). Derudover har ansøger anvendt data publiceret i det Europæiske Lægemiddelagenturs (EMA) *European Public Assessment Report* (EPAR) [14] og produktresumé (SmPC) [15], der indeholder data fra samme studier, men med et senere data cut-off (31. oktober 2018). Det er dette data cut-off, som ansøger baserer effektanalyserne på.

Tabel 5-1. Oversigt over anvendt litteratur for entrectinib.

Reference	Studier (NCT-nummer)	Beskrivelse	Data cut-off og median opføgningstid	Antal patienter
Doebele et al. 2020 [13]	ALKA-372-001, (Ikke registreret NCT- EudraCT nr: 2012-000148-88), voksne, fase I STARTRK-1, (NCT02097810), voksne, fase I STARTRK-2, (NCT02568267), voksne, fase II	Samlet analyse af entrectinibs sikkerhed og effekt i voksne på tværs af de tre studier ved første publicerede cut-off. Data medtages kun fra patienter med påvist NTRK-fusion	31. maj 2018, 12,9 måneders median opfølgningstid	54 / 355 til sikkerhedspopulationen
EPAR [14] og SmPC [15]	ALKA-372-001, STARTTRK-1 og STARTRK-2	Samme studier og analyser, men med et senere data cut-off og flere patienter	31. oktober 2018, 14,2 måneders median opfølgningstid	74 / 475 til sikkerhedspopulation

Ud over de publicerede data (se Tabel 5-1) har ansøger anvendt ikke-fagfællebedømte konferenceabstracts samt 'data on file' fra de samme kliniske studier til at belyse effekten af entrectinib på samlet overlevelse (OS), progressionsfri overlevelse (PFS) og objektiv responsrate (ORR) på tumortypeniveau [16,17] samt livskvalitet [18]. Medicinrådet har konkret vurderet, at data kan indgå i bedømmelsen, jf. Medicinrådets kriteriepapir om anvendelsen af upublicerede data. Dette skyldes, at data giver muligheden for at vurdere entrectinibs effekt på enkelttumorniveau, og at de stammer fra de samme kliniske studier som det publicerede data og derved kan valideres overfor disse.

Baselinekarakteristika for effektpopulationen fra entrectinibstudierne er opsummeret nedenfor. Effektpopulationen er defineret som havende påvist NTRK-fusion og minimum 6 måneders opfølgning efter første entrectinib-dosering.

Tabel 5-2. Demografi og baselinekarakteristika for entrectinib-effektpopulationen ved data cut-off den 31. oktober 2018.

Hovedkategori	Underkategori	Entrectinib-effektpopulation (Data cut-off den 31. oktober 2018)
Alder	Medianalder, år (rækkevidde)	57 (21-83)
	Andel over 65 år, n (%)	26 (35,1)
Køn, n (%)	Kvinde	39 (52,7)
Eastern Cooperative Oncology Group - performance score, n (%)	0	30 (40,5)
	1	34 (45,5)
	2	10 (13,5)
Tidligere eller nuværende ryger, n (%)		23 (40,3)
Overordnet tumorhistologi, n (%)	Sarkom	16 (21,6)
	Ikke-småcellet lungekræft	13 (17,6)
	Spytkirtelkræft	13 (17,6)
	Skjoldbruskkirtelkræft	7 (9,5)
	Kolorektalkræft	7 (9,5)
	Brystkræft	6 (13)
	Neuroendokrin kræft	4 (5,4)
	Bugspytkirtelkræft	3 (4,1)
	Kræft i æggestokkene	1 (1,4)
	Endometrialkræft	1 (1,4)
	Kolangiokarcinom	1 (1,4)
	Anden mave-tarmkræft	1 (1,4)
	Neuroblastom	1 (1,4)
NTRK-genfusion, n (%)	NTRK1	30 (40,5)
	NTRK2	2 (2,7)

Hovedkategori	Underkategori	Entrectinib-effektpopulation (Data cut-off den 31. oktober 2018)
	NTRK3	42 (56,8)
Mediantid siden diagnose, måneder (rækkevidde)		21,0 (2,1 – 433,1)
Sygdomsstadie ved diagnosetidspunkt, n (%)	≤ III	37 (50)
	IV	30 (41,1)
	Ukendt	7 (9,6)
Metastaser ved studiestart, n (%)	Fjernmetastase generelt	72 (97,3)
	Hjerne	19 (25,7)
Antal tidligere systemiske behandlingslinjer	0	20 (27,0)
	1	21 (28,4)
	2	20 (27,0)
	> 3	13 (17,6)
Tidligere behandling	Enhver systemisk behandling	64 (86,5)
	Operation	61 (82,4)
	Strålebehandling	47 (63,5)

De tre kliniske studier, som data stammer fra, er såkaldte 'basket trials', som i hovedtræk, uafhængigt af histologi, inkluderer patienter med NTRK-, ALK- eller ROS1-fusion, hvor øvrige behandlingsmuligheder er udtømte (ALKA-372-001, STARTRK-1 og STARTRK-2; se bilag 1, Tabel 12-1, Tabel 12-2 og Tabel 12-3. De hyppigste kræftformer er sarkom, ikke-småcellet lungekræft og spytkirtelkræft (13-16 patienter i hver gruppe). De øvrige kræftformer er hver repræsenteret med kun 1-7 patienter. Vurderingen af uønskede hændelser foretages dels i effektpopulationen, dels i en sikkerhedspopulation, der består af alle patienter, der har modtaget minimum én dosis entrectinib uagtet fusionsstatus. Fagudvalget bemærker desuden, at der i studierne indgår 8 patienter med primære NTRK-fusion-positive CNS-tumorer, og at disse ikke er medtaget i effektpopulationen.

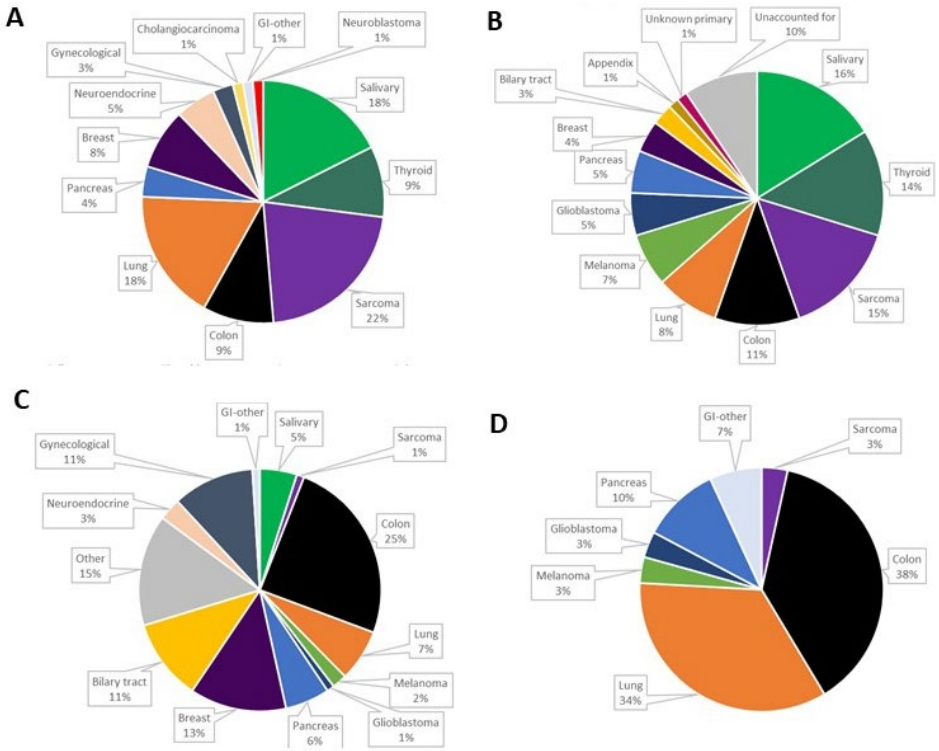
Studier af placebo eller anden systemisk behandling hos lignende patientgrupper
Studierne af entrectinib er alle non-komparative, og ansøger har derfor jf. protokollen søgt efter studier, der kan anvendes til en indirekte sammenligning med entrectinib, hvilket har resulteret i følgende tre mulige sammenligningsgrundlag, der herefter

gennemgås.

Tabel 5-3. Oversigt over mulige sammenligningsgrundlag.

Reference	Studiedesign	Beskrivelse	NTRK-fusion	Placebo-arm	Antal patienter
Rosen et al. [19]	Retrospektivt	Patienter med NTRK-fusion, som modtog anden systemisk behandling	Ja	Nej	76
Tuxen et al. [20]	Prospektivt enkeltarmet	Eksperimentel, targeteret sidstelinjebehandling	Nej	Nej	101
Placebo-analyse	Analyse af placeboarmene fra 28 RCT'er	Patienter uden kendt NTRK-fusion behandlet med placebo.	Nej	Ja	Median patientantal: 94 (range: 23 – 563)

Nedenfor illustreres, hvilke tumortyper der indgår i henholdsvis entrectinibpopulationen og de tre mulige sammenligningsgrundlag.



Figur 5-1: Oversigt over de repræsenterede tumortyper i entrectinib-effektpopulationen (A), Rosen et al. (B), Tuxen et al. (C) og placeboanalysen (D).

Rosen et al. er et retrospektivt studie fra 2020, som rapporterer data for OS, PFS og ORR for 76 patienter med NTRK-fusion på tværs af en række kræfttyper. Heraf udviklede 51 fremskreden/metastatisk sygdom i observationsperioden på 37,2 måneder, og 35 patienter modtog kemoterapibehandling for deres fremskredne sygdom [19].

Fagudvalget vurderer, at det er det største observationelle datasæt, der findes for patienter med kræft med NTRK-fusion, og at alder og fordelingen af kræfttyper (se Figur 5-1) i nogen grad svarer til de patienter, der indgår i studierne af entrectinib. Studiet giver information om effekten af andre typer af systemisk behandling hos en patientgruppe tilsvarende entrectinib-effektpopulationen, men giver ingen information omkring effekten af placebo. Studiet indeholder ingen data for uønskede hændelser og livskvalitet. Populationskarakteristika for Rosen et al. fremgår nedenfor.

Tabel 5-4. Patientkarakteristika for Rosen et al. 2020

Kategori	**Rosen et al.** [19]
Totalt antal patienter	76*
Median alder, år (spænd)	52 (0-78)
Antal patienter < 18 år[1], n (%)	10 (13,2)
Antal kvinder, n (%)	47 (61,8)
Kræfttype	
Sarkom, n (%)	9 (11,8)
Ikke-småcellet lungekræft, n (%)	6 (7,9)
Spytkirtelkræft, n (%)	0
Skjoldbruskkirtelkræft, n (%)	10 (13,2)
Kolorektalkræft, n (%)	8 (10,5)
Brystkræft, n (%)	0
Neuroendokrin kræft, n (%)	0
Bugspytkirtelkræft, n (%)	4 (5,3)
Kræft i æggestokkene, n (%)	0
Endometrialkræft, n (%)	0
Kolangiokarcinom, n (%)	0
Anden mave-tarmkræft, n (%)	0

Kategori	Rosen et al. [19]
Neuroblastom, n (%)	4 (5,3)
Andre, n (%)	35 (46,1)
Kræftstadie på diagnosetidspunkt	
Lokaliseret (I-III), n (%)	34 (58,6)
Metastatisk (IV), n (%)	24 (41,4)
Tidligere behandling	
Antal behandlingslinjer	Ikke angivet
Kirurgi, n (%)	65 (87,8) (n = 74)
Strålebehandling, n (%)	33 (47,1) (n = 70)
Systemisk behandling, n (%)	57 (75)

*Med mindre andet angives. [1] NB: ekstraheret på baggrund af offentligt tilgængeligt rådata fra studiet (tilgængeligt her).

Studiepopulationen afviger fra entrectinib-effektpopulationen på flere parametre.

- 41 % af patienterne havde metastatisk kræft ved diagnosetidspunktet. I entrectinibstudiet havde 97 % af patienterne fjernmetastaser ved studiestart.
- Studiet estimerer OS-rater og median OS med udgangspunkt i tidspunktet for den oprindelige diagnose (uanset stadie), hvorfor disse estimater er usammenlignelige med tilsvarende resultater fra studierne af entrectinib.
- 45 % af patienterne modtager på et tidspunkt i forløbet behandling med en TRK-hæmmer, hvilket påvirker effektestimaterne. Estimaterne for ORR er dog opgivet som bedste ORR efter kemoterapi på tværs af behandlingslinjer, hvorved TRK-hæmmere ikke indgår i dette.
- Fire ud af 76 patienter har primære CNS-tumorer (glioblastoma multiforme). I entrectinibpopulationen indgår 8 patienter med primære CNS-tumorer, men disse indgår ikke i effektanalyserne.

Fagudvalget vurderer, at studiet af Rosen et al. kan bidrage med information om effektmålene ORR og PFS for patienter med NTRK-fusion-positiv kræft som helhed. Studiet rapporterer dog kun resultater af aktive behandlinger og kan således ikke bruges som en komparator for entrectinib. Resultaterne for disse effektmål kan dog anvendes til at sætte effekterne for entrectinib i perspektiv i forhold til, hvad der kan forventes ved andre systemiske behandlinger af NTRK-fusion-positiv kræft.

Tuxen et al. er et studie af eksperimentel behandling af avancerede eller metastatiske tumorer, hvor alle andre tilfredsstillende behandlingsalternativer var udtømte [20].

Patienterne blev screenet for eventuelt targeterbare mutationer og derefter allokeret til eksperimentelle targeterede behandlinger. Der blev fundet 101 patienter med targeterbare mutationer, og disse blev fulgt op mht. ORR og PFS ved den targeterede behandling. Studiet kunne eventuelt bidrage til at sætte entrectinibs effekt i perspektiv, i forhold til hvad der generelt kan forventes ved sidstelinje eksperimentel targeret behandling. Patienterne er dog langt fra sammenlignelige med patienterne i studierne af entrectinib, da tumortyperne afviger væsentligt mellem studierne (se Figur 5-1). Fagudvalget vurderer derfor, at dette studie ikke er relevant som supplerende sammenligningsgrundlag.

Ansøgers placeboanalyse rapporterer data fra 28 fuldtekstartikler af i alt 28 randomiserede kliniske studier med patienter med ikke kendt NTRK-fusion. Ansøger har ekstraheret og opgjort samlede estimater for effektmålene OS, PFS, ORR og livskvalitet. Studierne omhandler sene behandlingslinjer i kræftformer uden kendte onkogene drivere. De kræftformer, der indgår, er kolorektalkræft (10 artikler), ikke-småcellet lungekræft (10 artikler), kræft i bugspytkirtlen (3 artikler), gastrointestinal stromal tumor (2 artikler), glioblastom (1 artikel), melanom (1 artikel) og sarkom (1 artikel). Placeboanalysen er det eneste tilgængelige grundlag til at vurdere effekten af placebo ved senlinjebehandling af de relevante kræftformer.

De repræsenterede tumortyper varierer dog væsentligt fra sammensætningen i entrectinibpopulationen (se Figur 5-1). Samtidig kendes den prognostiske betydning af NTRK-fusion ved de forskellige kræftformer ikke.

Fagudvalget vurderer, at de samlede effektestimater på tværs af alle tumortyper ikke kan anvendes som sammenligningsgrundlag. Fagudvalget vurderer dog, at OS- og PFS-data fra de individuelle tumortyper i placeboanalysen kan anvendes som supplerende sammenligningsgrundlag for entrectinib, hvor data er opgivet på enkelttumorniveau.

Growth modulation index

Ansøger har indsendt en analyse baseret på 'data on file', som sammenligner hver enkelt patients 'tid til næste behandling' ved den forudgående behandling med PFS/'tid til næste behandling' for entrectinib (intrapatientanalyse/growth modulation index (GMI)). [redacted]. Fagudvalget har konkret vurderet, at data kan indgå i bedømmelsen som supplerende sammenligningsgrundlag til at understøtte data for PFS, jf. Medicinrådets kriteriepapir om anvendelsen af upublicerede data. Dette skyldes, at de adresserer et specifikt ønske fra protokollen om at sammenholde effekten af entrectinib med den umiddelbart foregående behandlingslinje, og at data stammer fra de samme studier, som de publicerede.

5.1.2 Databehandling og analyse

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

Datagrundlaget for EMA's godkendelse samt den nærværende vurdering af entrectinib er baseret på tre single-arm-studier. Ansøger er blevet bedt om at søge efter data, som tillader en naiv sammenstilling, men har ikke identificeret studier, som tillader dette. Ansøger har indsendt tre forskellige bud på sammenligningsdata samt den ovennævnte GMI-analyse.

Fagudvalget vurderer, at ingen af de indsendte data tillader en kvantitativ sammenligning, der kan ligge til grund for en kategorisering af entrectinibs værdi ud fra Medicinrådets metoder.

I gennemgangen af resultater vil de poolede data for entrectinib (data cut-off den 31. oktober 2018) alene blive sammenholdt med udvalgte data fra studiet af Rosen et al. [19]. Ansøgers placeboanalyse bliver kun anvendt som supplerende information til at belyse effekten på de specifikke kræftformer. For uønskede hændelser har ansøger indsendt en oversigt for både den samlede sikkerhedspopulation (alle patienter, der har modtaget minimum 1 dosis entrectinib) samt for den NTRK-fusion-positive population. Fagudvalget lægger størst vægt på data fra populationen med påvist NTRK-fusion, da disse må formodes at have modtaget en behandling, der er mere repræsentativ for, hvad patienterne vil modtage i klinisk praksis.

5.1.3 Evidensens kvalitet

Der er tale om en narrativ syntese uden kvantitative sammenligninger på baggrund af fase I/II-single-arm-data. 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.

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

Fagudvalget bemærker dog, at på grund af sjældenheden af NTRK-fusion, entrectinibs vævsagnostiske indikation og det forhåndenværende data fra single-arm-forsøg er det vanskeligt at foretage en retvisende vurdering af entrectinibs kliniske værdi ved brug af Medicinrådets metoder.

5.1.4 Effektestimater og kategorier

I tabellen herunder fremgår de samlede effektestimater for alle kræftformer for klinisk spørgsmål 1, kategorier per effektmål, den samlede kategori samt kvalitet af evidensen. Heraf fremgår det, at effekten for entrectinib overfor placebo ikke kan kategoriseres, og at den samlede evidenskvalitet er meget lav. Fagudvalgets vurdering af effekten på de enkelte kræftformer/tumortyper gennemgås under de enkelte effektmål.

Tabel 5-5. Resultater for klinisk spørgsmål 1.

Effektmål	Målenhed (MKRF)	Vigtighed	**Entrectinib** [14,15]	**Anden systemisk behandling af patienter med NTRK-fusion-positiv kræft***	**Aggregeret værdi for effektmålet**
			Estimat [95 % CI]	**Rosen et al. 2020** [19] **(Estimat [95 % CI])**	
Overlevelse	Median OS i antal måneder (MKRF: 3 måneder)	Kritisk	23,9 måneder [16; IN]	**	Kan ikke kategoriseres
	OS-rate ved 24 måneder (MKRF: 5 %)		45 % (aflæst fra Kaplan-Meier kurve)	**	
	Andel patienter med komplet patologisk respons (MKRF: 5 %)		0 % (n = 0) [1]	Ikke angivet	
Livskvalitet	Forskel i gennemsnitlig ændring i EORTC-QLQ-C30 (MKRF: 10 point)	Kritisk	Ændring præ- vs. post-baseline: 5,3 point (n = 61 post-baseline, n = 11 ved sidste måling)	Ikke angivet	Kan ikke kategoriseres
Objektiv responsrate	Samlet ORR for hele den voksne patientpopulation (MKRF: narrativ vurdering)	Vigtig	63,5 % [51,5; 74,4]	62,5 % [40,6; 81,2] [3]	Kan ikke kategoriseres
Progressionsfri overlevelse	Median PFS (MKRF: 3 måneder)	Vigtig	11,2 måneder [8,0; 15,7]	9,1 måneder [4,8; 13,1]	Kan ikke kategoriseres

Effektmål	Målenhed (MKRF)	Vigtighed	Entrectinib [14,15]	Anden systemisk behandling af patienter med NTRK-fusion-positiv kræft*	Aggregeret værdi for effektmålet
			Estimat [95 % CI]	Rosen et al. 2020 [19] (Estimat [95 % CI])	
Uønskede hændelser	Andel patienter med én eller flere uønskede hændelser grad 3-4 (MKRF: 5 %-point)	Vigtig	73,5 % [2]	Ikke angivet	Kan ikke kategoriseres
	Kvalitativ gennemgang af uønskede hændelser				

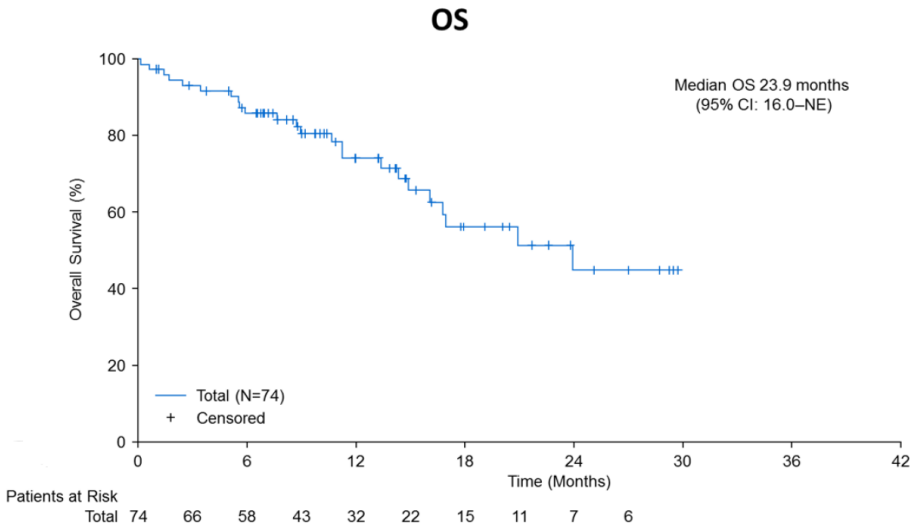
Konklusion	
Samlet kategori for lægemidlets værdi	Kan ikke kategoriseres. Fagudvalget vurderer dog, at resultaterne tyder på, at entrectinib er mere effektivt og forbundet med flere uønskede hændelser end placebo
Kvalitet af den samlede evidens	Meget lav.

* Data fra Rosen et al. 2020 [19] er ikke et indirekte sammenligningsgrundlag for entrectinib, men fungerer til at perspektivere effekten af entrectinib i forhold til anden systemisk behandling af patienter med NTRK-fusion-positiv kræft. ** Data for overlevelse fra Rosen et al. 2020 er ikke angivet, da de ikke er sammenlignelige med data for entrectinib (se afsnit 5.1.1). [1] Komplet patologisk respons er ikke dokumenteret i nogen patienter. Det vides dog ikke, om nogle af patienterne ville have komplet patologisk respons, hvis dette var undersøgt. [2] Fagudvalget bemærker, at estimatet reflekterer akkumulation af hændelser over en lang behandlingsperiode, hvilket er usædvanligt i en palliativ population. [3] Bedste respons på kemoterapi på tværs af alle behandlingslinjer. CI = konfidensinterval. IN = ikke nået.

Overlevelse

Effektmålet overlevelse er kritisk for vurderingen af lægemidlets værdi for patienterne. Forbedret samlet overlevelse (OS) med bedst mulig livskvalitet og mindst mulig toksicitet er det optimale mål for livsforlængende kræftbehandling. Overlevelse vurderes desuden ved hjælp af komplet patologisk respons, som betyder, at patienten har fået bortopereret resttumor og derefter fået påvist fravær af sygdom ved en histologisk undersøgelse af det bortopererede væv.

Ved det senest angivne data cut-off for entrectinib (31. oktober 2018) var der observeret 24 dødsfald svarende til 32,4 % af de evaluerbare voksne patienter (median opfølgningstid på 14,2 måneder). Medianoverlevelsen var 23,9 måneder (CI = [16; ikke nået]) [14]. Overlevelsesraten efter 24 måneder er ikke angivet i ansøgningen, men kan aflæses fra den tilhørende Kaplan-Meier kurve til ca. 45 %. Fagudvalget bemærker, at der er væsentlig usikkerhed omkring dette estimat, da der kun er 7 patienter, der ikke er bortcensureret eller døde efter 24 måneders opfølgning.



Figur 5-2. Samlet overlevelse (OS) for NTRK-fusion-positive voksne i behandling med entrectinib med minimum 6 måneders opfølgning.

Der findes ikke et egnet sammenligningsgrundlag til at vurdere entrectinibs effekt på OS overfor placebo set over hele gruppen.

Overlevelsesdata inddelt efter tumortype for hhv. entrectinib og ansøgers placeboanalyse er sammenstillet i tabellen nedenfor. Dette bygger på små populationer og skal tolkes med forsigtighed. Det giver dog i nogle tilfælde mulighed for en naiv sammenstilling af overlevelsen ved entrectinibbehandling overfor placebo ved tilsvarende tumortyper.

Tabel 5-6. Median overlevelse (OS) ved entrectinibbehandling fordelt per tumortype og tilsvarende median OS-estimater fra ansøgers placeboanalyse.

Tumortype	Median OS i måneder ved entrectinib, [95 % CI], (antal patienter)	Median OS ved placeboanalyse [range] (antal studier)
[redacted]	[redacted]	[redacted]
Ikke-småcellet lungekræft	14,9 [5,9; IN] (13)	5,1 [1,95; 8,5] (10 studier)
Kolorektalkræft	16,0 [2,9; IN] (7)	4,9 [2,8; 6,9] (10 studier)
Spytkirtelkræft	Ikke nået (7)*	Indgår ikke
[redacted]	[redacted]	[redacted]
Skjoldbruskkirtelkræft	Ikke nået (5)*	Indgår ikke
Bugspytkirtelkræft	13,4 [13,4; IN] (3)	2,7 [2,3; 2,76] (3 studier)

* Data stammer fra det tidligere data cut-off brugt i Doebele et al. [13].

[redacted]. Ikke-småcellet lungekræft og kolorektalkræft er ligeledes hyppigt repræsenterede. Her ses, at median OS er 10 – 11 måneder længere ved entrectinib. Ved kræft i bugspytkirtlen indgår kun tre patienter i entrectinibpopulationen, hvilket er så få, at en sammenligning ikke er meningsfuld.

Der er ikke påvist komplet patologisk respons i nogen voksne patienter. Fagudvalget bemærker dog, at dette i praksis meget sjældent observeres for patienter med metastatisk kræft, hvorved det ikke vil være realistisk at forvente komplet patologisk respons i denne patientgruppe, og det vides ikke, om patienterne er undersøgt for dette.

Idet der ikke foreligger data, som tillader en sammenligning mellem entrectinib og placebo, kan lægemidlets værdi ikke kategoriseres for overlevelse.

Fagudvalget vurderer, at entrectinibs effekt på OS er meget usikker. Dog er medianoverlevelserne per tumortype i alle tilfælde længere ved entrectinibbehandlingen end i placeboanalysen, hvilket kan indikere en effekt på den samlede overlevelse.

Livskvalitet

Livskvalitet er et kritisk patientrelateret effektmål, da patienter, der responderer på entrectinib, kan være kandidater til langvarig behandling. Derfor er det relevant at vurdere både negative effekter, der kunne forårsages af bivirkninger, og positive effekter, eksempelvis fra færre tumor-relaterede komplikationer.

Livskvalitet er undersøgt vha. EORTC-QLQ-C30 i STARTRK-2-studiet. Det data med længst opfølgningstid stammer fra en posterpræsentation på ESMO 2020, hvor ændringerne fra baseline indtil behandlingscyklus nr. 13 er rapporteret [18]. Her blev der rapporteret om en gennemsnitlig stigning i global health status på 5,3 point. Fagudvalget bemærker dog, at blot 25 % af patienterne indgår i målingerne ved cyklus 13, og at blot 60 % af de adspurgte patienter på dette tidspunkt svarede på spørgeskemaet. Der er ikke rapporteret et usikkerhedsestimat på den gennemsnitlige øgning, og det kan derfor ikke konkluderes, om stigningen er statistisk signifikant. Punktestimatet for en eventuel stigning er dog under den fastsatte minimale klinisk relevante forskel på 10 point. Ansøger har indsendt data for patientpopulationen med ikke-småcellet lungekræft og kolorektalkræft. Data er dog så sparsomme, at de ikke bidrager yderligere til at belyse effektmålet. Der er ikke rapporteret data for livskvalitet i Rosen et al. [19].

Entrectinibs foreløbige værdi for livskvalitet kan ikke kategoriseres. Fagudvalget kan ikke vurdere, om entrectinib øger livskvaliteten.

Objektiv responsrate

Objektiv responsrate (ORR) er et vigtigt effektmål for vurderingen af lægemidlets værdi for patienterne. ORR anvendes til belysning af behandlingsrespons og afspejler interventionens effekt på tumoren. ORR for den samlede voksenpopulation ved det seneste data cut-off (31. oktober 2018) ses i Tabel 5-7.

Tabel 5-7. Objektiv responsrate (ORR) for den samlede voksenpopulation. Data er publiceret i EMAs SmPC [15].

Kategori	Entrectinib [15]	Kemoterapi hos patienter med NTRK-fusion-positiv kræft (Rosen et al. [19])
Total antal respons (antal patienter i alt)	47 (n = 74)	15 (24)
ORR [95 % CI]	63,5 % [51,5; 74,4]	62,5 % [40,6 %; 81,2 %]
Komplet respons	5 (6,8 %)	4 (11,4 %)
Partielt respons	42 (56,8 %)	11 (31,4 %)

Den samlede voksenpopulation havde en ORR på 63,5 %, hvoraf størstedelen opnåede et partielt respons. I studiet af Rosen et. al opnåede gennemsnitlig 62,5 % et objektivt respons [19]. Dette var dog angivet som det bedste respons på kemoterapi på tværs af behandlingslinjer og er derved ikke nødvendigvis repræsentativt for respons på en sidstelinjebehandling.

ORR er yderligere rapporteret opdelt per tumortype (Tabel 5-8).

Tabel 5-8. Oversigt over objektiv responsrate (ORR) opgjort per tumortype i voksenpopulationen. Data er fra EMAs SmPC og opgjort ved seneste data cut-off [15].

Tumortype	Antal patienter (n = 74)	ORR ved entrectinib %	95 % CI	ORR ved placeboanalysen median (antal studier)
Sarkom	16	56,3 %	[30; 80]	Ikke rapporteret
Ikke-småcellet lungekræft	13	69,2 %	[39; 91]	2 % (3 studier)
Spytkirtelkræft	13	92,3 %	[64; 100]	Indgår ikke
Skjoldbruskkirtelkræft	7	42,9 %	[10; 82]	Indgår ikke
Kolorektalkræft	7	28,6 %	[4; 71]	1,88 % (10 studier)
Brystkræft	6	80 %	[40; 100]	Indgår ikke
Neuroendokrin kræft	4	50 %	[7; 93]	Indgår ikke
Bugspytkirtelkræft	3	67 %	[9,4; 99,2]	0,32 % (2 studier)
Kræft i æggestokkene	1	0 %	-	Indgår ikke
Endometrialkræft	1	100 %	-	Indgår ikke
Kolangiokarcinom	1	100 %	-	Indgår ikke
Anden mave-tarmkræft	1	100 %	-	1,95 % (2 studier)
Neuroblastom	1	0 %	-	Indgår ikke

I alt 7 af tumortyperne var repræsenteret af mindre end 5 patienter. Fagudvalget vurderer, at det for disse ikke er meningsfyldt at evaluere ORR. For de resterende 6 tumortyper repræsenteret ved minimum 5 patienter (6 – 16) sås varierende ORR fra 28,6 % (kolorektalkræft, n = 7) til spytkirtelkræft (92,3 %, n = 13). Konfidensintervallerne for alle tumortyperne overlapper det samlede ORR-estimat. Datagrundlaget er derfor ikke stærkt nok til at kunne konkludere, om effekten adskiller sig signifikant mellem tumortyperne. For alle tilfælde ses dog, at ORR er væsentlig højere ved entrectinib end i placeboanalysen af den tilsvarende tumortype.

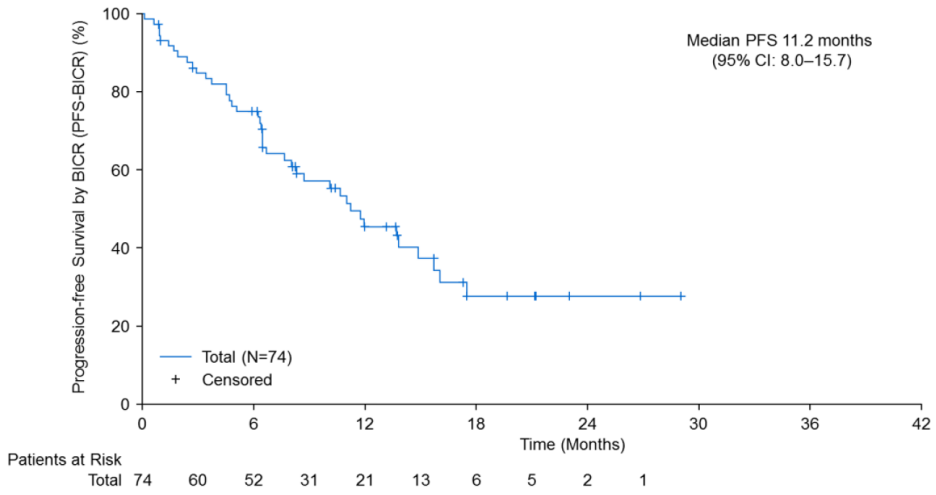
Entrectinibs værdi kan ikke kategoriseres pga. manglende komparativt data. Fagudvalget vurderer dog, at ORR er høj på tværs af voksenpopulationen. Her tages højde for, at

størstedelen af patienterne (ca. 80 %) tidligere har modtaget én eller flere systemiske behandlinger, og at ORR ved placebobehandling generelt ses at være tæt på 0 %. Yderligere bemærker fagudvalget, at et væsentligt antal patienter uden respons på foregående systemisk behandling udviste et objektivt respons på entrectinib (se GMI afsnit 6.1).

Progressionsfri overlevelse

Progressionsfri overlevelse (PFS) bliver anvendt til at vurdere, hvor lang tid der går, inden sygdommen udvikler sig. Fagudvalget vurderer, at det er vigtigt for patienterne ikke at have sygdomsprogression i længst mulig tid. Patienter med sygdomsprogression kan have generende symptomer, og den aktuelle patientgruppe har ingen efterfølgende behandlingsalternativer. Den mindste klinisk relevante forskel blev i protokollen fastsat til 3 måneder.

Median progressionsfri overlevelse for voksne patienter var 11,2 måneder [8,0; 15,7]. PFS-raten ved 12 måneder angives ikke, men kan aflæses fra kurven til ca. 45 %.



Figur 5-3. Progressionsfri overlevelse (PFS) for NTRK-fusion-positive voksne i behandling med entrectinib med minimum 6 måneders opfølgning.

I studiet af Rosen et al. var median PFS 9,1 måneder [4,8; 13,1], og 37 % [24; 51] var progressionsfri efter 12 måneder [19]. Disse data stammer kun fra patienter med lokalfremskreden eller metastatisk sygdom og er derfor mere sammenlignelige, end det er tilfældet for data vedr. overlevelse. Dog repræsenterer PFS-data fra Rosen et al. en aktiv behandling i førstelinje, og det kan derfor ikke anvendes til at vurdere effekten af entrectinib overfor placebo.

Ansøger har indsendt PFS-data inddelt på tumortypeniveau.

Tabel 5-9. Median progressionsfri overlevelse (PFS) ved entrectinibbehandling fordelt per tumortype og tilsvarende median PFS-estimater fra ansøgers placeboanalyse.

Tumorhistologi	Median PFS i måneder ved entrectinib, [95 % CI], (antal patienter)	Median PFS ved placeboanalyse [range] (antal studier)
[redacted]	[redacted]	[redacted]
Ikke-småcellet lungekræft	14,9 [4,7; IN] (13)*	1,8 [0,5; 7] (10 studier)
Kolorektalkræft	2,4 [1,0; 16] (7)	1,8 [1,68; 2,63] (10 studier)
Spytkirtelkræft	Ikke nået (7)**	Indgår ikke
[redacted]	[redacted]	[redacted]
Skjoldbruskkirtelkræft	Ikke nået (5)**	Indgår ikke
Bugspytkirtelkræft	8,0 [6,2; 17,5] (3)	1,41 [ikke relevant] (1 studie, 155 patienter)

* Bemærk, at PFS er vurderet som samme punktestimat som OS. Dette er også tilfældet ved opslaget i referencen, som er et posterabstract fra ESMO 2020 [17]. Dette skyldes meget få patienter og tilfældigheder.
** Data stammer fra det tidligere data cut-off brugt i Doebele et al. [13].

Generelt er PFS længere i entrectinibpopulationen end ved placeboanalysen for samtlige undersøgte tumortyper. Den absolutte forskel varierer dog fra 0,6 måneder ved kolorektalkræft til 13 måneder ved ikke-småcellet lungekræft.

Ved kræft i bugspytkirtlen er antallet af patienter så få, at en sammenligning ikke er meningsfuld.

Samlet set kan entrectinibs foreløbige værdi for effektmålet PFS ikke kategoriseres grundet manglende komparativt data. Den naive sammenstilling med patienterne i Rosen et al. viser en absolut forskel på ca. 2 måneder, hvilket er mindre end den mindste klinisk relevante forskel. PFS i Rosen et al. er dog angivet for førstelinje-kemoterapi. Fagudvalget bemærker, at data på enkelttumorniveau tyder på en længere PFS ved entrectinib end ved placebo for tilsvarende tumortype. Data fra GMI-analysen støtter yderligere op om en forlænget PFS (se afsnit 6.1 om GMI). Derfor vurderer fagudvalget, at resultaterne tyder på, at PFS ved entrectinibbehandling sandsynligvis er længere end ved placebobehandling.

Uønskede hændelser

Ansøger har indsendt en opgørelse over uønskede hændelser af grad 3-5. Fagudvalget havde efterspurgt en opgørelse over uønskede hændelser af grad 3-4. Dette findes dog ikke i publikationer, EMAs SmPc eller EPAR, og derfor tager fagudvalget i stedet udgangspunkt i opgørelserne, der inkluderer grad 5.

I populationen med påvist NTRK-fusion (n = 68) oplevede 73,5 % minimum 1 uønsket hændelse af grad 3-5, og uønskede hændelser var årsag til behandlingsstop i 13,2 % af

patienterne. De mest almindelige uønskede hændelser af grad 3-5 var anæmi (19,1 %), vægtøgning (13,2 %), træthed (11,8 %), hypoxi (7,4 %), dypsnø (5,9 %) og lungebetændelse (5,9 %). 6 patienter (8,8 %) døde som følge af uønskede hændelser. Ingen af disse blev dog vurderet at være behandlingsrelaterede.

Den samlede profil for uønskede hændelser var ikke væsentlig forskellig i den samlede sikkerhedspopulation, selvom der generelt blev rapporteret om lidt færre uønskede hændelser af grad 3-5 (61,5 %) og en lidt mindre andel af patienter, der måtte stoppe behandlingen grundet uønskede hændelser (9,1 %).

Samlet set var de uønskede hændelser håndterbare ved hjælp af dosisreduktion (26 %) eller pausering (45,9 %).

Den kliniske værdi af entrectinib ift. placebo kan ikke kategoriseres på baggrund af det forhåndenværende data.

Fagudvalget vurderer dog, at entrectinib sandsynligvis er forbundet med flere uønskede hændelser end placebo. Fagudvalget bemærker dog, at resultaterne reflekterer akkumulation over en lang behandlingsperiode. Samlet set vurderer fagudvalget, at de uønskede hændelser forbundet med entrectinib er håndterbare.

CNS-progression
CNS-progression blev i protokollen defineret som et mindre vigtigt effektmål, hvorfor det ikke fremgår i den samlede oversigt over effektmålene (Tabel 5-5). Fagudvalget har alligevel fundet det relevant at beskrive disse data, da CNS-progression medfører betydelig morbiditet og forkortet overlevelse.

Ansøger har indsendt data for CNS-progression på baggrund af den opdaterede effektanalyse (n = 74). I denne population oplevede 36,5 % CNS-progression og med en median tid til CNS-progression på 16,8 måneder. Der er dog en væsentlig usikkerhed omkring medianen, da patienter uden CNS-metastaser ved studiets start ikke blev undersøgt for dette hver 8. uge.

Effekten på diagnosticerede CNS-metastaser ved studiestart er undersøgt i en opdateret analyse præsenteret ved ESMO 2020 [21]. Ud af 74 patienter havde 16 CNS-metastaser ved behandlingsstart, og 8 af disse havde målbare læsioner. Patienterne med målbare CNS-læsioner ved behandlingsstart havde en samlet mediantid til CNS-progression på 10,1 måneder.

Fagudvalget vurderer, at de tilgængelige data for effekt på CNS-metastaser ikke indikerer, at der skulle være en dårligere effekt af entrectinib på CNS-metastaser end på metastaser generelt.

5.1.5 Fagudvalgets konklusion

Værdien af entrectinib overfor placebo til behandling af voksne med NTRK-genfusion-positiv kræft **kan ikke kategoriseres**. Dette skyldes mangel på et komparativt datagrundlag.

Fagudvalget bemærker dog, at evidensen, trods manglende komparativt data, indikerer, at entrectinib er mere effektivt og forbundet med flere uønskede hændelser end placebo. Samlet vurderer fagudvalget, at entrectinib kan være en god behandlingsmulighed for en række kræftformer hos voksne, der ikke har andre tilfredsstillende behandlingsmuligheder. Dette er baseret på:

- Høj ORR og lang PFS, særligt når man tager i betragtning, at det er patienter, der i forvejen har modtaget tidligere systemiske behandlingslinjer og ikke har andre behandlingsmuligheder.
- Data, som indikerer, at entrectinib også har en effekt på eventuelle CNS-metastaser.
- Data, som indikerer, at entrectinib er mere effektivt, end den behandling patienterne modtog i linjen umiddelbart inden behandling med entrectinib (se afsnit 6.1).
- Håndterbare bivirkninger i en population, der er behandlet i forholdsvis lang tid.

5.2 Klinisk spørgsmål 2

5.2.1 Litteratur

Entrectinibs effekt og sikkerhed er undersøgt i et klinisk studie, der inkluderer børn (STARTRK-NG). Dette er et enkeltarmet basket trial, der inkluderer børn med fusions-positiv (NTRK, ALK eller ROS1) kræft (se Tabel 12-4. Oversigt over STARTRK-NG. Tabel 12-4). Studiet er delt i flere faser inklusive en dosiseskalation og dosisekspansion. I dosiseskalationen indgår børn uden fusions-positiv kræft (13/16). I vurderingerne af entrectinibs effekt på ORR indgår kun 8 patienter med bekræftet NTRK-fusion. Alle patienter, der har modtaget minimum én dosis entrectinib, medtages i sikkerhedsanalyserne (32 patienter). Disse data fremgår af EMAs EPAR [14]. Ansøger har herudover indsendt et konferenceabstract, der beskriver data for ORR i subpopulationen med CNS-tumorer (alle fusionstyper) [22].

Der findes intet sammenligningsgrundlag for entrectinibs effekt i børn. Studierne, der blev anvendt som supplerende information ved de voksne patienter, indeholder ingen eller meget få børn, og de indgår derfor ikke i gennemgangen her.

5.2.2 Databehandling og analyse

I effektanalyserne tages kun udgangspunkt i data rapporteret i EMAs EPAR og SmPC.

5.2.3 Evidensens kvalitet

Datagrundlaget for klinisk spørgsmål 2 er yderst sparsomt. Der gælder de samme forbehold som ved klinisk spørgsmål 1 (afsnit 5.1.3). Derudover indgår der i alt kun 32 patienter under 18 år i de kliniske studier med entrectinib, og kun 8 af disse har NTRK-fusion-positiv kræft [15], hvorved de samlede effektmål skal vurderes på baggrund af data fra 8 patienter.

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

5.2.4 Effektestimater og kategorier

Ansøger har kun indsendt data for effektmålene objektiv responsrate samt uønskede hændelser. Der findes intet sammenligningsgrundlag for patienter under 18 år. De indsendte effektestimater fremgår af tabellen nedenfor (Tabel 5-10). Herudover fremgår kategorierne og den samlede kvalitet af evidensen for klinisk spørgsmål 2. Samlet set kan effekten ikke kategoriseres og den samlede evidenskvalitet er meget lav.

Tabel 5-10. Resultater for klinisk spørgsmål 2

Effektmål	Målenhed (MKRF)	Vigtighed	Entrectinib	Supplerende sammenligningsdata*	Værdi for effektmålet
			Estimat [95 % CI]	Inget sammenligningsgrundlag	
Overlevelse	Median OS i antal måneder (MKRF: 3 måneder)	Kritisk	Ingen data		Kan ikke kategoriseres
	OS-rate ved 24 måneder (MKRF: 5 %)		Ingen data		
	Andel patienter med komplet patologisk respons (MKRF: 5 %)		Ingen data		
Livskvalitet	Forskel i gennemsnitlig ændring i EORTC-QLQ-C30 (MKRF: 10 point)	Kritisk	Ingen data		Kan ikke kategoriseres
Objektiv responsrate	Samlet ORR for hele den voksne patientpopulation (MKRF: narrativ vurdering)	Vigtig	87,5 % [ikke angivet]		Kan ikke kategoriseres
Progressionsfri overlevelse	Median PFS (MKRF: 3 måneder)	Vigtig	Ingen data		Kan ikke kategoriseres

Effektmål	Målenhed (MKRF)	Vigtighed	Entrectinib	Supplerende sammenligningsdata*	Værdi for effektmålet
			Estimat [95 % CI]	Inget sammenligningsgrundlag	
Uønskede hændelser	Andel patienter med én eller flere uønskede hændelser grad 3-4 (MKRF: 5 %-point)	Vigtig	65,6 %		Kan ikke kategoriseres
	Kvalitativ gennemgang af uønskede hændelser				

Konklusion

Samlet kategori for lægemidlets værdi	Kan ikke kategoriseres. Fagudvalget finder dog ikke nogen grund til at antage, at effekten af entrectinib på børn mellem 12 og 18 år skulle afvige betydeligt fra effekten på voksne generelt, i hvert fald ikke i negativ retning
Kvalitet af den samlede evidens	Meget lav

Overlevelse
Ansøger angiver, at der ikke findes data for overlevelse hos børn. Fagudvalget kan derfor ikke tage stilling til dette effektmål.

Livskvalitet
Ansøger angiver, at der ikke findes data for livskvalitet hos børn. Fagudvalget kan derfor ikke tage stilling til dette effektmål.

Objektiv responsrate
Samlet set er der rapporteret data for 8 patienter med NTRK-fusion-positiv kræft. Af disse oplevede 7 patienter et respons fordelt som 5 komplet respons og 2 partiel respons. Den sidste patient oplevede progressiv sygdom.

Fagudvalget bemærker, at ORR hos børn er høj. Effekten kan dog ikke kategoriseres pga. manglende komparator og det minimale antal patienter.

Progressionsfri overlevelse
Ansøger angiver, at der ikke findes data for PFS. I stedet har ansøger indsendt data fra STARTRK-NG, som baserer sig på børn med 'fusions-positiv kræft', hvilket dækker over NTRK-, ROS1- eller ALK-fusion og kan derfor ikke anvendes til at vurdere effekten af entrectinib på NTRK-fusion-positiv kræft. Fagudvalget kan derfor ikke tage stilling til dette effektmål.

Uønskede hændelser
Ansøger har indsendt data fra hele sikkerhedspopulationen, dvs. alle børn, der har modtaget minimum en dosis entrectinib. Den samlede sikkerhedspopulation for børn indeholder 32 patienter ved det seneste data cut-off [14,15]. Opgørelserne indeholder uønskede hændelser af grad 3-5. Derudover angiver ansøger, at 7 ud af de 32 børn var mellem 12 og 18 år. Fagudvalget har taget udgangspunkt i den samlede sikkerhedspopulation for børn, da data ikke er opdelt efter NTRK-, ROS1- og ALK-fusioner. I den samlede sikkerhedspopulation for børn oplevede 65,6 % af patienterne minimum 1 uønsket hændelse af grad 3-5, og uønskede hændelser var årsag til behandlingsstop hos 9,4 % af patienterne. Der var ingen dødsfald med relation til uønskede hændelser.

Hændelsesprofilen afviger på nogle områder fra voksenpopulationen, idet neutropeni (28,1 % / 9 patienter), vægtøgning (21,9 % / 7 patienter), knoglefraktur (12,5% / 4 patienter) og hovedpine (6,3 % / 2 patienter) var hyppigere repræsenteret hos børn.

Knoglefrakturerne opstod uden eller efter minimalt traume. Der var oftest tale om hoftenære- og underekstremitetsfrakturer [14].

Samlet set var de uønskede hændelser håndterbare ved hjælp af dosisreduktion (34,4 %) eller pausering (46,9 %).

Den kliniske værdi af entrectinib ift. placebo kan ikke kategoriseres på baggrund af det foreliggende data.

Fagudvalget vurderer dog, at entrectinib sandsynligvis er forbundet med flere uønskede hændelser end placebo. Fagudvalget bemærker dog, at de grad 3-4-hændelser, som er forbundet med behandling med entrectinib, generelt er håndterbare.

5.2.5 Fagudvalgets konklusion

Værdien af entrectinib overfor placebo til behandling af børn med NTRK-genfusion-positiv kræft **kan ikke kategoriseres**. Dette skyldes, at datagrundlaget er yderst sparsomt. Der er ikke data for de kritiske effektmål, overlevelse og livskvalitet, eller det vigtige effektmål, progressionsfri overlevelse, samt meget begrænsede data for effektmålene, objektiv responsrate og uønskede hændelser. Derudover er der intet komparativt datagrundlag.

Fagudvalget bemærker dog, at der ikke er nogen grund til at antage, at effekten af entrectinib i børn mellem 12 og 18 år skulle afvige betydeligt fra effekten i voksne generelt, i hvert fald ikke i negativ retning. Dette underbygges af, at 7 ud af de 8 behandlede børn med NTRK-fusion-positiv kræft oplevede et objektivt respons.

6. Andre overvejelser

6.1 Growth modulation index

Fagudvalget har, i forventning om manglende komparativt data, i protokollen bedt ansøger indsende data for growth modulation index (GMI). GMI er en 'før-og-efter' *intra-patient*-analyse, som beskriver ratioen imellem patienternes tid til progression (TTP) på entrectinib og patienternes TTP på den behandling, de modtog umiddelbart inden (forskellige præparater fra patient til patient). Analysen fortæller således kun noget om entrectinibs antineoplastiske effekt i relation til den forudgående behandling. Hvis TTP for interventionen er lig med TTP for den forudgående behandling, er GMI = 1. Er TTP længere for interventionen end for den forudgående behandling, vil GMI være > 1 og omvendt. I litteraturen er en GMI-ratio på 1,33 fremhævet som en meningsfuld om end arbitrær tærskelværdi. GMI er et relativt effektmål, så en GMI på 1,33 kan både dække over f.eks. en median PFS-gevinst på 3,3 måneder (hvis TTP på forudgående behandling var 10 måneder) eller 0,3 måneder (hvis TTP på den forudgående behandling var 1 måned). GMI skal fortolkes i lyset af, at TTP som hovedregel vil være kortere i senere behandlingslinjer sammenlignet med tidligere behandlingslinjer.

[redacted]

[redacted]

[redacted]

6.2 Screening for NTRK-fusion

Der findes internationalt en række foreslåede strategier, for hvordan screening for NTRK-fusioner bør foregå [23,24]. Ansøger har også redegjort for mulige strategier, bl.a. de igangværende *next generation sequencing* (NGS) analyser og eventuelt *whole genome sequencing* under National Genom Center vil kunne diagnosticere hovedparten af relevante patienter.

Fagudvalget vurderer, at følgende er en hensigtsmæssig fremgangsmåde til at teste for NTRK-fusioner i danske patienter:
Indledende screening kan foretages ved brug af immunohistokemi (IHC). Påvises NTRK-fusion ved IHC, bør det følges op med en NGS mRNA-fusionsanalyse, hvor analysen er uafhængig af fusionspartner. Indledende screening kan også foretages med NGS for andre driver-mutationer. Ved negativt resultat af NGS for andre driver-mutationer kan der ligeledes følges op med en NGS mRNA-fusionsanalyse, hvor analysen er uafhængig af fusionspartner.

I histologier, hvor NTRK-fusioner hyppigt forekommer med en kendt fusionspartner, kan *fluorescense in situ hybridization* (FISH) anvendes som primær screeningsmetode. Ved negative resultater af FISH bør der følges op med NGS af mRNA, hvor kendskab til fusionspartner ikke er påkrævet.

Ved udelukkende at anvende NGS af mRNA med en metode, der er uafhængig af fusionspartneren, kan man undgå at teste ad flere omgange og opnå det mest præcise resultat. Dette skal dog vejes op imod pris og tilgængelighed.

Generelt gælder det, at screening som udgangspunkt kun bør finde sted hos patienter, hvor der er klinisk indikation for anvendelse af NTRK-fusionshæmmere. Undtagelser inkluderer dog kræfttyper, hvor der allerede foretages relevant NGS-screening *up front,* og hvor denne evt. kan udvides til også at screene for NTRK-fusioner.

For yderligere overvejelser vedr. screeningsmetodik henvises der til Bilag 2: Screening for NTRK-fusion.

7. Fagudvalgets samlede konklusion

Værdien af entrectinib overfor placebo til behandling af børn og voksne med NTRK-fusion-positiv kræft kan ikke kategoriseres ved brug af Medicinrådets metoder pga. manglende komparativt datagrundlag.

Fagudvalget finder det sandsynligt, på baggrund af datagrundlaget for voksne, at entrectinib har en klinisk relevant effekt i en række kræfttyper, hvor patienterne ikke vil have andre tilfredsstillende behandlingsmuligheder. Forekomsten af uønskede hændelser er lav, og hændelserne er håndterbare. Konklusionen er hovedsageligt baseret på:

- Høje objektive responsrater og lang PFS, særligt når man tager i betragtning, at det er patienter, der i forvejen har modtaget tidligere systemiske behandlingslinjer og ikke har andre behandlingsmuligheder.
- Data, som indikerer, at entrectinib også har en effekt på eventuelle CNS-metastaser.
- Data, som indikerer, at entrectinib er mere effektivt, end den behandling patienterne modtog i linjen umiddelbart inden behandling med entrectinib.
- Håndterbare bivirkninger i en population, der er behandlet i forholdsvis lang tid.

Datagrundlaget for børn er yderst sparsomt (8 patienter), og effekten til denne gruppe kan ikke vurderes selvstændigt. Fagudvalget finder dog ikke grund til at antage, at effekten af entrectinib i børn mellem 12 og 18 år afviger betydeligt fra effekten i voksne, i hvert fald ikke i en negativ retning.

Vurderingen af entrectinib er baseret på evidens af meget lav kvalitet.
Fagudvalget bemærker, at det på grund af sjældenheden af NTRK-fusion og entrectinibs vævsagnostiske indikation er vanskeligt at foretage en nøjagtig vurdering af entrectinibs kliniske værdi ud fra Medicinrådets metoder.

8. Relation til behandlingsvejledning

Der findes ikke en behandlingsvejledning.

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10. Sammensætning af fagudvalg og kontaktinformation til Medicinrådet

Medicinrådets fagudvalg vedrørende tværgående kræftlægemidler

Sammensætning af fagudvalg	
Formand	**Indstillet af**
Lars Henrik Jensen *Overlæge*	Region Syddanmark
Medlemmer	**Udpeget af**
Morten Ladekarl *Professor, overlæge, dr.med.*	Region Nordjylland
Deltager ikke	Region Nordjylland
Anni Ravnsbæk Jensen *Ledende overlæge*	Region Midtjylland
Pernille Wendtland *Overlæge*	Region Midtjylland
Karin Holmskov Hansen *Overlæge*	Region Syddanmark
Eckhard Schomerus *Overlæge*	Region Syddanmark
Karen Julie Gehl *Professor, overlæge, dr.med.*	Region Sjælland
Martin Højgaard *Afdelingslæge*	Region Hovedstaden
Lisa Sengeløv *Ledende overlæge, dr.med.*	Region Hovedstaden
Troels K. Bergmann *Overlæge, klinisk lektor*	DSKF
Torben Steiniche *Professor, overlæge, dr.med.*	Dansk Patologiselskab

Sammensætning af fagudvalg	
Karsten Nielsen *Overlæge, lektor, dr.med.*	Dansk Patologiselskab
Simone Møller Hede *Patient/patientrepræsentant*	Danske Patienter
Diana Kristensen *Patient/patientrepræsentant*	Danske Patienter

Medicinrådets sekretariat

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

11. Versionslog

Versionslog		
Version	**Dato**	**Ændring**
1.0	27. januar 2020	Godkendt af Medicinrådet

12. Bilag

Bilag 1: Studiekarakteristika for de inkluderede studier

ALKA-372-001 er et 'first-in-human'dosiseskalationsstudie med det formål at bestemme sikkerhed, farmakokinetik og anbefalet dosis af entrectinib til patienter med fusions-positiv (NTRK, ALK eller ROS1) kræft.

Tabel 12-1. Studiekarakteristika for ALKA-372-001

Studie **(NCT-nummer)**	**ALKA-372-001** **(Ikke registreret NCT- EudraCT nr: 2012-000148-88)**
Fase og studietype	Fase I, first-in-human, dosiseskalation.
Patientgruppe (n)	Voksne (61, heraf 1 med NTRK-fusion og > 6 måneders opfølgning).
Beskrivelse	Bestemmelse af sikkerhed, farmakokinetik og anbefalet dosis af entrectinib i patienter med faste tumorer med NTRK-, ALK- eller ROS1-fusioner.
Start- og slutdato	Ingen information.
Primært effektmål	Første cyklus dosisbegrænsende toksicitet og maximalt tolereret dosis.
Behandlingsregime	Patienter modtog entrectinib efter tre forskellige doseringsregimer: A (n = 19): 100, 200, 400, 800, 1200 eller 1600 mg/m^2 én gang dagligt i fire dage, derefter tre dage uden. Skemaet køres 3 gange, derefter 7 dages pause. B (n = 32): 200, 400 mg/m^2 eller 600 mg én gang dagligt i 4 ugers cyklus. C (n = 6): 400 eller 800 mg/m^2 én gang dagligt i 4 dage, derefter 3 dage uden i 4 ugers cyklus.

Studie (NCT-nummer)	ALKA-372-001 (Ikke registreret NCT- EudraCT nr: 2012-000148-88)
Vigtigste inklusionskriterier	Histologisk eller cytologisk bekræftet lokalt avanceret eller metastatisk solid tumor med molekylær ændring i NTRK1, NTRK2, NTRK3, ROS1 eller ALK. Ikke flere tilgængelige, acceptable standardbehandlingsmuligheder. Tidligere systemisk behandling tilladt (fra senere protokoltilføjelse, dog ikke tidligere TRK-targeteret behandling). Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≤ 2. Acceptabel hæmatologisk status, lever- og nyrefunktion. Ingen akutte bivirkninger af grad 2 eller højere ifølge National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 4.03. Voksne (18 år eller ældre). Minimum 3 måneders forventet restlevetid. Kontrolleret asymptomatisk CNS-sygdom var tilladt.
Eksklusionskriterier	Parallel deltagelse i andre kliniske studier. Aktiv sekundær kræftsygdom. Kendte sygdomme i hjerte/kredsløb. Forlænget QTc-interval. Aktive infektioner. Gastrointestinal sygdom, der kan påvirke lægemiddelabsorptionen. Kendt lungesygdom eller tidligere tyrosinkinasehæmmer-induceret lungeinflammation. Større kirurgiske indgreb inden for de seneste 4 uger.

STARTRK-1 er et fase I-studie med det formål at bestemme sikkerhed, farmakokinetik og anbefalet dosis af entrectinib til patienter med fusions-positiv (NTRK, ALK eller ROS1) kræft.

Tabel 12-2. Studiekarakteristika for STARTRK-1

Studie (NCT-nummer)	STARTRK-1 (NCT02097810)
Fase og studietype	Fase I, single-arm, dosiseskalation og dosisekspansion.

Studie (NCT-nummer)	STARTRK-1 (NCT02097810)
Patientgruppe (n)	Voksne (83, heraf 2* med NTRK-fusion og > 6 måneders opfølgning).
Beskrivelse	Bestemmelse af sikkerhed, farmakokinetik og anbefalet dosis af entrectinib i patienter med faste tumorer med NTRK-, ALK eller ROS1-fusioner.
Start- og slutdato	28. juli 2014 – 2. juni 2020.
Primært effektmål	Dosisbegrænsende toksicitet. Maximalt tolererede dosis. Anbefalet dosis til fase 2. Objektiv responsrate i dosisekspansionskohorten.
Behandlingsregime	Patienter modtog entrectinib oralt én gang dagligt i cykler af 28 dage.
Vigtigste inklusionskriterier	Histologisk eller cytologisk bekræftet lokalt avanceret eller metastatisk solid tumor med molekylær ændring i NTRK1, NTRK2, NTRK3, ROS1, eller ALK. Målbar sygdom ifølge RECIST version 1.1. Tidligere strålebehandling og systemisk behandling tilladt. Patienter med kontrolleret og asymptomatisk CNS-sygdom tilladt. Ingen akutte bivirkninger af grad 2 eller højere ifølge National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 4.03. Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≤ 2. Voksne (18 år eller ældre). Minimum 3 måneders forventet restlevetid.
Eksklusionskriterier	Nuværende deltagelse i et andet klinisk forsøg. Tidligere behandling med entrectinib. Forlænget QTc-interval. Aktive infektioner. Gastrointestinal sygdom, der kan påvirke lægemiddelabsorptionen. Kendt lungesygdom eller tidligere tyrosinkinasehæmmer-induceret lungeinflammation. Perifer neuropati ≥ Grad 2.

*Bemærk, der er en uoverensstemmelse mellem ansøgers angivelse og EMAs EPAR mht. antallet af patienter med NTRK-fusion af > 6 måneders opfølgning. I ansøgningen er angivet 4, mens EMAs EPAR angiver 2 [14]. Her er taget udgangspunkt i EPARen.

STARTRK-2 er et fase II-studie, med det formål at bestemme effekt og sikkerhed af entrectinib til patienter med lokalt avanceret eller metastatisk fusions-positiv (NTRK, ALK eller ROS1) kræft.

Tabel 12-3. Studiekarakteristika for STARTRK-2

Studie (NCT-nummer)	**STARTRK-2 (NCT02568267)**
Fase og studietype	Fase II, open label, enkelt-arm, basket-trial.
Patientgruppe (n)	Voksne (335, heraf 71* med NTRK-fusion og > 6 måneders opfølgning).
Beskrivelse	Bestemmelse af sikkerhed, farmakokinetik og anbefalet dosis af entrectinib i patienter med faste tumorer med NTRK-, ALK- eller ROS1-fusioner.
Start- og slutdato	19. november 2015 – 2. december 2024 (estimeret slutdato).
Primært effektmål	Objektiv responsrate (ORR).
Behandlingsregime	Patienter modtog entrectinib oralt, 600 mg én gang dagligt i cykler af 28 dage.
Vigtigste inklusionskriterier	Histologisk eller cytologisk bekræftet lokalt avanceret eller metastatisk solid tumor med molekylær ændring i NTRK1, NTRK2, NTRK3, ROS1 eller ALK. Målbar sygdom ifølge RECIST version 1.1. Tidligere strålebehandling og systemisk behandling tilladt. Patienter med kontrolleret og asymptomatisk CNS-sygdom tilladt. Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≤ 2. Voksne (18 år eller ældre). Minimum 4 ugers forventet restlevetid. Tidligere systemisk antineoplastisk behandling er tilladt, hvis behandlingen er afsluttet minimum 2 uger (små molekyler) eller 4 uger (antistoffer) før entrectinibbehandling. Tilstrækkelig leverfunktion.

Studie (NCT-nummer)	STARTRK-2 (NCT02568267)
Eksklusionskriterier	Tidligere kræft, der kan påvirke bestemmelsen af sikkerhed eller effekt af entrectinib. Ufuldstændig restitution efter operation. Enhver anden tilstand i de foregående 3 måneder, der vil kunne påvirke bestemmelsen af sikkerhed eller effekt af entrectinib. Forlænget QTc-interval. Aktive infektioner. Gastrointestinal sygdom, der kan påvirke lægemiddelabsorptionen. Kendt lungesygdom eller tidligere tyrosinkinasehæmmer-induceret lungeinflammation. Perifer neuropati ≥ Grad 2.

*Bemærk, der er en uoverensstemmelse mellem ansøgers angivelse og EMAs EPAR mht. antallet af patienter med NTRK-fusion af > 6 måneders opfølgning. I ansøgningen er angivet 69, mens EMAs EPAR angiver 71 [14]. Her er taget udgangspunkt i EPARen.

STARTRK-NG er et singlearm-studie, basket trial, der inkluderer børn med fusions-positiv (NTRK, ALK eller ROS1) kræft. Studiet er delt i flere faser inklusive en dosiseskalation og dosisekspansion. I dosiseskalationen indgår børn uden fusions-positiv kræft (13/16). I vurderingerne af entrectinibs effekt medtages kun populationen med bekræftet NTRK-fusion.

Tabel 12-4. Oversigt over STARTRK-NG.

Studie (NCT-nummer)	STARTRK-NG (NCT02650401)
Fase og studietype	Fase I-II, open label, enkelt-arm, basket-trial. Dosiseskalation og dosisekspansion.
Patientgruppe (n)	Børn med fusions-positive solide tumorer, inklusive primære CNS-tumorer (32, heraf 8* med NTRK-fusion).
Beskrivelse	Bestemmelse af sikkerhed, farmakokinetik og anbefalet dosis af entrectinib i børn med faste tumorer med NTRK-, ALK eller ROS1-fusioner.
Start- og slutdato	3. maj 2016 – 30. august 2029 (estimeret slutdato).
Primært effektmål	Maksimalt tolereret dosis. Anbefalet dosis til fase II-forsøg med forskellige formuleringer. Objektiv responsrate (ORR).

Studie (NCT-nummer)	STARTRK-NG (NCT02650401)
Behandlingsregime	Patienter modtog entrectinib oralt i flere forskellige formuleringer og doser.
Vigtigste inklusionskriterier	Recidiverende solid tumor, ikke nødvendigvis fusionspositiv (for dosiseskalationen). Histologisk eller cytologisk bekræftet lokalt avanceret eller metastatisk solid tumor inklusive primær CNS-tumor med molekylær ændring i NTRK1, NTRK2, NTRK3, ROS1 eller ALK for dosisekspansionen. Målbar sygdom ifølge RECIST version 1.1. eller RANO for CNS-tumorer. Lokalt avanceret eller metastatisk tumor, hvor der ikke findes andre tilfredsstillende behandlingsalternativer, eller hvor operation ville resultere i svær morbiditet. Patienter med kontrolleret og asymptomatisk CNS-sygdom tilladt. Lansky eller Karnovsky score ≥ 60 % samt minimum 4 ugers forventet restlevetid. Børn (18 år eller yngre). Tilstrækkelig organfunktion.
Eksklusionskriterier	Anden eksperimentel behandling. Kendt medfødt forlænget QT-syndrom. Kendte medfødte knoglesygdomme. Tidligere modtaget behandling med eksperimentel TRK eller ROS1-hæmmer. Ufuldstændig restitution efter operation. Aktive infektioner. Gastrointestinal sygdom, der kan påvirke lægemiddelabsorptionen. Behandling med antiepileptika med enzyminducerende effekt inden for de sidste 14 dage før entrectinibdosering.

Bilag 2: Screening for NTRK-fusion.

NTRK-fusioner opstår ved større kromosomale forandringer, som resulterer i at 3'-enden af NTRK-genet fusioneres med 5'-enden af en fusionspartner. 5'-enden af NTRK-genet koder for ligandbindingsdomænet, og når dette erstattes af 5'-enden af fusionspartneren, kan en konstitutivt aktiv TRK-receptor opstå, der signalerer uafhængigt af ligandbinding [25]. Der kendes mere end 80 forskellige NTRK-fusionspartnere, og forskellige fusionspartnere er kendt for henholdsvis NTRK1/2/3 [25,26].

NTRK-fusioner kan detekteres ved at teste DNA, mRNA eller protein fra en vævsprøve og kan detekteres ved en række forskellige metoder, herunder *fluorescense in situ hybridization* (FISH*), next generation sequencing* (NGS), immunohistokemi (IHC) og *reverse transcriptase polymerase chain reaction* (dog kun ved kendt fusionspartner og breakpoint). Metoderne adskiller sig fra hinanden i følsomhed/detektionsniveau, tilgængelighed og pris, se nærmere herom i [25].

I Danmark anvendes ofte FISH, IHC og NGS til screening for genændringer hos kræftpatienter. Der screenes i dag ikke rutinemæssigt for NTRK-fusioner.
IHC har lav specificitet men en tilstrækkelig sensitivitet til at kunne fungere som indledende screeningsmetode. IHC detekterer overekspression af NTRK-proteiner, og et positivt resultat bør følges op med NGS for at bekræfte, at overekspression skyldes en NTRK-fusion. FISH kan identificere NTRK-fusioner med kendte fusionspartnere og er anvendeligt som primær screeningsmetode i histologier, hvor NTRK-fusioner hyppigt forekommer med en kendt fusionspartner. Et negativt resultat for FISH bør dog følges op med NGS af mRNA med et assay, der er uafhængigt af fusionspartner. Påvisning af andre driver-mutationer kan også fungere som en primær screeningsmetode, idet tilstedeværelse af sådanne i langt de fleste tilfælde vil udelukke NTRK-fusioner.
NGS kan foretages af genomisk DNA eller mRNA. NGS af DNA kan detektere en lang række fusioner afhængigt af, hvilket assay der anvendes men kan på nuværende tidspunkt ikke detektere alle mulige fusioner. Selvom NGS af genomisk DNA allerede foretages for en række kræftformer, vil disse analyser ikke nødvendigvis kunne udvides til at detektere NTRK-fusioner. For de fleste kræftformer (f.eks. NSCLC, kolorektalkræft, ovariekræft og hjernetumorer), hvor der allerede screenes med NGS, foregår analysen af genomisk DNA.

NGS af mRNA foretages i dag kun rutinemæssigt for ganske få kræftformer, f.eks. NSCLC, hvor der screenes for ALK og ROS1-fusioner. En del af de kits, som i dag anvendes til påvisning af mRNA-fusioner, kan kun påvise NTRK-fusioner med kendt fusionspartner eller give indikation omkring tilstedeværelse af en evt. NTRK-fusion via et såkaldt 5´-3´ imbalance assay. NTRK-fusioner kan påvises med sikkerhed ved mRNA-sekventering ved brug af et assay, der er uafhængigt af fusionspartner.

NGS vil typisk være tilgængeligt uafhængigt af behandlingssted men foregår oftest på Universitetshospitalerne.

Final application for Rozlytrek (entrectinib) for the treatment of NTRK fusion-positive cancer

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	ATC application submitted. The class is LO1XE
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 given orally, once daily Children (with body surface area ≤1.50): 300 mg/m^2 orally, once daily.

Therapeutic indication relevant for assessment (as defined by the European Medicines Agency)	*Entrectinib as monotherapy is indicated for treatment of adult and paediatric patients >12 years of age and older, with solid tumours that have a neurotrophic tyrosine receptor kinase (NTRK) gene fusion,* *- who have a disease that is locally advanced, metastatic or where surgical resection is likely to result in severe morbidity* *- who have not received a prior NTRK inhibitor, and* *- who have no satisfactory treatment options*
Other approved therapeutic indications	N/A
Will dispensing be restricted to hospitals?	Yes
Combination therapy and/or co-medication	N/A
Packaging types, sizes/number of units, and concentrations	100 mg, 30 stk. kapsler, hårde 200 mg, 90 stk. kapsler, hårde
Orphan drug designation	N/A

2 Abbreviations

AE	Adverse event
ALK	Anaplastic Lymphoma Kinase
ALT	Alanine aminotransferase
AST	Aspartate aminotransaminase
BSC	Best supportive care
CCoD	Clinical Cut of Date
CI	Confidence Interval
CNS	Central nervous system
CR	Complete response
CRC	Colorectal Cancer
DNA	Deoxyribonucleic acid
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EGFR	Epidermal growth factor receptor
EMA	European Medicines Agency

ESMO	European Society of Medical Oncology
FISH	Fluorescence in situ hybridization
GI	Gastrointestinal
GIST	Gastrointestinal stromal tumours
GMI	Growth Modulation Index
HRQoL	Health related Quality of life
IHC	Immunohistochemistry
MASC	Mammary Analogue Secretory Carcinoma of the Salivary Gland
MSI	Microsatellite instability
NE	Not estimable
NGS	Next-generation sequencing
NSCLC	Non-Small Cell Lung Cancer
NTRK	Neurotrophic Receptor Tyrosine Kinase
ORR	Objective response rate
OS	Overall Survival
PD	Progressive disease
PD-L1	Programmed death-ligand 1
PFS	Progression-free survival
PR	Partial Response
RECIST	Response Evaluation Criteria in Solid Tumours
RCT	randomized controlled trials
RNA	Ribonucleic acid
RT-PCR	Reverse Transcriptase Polymerase Chain Reaction
SCE	Summary of Clinical Efficacy
SD	Stable Disease
TKI	Tyrosine kinase inhibitor
TRK	Tropomyosin Receptor Kinase

TTNT	Time to Next Treatment
QoL	Quality of Life
WES	Whole Exome Sequencing
WGS	Whole Genome Sequencing

3 Summary

The following application for Rozlytrek (entrectinib) was approved by the European Commission and the European Medicines Agency on 03.08.2020.

The application deals with the entrectinib indication for NTRK-fusion positive patients, and is submitted to the Danish Medicines Council on the 15th of October 2020 with an aim to provide an overview of the basic information, a literature search and the analysis results on the outcomes defined in the protocol by the Danish Medicines Council [1]. The application should provide a basis for assessing the added clinical value of entrectinib in NTRK-fusion positive patients without prior TKI treatment compared to best supportive care.

The application is structured as follows:

- Background sections on NTRK fusion-positive cancer, including sections on the NTRK-fusion, incidence, testing, and reflections on the rationale for using entrectinib in the target population.
- Sections with information on the literature search and the study selection process, and the final results including study characteristics of included studies.
- Sections on the clinical questions with data extraction on the predefined outcomes for both the adult and the paediatric population.
- Finally, a section is added regarding other considerations mentioned in the protocol.

[redacted]

3.1 Summary of results

Comparative analyses were carried out for each outcome included in the protocol. The primary comparative sources were an intrapatient analysis, a retrospective analysis of treatment outcomes for TRK fusion-positive patients, as well as a study on treatment outcomes of experimental treatments in later lines. A supplementary analysis of the prognosis on best supportive care was also included.

Overall survival: *Clinical Question 1:* Entrectinib has demonstrated a median overall survival of 23.9 months (16.0, NE) with 67.6% of patients still alive after median 14.2 months of follow-up). This result was longer than the overall median OS of 4.9 months observed for best supportive care in the literature

searches, but OS was not reported in any of the included comparator studies. *Clinical Question 2:* Overall survival is currently immature for the paediatric population.

Quality of life: *Clinical question 1:* Patients tended to improve or maintain high baseline HRQoL scores. An update presented at ESMO showed a mean change from baseline (68.6) of +5.3 at cycle 13 in global health status scores. Quality was only measured in the supplementary analysis of BSC. None of the studies showed an improvement in QLQ-C30 scores. *Clinical question 2:* Quality of life is not reported separately for the pediatric population.

Objective response rate (ORR):

Clinical question 1: Entrectinib has demonstrated an ORR of 63.5% across tumour types. This response rate was higher than those observed in comparator studies. This response rate was higher than what was observed in the most recent line of therapy [2,3], in experimental late line therapies [4], and in the first-line therapies and chemotherapy-containing regimens in the retrospective study on TRK fusion-positive patients [5]. *Clinical question 2:* Of the 6 efficacy-evaluable patients, all achieved an objective response by BICR (2 CR and 4 PR). DOR ranged between 1.8 and 9.3 months.

Progression-free survival (PFS):

Clinical question 1: The progression survival of entrectinib was 11.2 months (8.0, 15.7). This was longer than that observed in the retrospective analysis on TRK fusion-positive patients [5], in experimental treatment in later lines [4], and in the analysis of best supportive care. The PFS of entrectinib was also markedly longer than the treatment lengths observed in the most recent prior therapy [2,3]. *Clinical question 2:* Median PFS was 17.5 months (7.4, NE) in fusion-positive patients and 1.9 months in non-fusion-positive patients.

Safety:

Clinical question 1: Entrectinib was well tolerated with a manageable safety profile. 99.1% of patients experienced at least 1 adverse event. Grade 3-4 adverse events was reported in 61.1% of patients in the overall safety population. Safety was not reported in any of the comparator studies. *Clinical question 2:* The overall safety profile for the paediatric population was overall similar to the adult population with some adverse events (neutropenia, weight increased, headache, and bone fractures).

Time to CNS progression:

Clinical question 1: Time to CNS progression was 16.8 months (14.3, NE) for entrectinib. ORR was consistent across patients with CNS disease (54.5%) and without (58.1%). *Clinical question 2:* Time to CNS progression was not reported for the paediatric population.

4 NTRK-fusion positive cancer

Knowledge about molecular alterations and biomarkers in cancer has increased in recent years and some of these alterations have been identified as oncogenic drivers. One such oncogenic driver is the chromosomal rearrangement of the encoding genes in the neurotrophic receptor tyrosine kinase (NTRK) 1/2/3 for the tropomyosin receptor kinase (TRK) A/B/C cell surface receptors. This driver can lead to

constitutively activation of the downstream tumour pathway resulting in cancer growth and invasiveness [6].

NTRK-fusion positive solid tumours are rare with an overall prevalence of ~0.3% assessed in >20 tumour types [6-13]. The frequency of NTRK-fusions in solid tumours vary across different tumour types in adults and children. In a few rare cancers such as Mammary Analog Secretory Carcinoma of the salivary gland (MASC) and secretory breast carcinoma, there is a high prevalence of NTRK fusions in 90-100 % of cases. In more common cancers such as lung, breast, and colorectal cancer, the frequency is much lower ranging from <5% to 0.1 % [6-11,14]. These variations in the frequencies of NTRK-fusion positive tumours can be a challenge when defining a test strategy.

Several international medical societies have published guidelines on NTRK testing and treatment. The current European Society of Medical Oncology (ESMO) guidelines recommend immunohistochemistry (IHC) as a screening tool in low prevalence tumours if no sequencing platform is available and Next-Generation Sequencing (NGS), Reverse Transcriptase Polymerase Chain Reaction (RT-PCR), or Fluorescence In Situ Hybridization (FISH) in high prevalence tumours [15]. ESMO have also just published a guideline on NGS for patients with metastatic cancers [16]. In this guideline, it is recommended to NGS-test Non-Small-Cell Lung Cancer (NSCLC), cholangiocarcinoma, prostate, and ovarian cancers, and that Academic research centres should perform multigene NGS to better enable access to innovative treatments [16]. The World Sarcoma Network have also published a guideline on NTRK testing of sarcomas, and like ESMO also recommends NGS testing in infantile fibrosarcomas and inflammatory myofibroblastic tumours negative for other common biomarkers [17]. Please also refer to section 4.2 for a more detailed overview of current and future testing in Denmark.

For each of the three NTRK fusions, different fusion partners and frequencies have been observed but in all cases, the NTRK domain is maintained regardless of the 5' partner [18]. NTRK fusions tend to be mutually exclusive from other actionable targets [9,19]. Therefore it can be assumed that if a NTRK-fusion positive patient is not identified and treated with available NTRK targeted therapy, this patient is often treated similarly to patients without an identifiable and targetable oncogenic driver (i.e., with cytotoxic chemotherapies).

4.1 NTRK-fusion positive cancer in Denmark

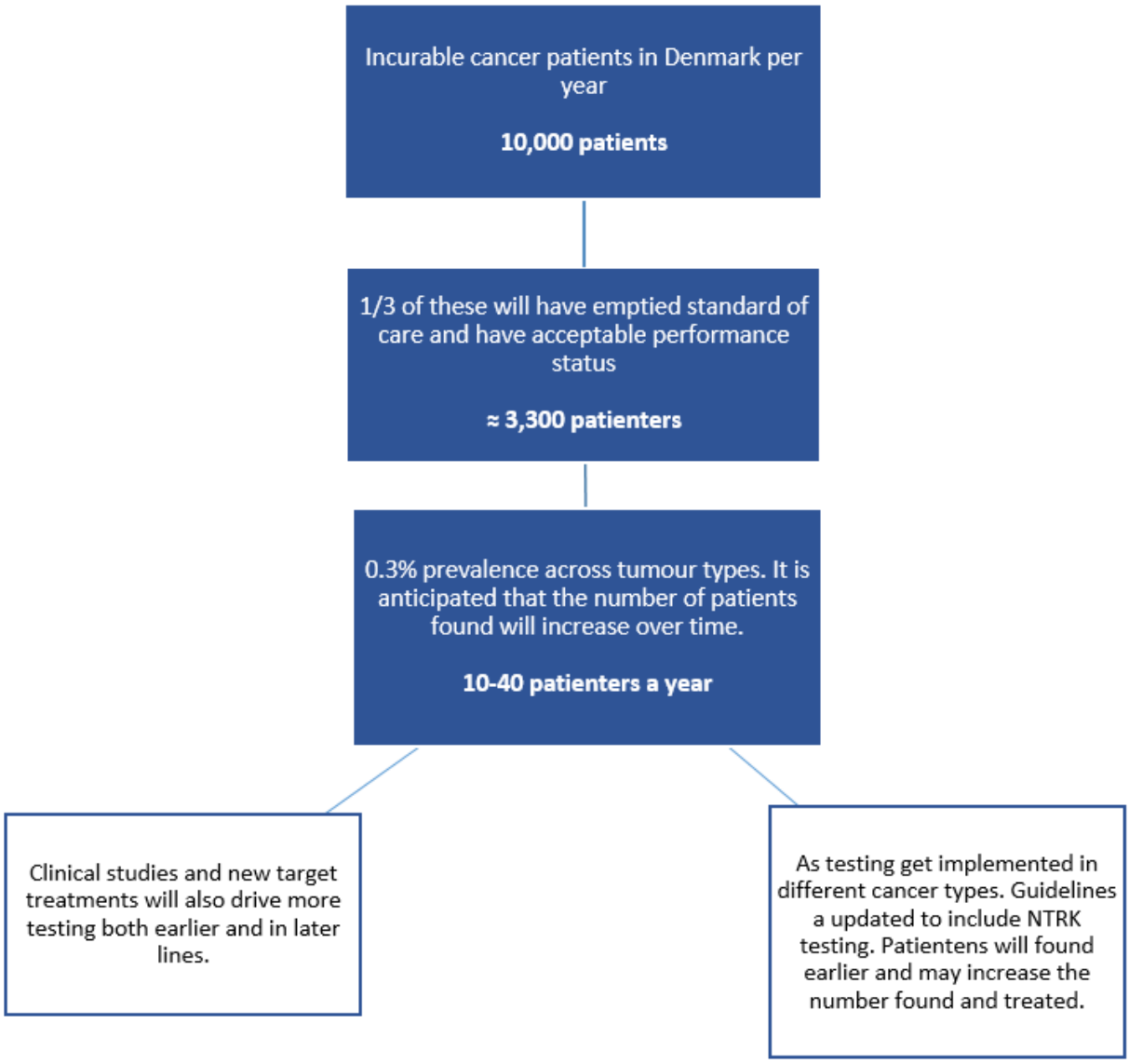
According to dialogue with physicians, only very few patients have, until now, been diagnosed with NTRK fusion-positive solid tumours in Denmark and therefore physicians have limited experience with treatment of NTRK-fusion positive cancers. Due to relatively recent European Medicines Agency (EMA) approvals of NTRK-fusion TKIs, testing and treatment of NTRK-fusions is not included in Danish clinical guidelines.

44.274 patients were diagnosed with cancer in 2018 [20]. The majority of these patients receive standard treatment depending on their tumour type and stage, with curative treatment being the primary objective.
Based on the protocol from the Danish Medicines Council, 10.000 cancer patients a year will experience progression of their cancers reaching an incurable stage. Of these, the scientific committee assess that approximately 3.300 will exhaust other treatment options, but still be in sufficient performance status (PS) to receive further treatment. Taking into account the incidence of NTRK-fusions (≈0.3%) and the number of patients with brain tumours who could benefit from the treatment, the scientific committee has estimated that approximately 10-40 patients per year would be candidates for treatment with entrectinib [1]. Roche deems this estimate plausible, although more research into the incidence of NTRK fusions in Denmark will help provide more accurate patient numbers.

The number of patients who test positive for NTRK-fusions depend on the incidence of NTRK fusions in a Danish population but will to a large degree also depend on the degree and timing of testing for the fusion across different cancer specialties. With the implementation and increasing use of comprehensive genome sequencing in Denmark (e.g. NGS, Whole Exome Sequencing (WES), Whole Genome Sequencing (WGS) and RNA-NGS) the number of patients identified will likely increase in the future. According to clinical experts, testing and sequencing is more widespread in some cancer types than others (e.g. NSCLC and Colorectal Cancer (CRC)) [21]. In some of the highly specialised hospitals such as Rigshospitalet and Aarhus University Hospital, technologies for testing have already been implemented, including: NGS, WES, WGS and RNA-NGS [21]. In general, use of NGS is becoming more widespread to test rare tumours, cancers in later treatment lines and tumours with a low five-year survival rate. Testing still needs to be implemented further such as; used upfront at diagnosis and implementation in guidelines.

Figure 1 contains the expected patient flow of NTRK fusions in Denmark. The number of patients is estimated based on the considerations by experts mentioned above and the indication for entrectinib (locally advanced, metastatic or where surgical resection is likely to result in severe morbidity), depletion of treatments in standard of care and current testing for NTRK.

Figure 1. Patient flow for NTRK fusion-positive patients



Currently, there are no Danish guideline recommendations for NTRK fusion treatments for the population and therefore there is no established standard of care specifically for patients with NTRK fusion-positive tumours.

4.2 NTRK fusion testing

As requested by the scientific committee in the protocol, a discussion on NTRK-fusion testing is provided:

Rozlytrek is only considered relevant for patients, if a NTRK fusion gene has been identified in the tumour. Specific genetic testing of NTRK fusion genes will therefore be required to initiate Rozlytrek treatment.

Even though NTRK-fusion testing is currently not implemented in Danish clinical guidelines, several factors impact current and future testing for this mutation. We will discuss these factors and their impact on NTRK-fusion testing and patient identification.
In Section 4 and 4.1, we describe how medical societies have published recommendations on NTRK testing. Because there are no Danish guidelines on NTRK-fusion testing, we have provided information from the ESMO guidelines on NTRK testing [15,16]. ESMO recommends IHC as a screening tool in low prevalence tumours if no sequencing platform is available and NGS, RT-PCR or FISH in high prevalence tumours. Another recently published ESMO guideline recommends multigene NGS in NSCLC, cholangiocarcinoma, prostate and ovarian cancers [16]. This guideline also recommends that university hospitals should perform multigene NGS as part of their mission to enable access to innovative treatments [16].

The EMA indication for entrectinib includes patients with locally advanced, metastatic tumours or where surgical resection is likely to result in severe morbidity, and who have not received a prior NTRK inhibitor, and who have no satisfactory treatment options. These patients are potential candidates for several targeted treatments, of which entrectinib is one of the possible targeted therapies. NGS testing should therefore primarily happen in this patient group to clarify whether their cancer is positive for a relevant biomarker, including NTRK fusion. Additionally, from a clinical and economic perspective, testing is only indicated for incurable cancer patients with a good enough PS to receive systemic treatment.

Currently for certain cancers, tissue availability can be a factor in diagnosis and tests. In some cancer types, several tests are performed with e.g. IHC, FISH, PCR or NGS. In NSCLC, tissue samples are routinely tested for both histology and biomarkers such as EGFR, ALK, ROS1, and PD-L1. Performance of all these tests can lead to lack of tissue from the biopsy, leading clinicians and pathologists to a situation where they will have to choose between the relevant biomarkers. By using an NGS analysis instead, clinicians and pathologists gain knowledge of several potential actionable biomarkers without having to choose between which biomarkers to test for.

In later lines, NGS testing is today commonly used to assign cancer patients to clinical protocols. Today three regions The North Denmark Region, the Central Denmark Region and the Capital Region of Denmark have screening protocols/programs for incurable cancer patients without standard of care, in order to offer participation in clinical trials or experimental treatment [22,23]. In alignment with the ESMO recommendations University hospitals in Denmark use broader NGS panels with NTRK 1/2/3 fusions included e.g. MSK impact [21]. Several studies and protocols, both industry-founded and investigator initiated, that are utilising DNA and/or RNA-NGS testing in later lines are currently running or planned in Denmark [4,24,25]. One of these studies is an investigator-initiated study called Protarget [24]. The study is a phase II, prospective, non-randomized clinical trial with the primary purpose of investigating the safety and efficacy of commercially available cancer drugs that target specific changes in cancer cell DNA to treat patients with advanced cancer. Screening programs and trials like these have increasingly overlapped and

lead to synergies with the testing of e.g. NTRK and other targetable biomarkers. This increases the utility of more comprehensive testing in oncology generally.

Besides NGS testing in solid tumours, research in liquid biopsy is currently in development and could also be a possible option for patients where solid biopsy are not possible or as an option to monitor the development of resistance in the driver mutations.

The national genome center is by the end of 2020 expected to present which patient groups should be part of the 60.000 WGS tests. How many of these tests will be allocated to oncology is still unknown, but we expect that a significant number of the planned WGS tests will be within oncology.

When combining the terms of entrectinib's indication with the different clinical initiatives and general development of NGS testing within oncology in Denmark, Roche expects there will be limited additional testing costs connected to the introduction of entrectinib in treatment guidelines. This is because most incurable cancer patients with performance status that allows for systemic treatment beyond SoC would already be offered NGS-testing.

Besides NTRK fusions, several other treatments and biomarkers are being tested and developed as new tumor agnostic treatments across pharma industry [26]. This development should also be taken into consideration when discussing testing, patient identification and implementation of these treatments. Please see Figure 2, which shows the projected approval of tumour agnostic treatments targeting genomic drivers from ongoing clinical trial programs

Figure 2. Projected approval of tumour-agnostic treatments targeting genomic drivers from ongoing clinical trial programmes [26]

Roche anticipates that the EMA guidelines, EMA approval of entrectinib and larotrectinib as well as the current processes in the Danish Medicines Council will contribute to the implementation of NTRK testing and treatment in Danish clinical guidelines.

5 Rationale for entrectinib in NTRK-fusion positive cancer

Rozlytrek (entrectinib) is an oral, central nervous system (CNS)-active, selective inhibitor of the tropomyosin receptor kinases (TRK) A/B/C, c-ros oncogene 1 (ROS1), and anaplastic lymphoma kinase (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 [6].

Entrectinib has been studied in four phase 1 or 2 trials with NTRK-fusion positive patients: ALKA-372-001, STARTRK-1, STARTRK-2 and STARTRK-NG. All of these showed a treatment effect significantly beyond historic controls.

The conditionally approved indication for entrectinib is:

"Rozlytrek as monotherapy is indicated for the treatment of adult and paediatric patients 12 years of age and older with solid tumours expressing a neurotrophic tyrosine receptor kinase (NTRK) gene fusion,

- *who have a disease that is locally advanced, metastatic or where surgical resection is likely to result in severe morbidity, and*
- *who have not received a prior NTRK inhibitor*
- *who have no satisfactory treatment options (see sections 4.4 and 5.1)."*

It is further described in Section 4.4 of the SmPC, that: "*Rozlytrek should only be used if there are no satisfactory treatment options (i.e., for which clinical benefit has not been established, or where such treatment options have been exhausted)" [27].*

Limitations of current standard of care in NTRK-fusion positive solid tumours

Patients with NTRK-fusion positive tumours are currently treated according to their histological tumour type. As NTRK fusions tend to be mutually exclusive from other actionable targets, patients are likely to receive non-targeted therapies such as chemotherapy or, in some tumour types, immunotherapy [5,9]. When standard of care has been exhausted, cancer patients are offered either participation in a clinical study or Best Supportive Care (BSC).

Since entrectinib is indicated for solid tumours and thus across multiple tumour types (tumour-agnostic), its position in clinical pathways can differ depending on the standard of care available in the various tumour types. However, given the indication, treatment with entrectinib would primarily occur in later treatment lines. For patients with advanced or metastatic disease, the expected response rate for later line therapies is typically <30% and the mDOR is in most cases <10 months across available approved

therapies for various tumour types [28,29] Prognosis at this stage is poor with 50% of patients dying within 18 months [30-55].

Naturally, the relevant patient population for entrectinib is diverse in terms of both the available treatment options and the number of treatment lines that they have received beforehand. In some tumour types, there are multiple lines of therapy available with established benefit. In other tumour types, patients have either no or limited treatment options and will thus quickly exhaust the relevant treatments. Although standard of care is diverse across the tumour types, a common characteristic for the relevant patient population for entrectinib no matter the tumour type, is that they will not have any satisfactory treatment options available (as per the Rozlytrek label). In general, patients with NTRK-fusion positive tumours are at this stage likely receiving a non-targeted treatment (e.g. chemotherapy), which could have off-target effects and damage normal cells and tissue [56] or a palliative treatment such as best-supportive care, which aims to reduce symptoms. Some patients will enter into phase I clinical trials with experimental treatment regimens, where the expected response rates vary greatly.

Unmet need in NTRK-fusion positive solid tumours

As mentioned, patients with NTRK-fusion positive solid tumours are likely treated with a non-targeted treatment option, an experimental treatment option or palliative care with the aim of reducing symptoms.

Due to NTRK fusions being a relatively new target there is still limited data on the natural history, and the prognostic value of NTRK still needs to be researched further. However, some evidence suggests that patients with tumours with NTRK fusion genes have a poorer prognosis than those without. A study on metastatic CRC patients showed that the patients bearing ALK, ROS1 or NTRK rearranged tumours had shorter median OS when compared with patients with re-arrangement negative tumours (15.6 vs 33.7 months), independent of tumour location and Microsatellite Instability (MSI) status [57]. Additionally, an expression analysis of 119 patients with papillary thyroid carcinoma found in a cumulative survival analysis that patients with NTRK1 rearrangement-positive tumours demonstrated a worse outcome when compared with patients with expression of RET proto-oncogene hybrids [58]. It should be noted that both populations described above are NTRK rearranged and not NTRK-fusion positive.

Patients with metastatic cancer also face risk of CNS tumours, which affect approximately 24-45% of all cancer patients [59,60]. Specifically for NTRK-fusion positive tumours, CNS metastases are common in some of the tumour types known to harbor NTRK fusions, such as NSCLC, triple-negative breast cancer, and melanoma [61]. CNS metastases affect both treatment outcomes and the morbidity of the disease with a median survival of 1-2 months if left untreated [61].

Based on both the treatment options available to NTRK-fusion positive patients in later treatment lines, the characteristics of NTRK-fusions and the tumour types known to harbor these mutations, there is a clear unmet need for targeted treatment options for patients with NTRK-fusion positive tumours. Due to

the risk of CNS metastases in tumour types known to harbor NTRK fusions and in cancers in general, there is also a need for a CNS active treatment for these patients.

Clinical experts state that for some patients chemotherapy is considered part of or an alternative to BSC [21]. Relevant chemo-regimens will however be different depending on the cancer type, but could also differ between the Danish regions. It is therefore difficult to determine a specific regiment as "tumour-agnostic" palliative chemotherapy as well as for the different tumour types.

Targeting treatment to specific mutations is generally considered effective, and are well known in different cancer types and new targeted treatments are under development. In addition to entrectinib, only few other drugs have been approved in the tumour agnostic setting.

Clinical trials in a tumour agnostic setting

Randomized controlled trials (RTCs) are the golden standard to assess the efficacy and safety of drugs, however these are not always the most feasible way to collect evidence. To overcome issues for rare genomic alterations in RCTs such as the prevalence of the target genomic alteration, the number of potential tumours indicated, the number of trials competing for the same pool of patients, as well as the unmet need in the patient population, single arm basket trials have become more and more used in recent years.

In the case of NTRK-fusions, Lozano-Ortega et al. assessed the feasibility of carrying out an RCT in this population [62]. In the assessment they evaluated a hypothetical NTRK RCT program that includes the 12 tumours assessed in the clinical trials of entrectinib. The analysis focused on PFS as the primary outcome of interest. The enrollment rate in each tumour type was dependent on the enrollment rate seen in the STARTRK-2 trial (4.25 patients per month over 150 sites). The analysis then calculated the estimated minimum sample size for each tumour as well as the estimated time it would take to generate results on this outcome.

Results of the analysis showed that the sample sizes needed in each tumour to achieve sufficient power ranged from 206 to 255 patients with a total study population of N=2387. The estimated time to reach study results ranged from 17 to 105 years depending on the tumour type. Using a threshold for feasibility of 5 years to generate the needed results, it was not deemed feasible to carry out an RCT in any of the tumour types.

Overall, the analysis showed that there are significant challenges to carrying out a RCT in the NTRK fusion positive tumours. Results of the analysis can be seen in Table 3 [62].

Table 3. Relevant studies included in the assessment [62]

Tumour type	Minimum sample size	Time to study results (years)	Is the study feasible?
Colorectal cancer	215	55	No
MASC	207	31	No
Papillary thyroid	255	87	No
Anaplastic thyroid	206	104	No
Squamous NSCLC	206	104	No
Non-squamous NSCLC	206	27	No
Pancreatic cancer	206	70	No
Sarcoma	209	17	No
Neuroendocrine	222	76	No
Secretory breast cancer	207	53	No
Non-secretory breast cancer	207	105	No
MASC, mammary analog secretory carcinoma; NSCLC, non-small cell lung cancer			

6 Literature search

The protocol for the assessment of entrectinib in solid tumours with NTRK fusions (dated: June 18 2020) was used as a guidance for performing a literature search. It is stated in the protocol, that the Medicines Council has not found any full text articles that contain a direct comparison between entrectinib and BSC (or placebo). For this reason, the application has to include a literature search for relevant studies that can be used as an indirect comparison [1].

The search strings have been defined by the Medicines Council and includes searches on both NTRK fusion-positive patients as well as patients with unknown NTRK status. Based on these search strings, 4 searches were carried out:

- Search 1: PubMed/MEDLINE - NTRK fusions - RCT (05-07-2020, 80 hits)
    - Search 1b PubMed/MEDLINE - NTRK fusions - Observational studies (05-07-2020, 90 hits)
- Search 2: CENTRAL (Cochrane Library) - NTRK fusions - RCT/Observational (21-06-2020, 2 hits)
- Search 3: PubMed/MEDLINE - NTRK status unknown - RCT (02-07-2020, 429 hits)
- Search 4: CENTRAL (Cochrane Library) - NTRK status unknown - RCT (05-07-2020, 90 hits)

The results of the literature searches have been described in details in Appendix 10.1 and 10.2. Two assessors independent of each other screened all references on title and abstract level according to established in- and exclusion criteria in a reference management tool. Selected articles went through a full text review to establish their relevance for inclusion.

The in- and exclusion criteria can be seen in Appendix 10.1. Overall, the search prioritized studies on NTRK fusion-positive patients. Due to NTRK fusions being a relatively new target, there is limited literature for NTRK fusion-positive populations. For this reason, the Medicines Council has also defined a search string

to find studies on populations where the NTRK fusion status is unknown or not reported [1]. This strategy will likely result in studies where the population is diverse in terms of possible target mutations although NTRK fusion-positive patients could be included as well. This might provide a limitation, since NTRK fusions could influence the prognosis of the patients.

Overall, the literature search was used to find all available literature within the clinical questions on entrectinib and/or BSC. To ensure the best possible degree of comparability to the NTRK fusion-positive population in the integrated analysis as well as patients in later treatment lines, exclusion criteria were set up to discard studies in an early setting, studies on other target mutations than NTRK (only wild-type mutations were included), and studies on Asian populations exclusively. As the scope of the application is later treatment lines/exhaustion of satisfactory treatment options, a criteria was added regarding the publication date to be within the last 20 years (2000 and forward). Across the various tumour types, significant changes can have occurred in the treatment landscapes and the introduction of new therapies over the years could have a significant influence on the compatibility to a population receiving best supportive care today.

The results of the literature search were used to generate a BSC arm. A description of this analysis can be found in Section 6.2.1 and in Appendix 10.4.

In addition to the 4 literature searches, 3 other studies were included via hand search. This includes:

- An intrapatient analysis on entrectinib, that compares data from the STARTRK-2 trial to their most recently received therapy [2]
- An article by Rosen et al. that examines treatment outcomes of TRK fusion patients at the Memorial Sloan Kettering Cancer Center [5]. Note that this article also appeared in search 1b but was excluded as the literature searches focused on evidence on entrectinib and/or BSC.
- An article describing the results of the CoPPO trial - a trial of late line experimental treatment based on the target mutation [4]

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 patients with advanced or metastatic NTRK fusion-positive solid tumours: Integrated analysis of three phase 1-2 trials. Doebele et al., The Lancet 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 and 2
	STARTRK-NG	NCT02650401	Study start date: May 2016 Estimated study completion date: Jun 2023	2
TRK Fusions are Enriched in Cancers with Uncommon Histologies and the Absence of Canonical Driver Mutations; Rosen et al.; Clinical cancer research; 2020	Genomic Profiling in Cancer Patients	NCT01775072	Study start date: Jan 2013 Estimated study completion date: Jan 2021	
Intrapatient comparisons in single arm trials for tumor agnostic indications with application to entrectinib; Bennett et al.; ISPOR 2019				
Copenhagen Prospective Personalized Oncology (CoPPO)—Clinical Utility of Using Molecular Profiling to Select Patients to Phase I Trials; Tuxen et al.; Clinical Cancer research; 2019	CoPPO	NCT02290522	Study start date: May 2013 Estimated study completion date: Dec 2022	1
Studies on BSC in later treatment lines	A description of the included studies can be found separately in Appendix 10.4.			

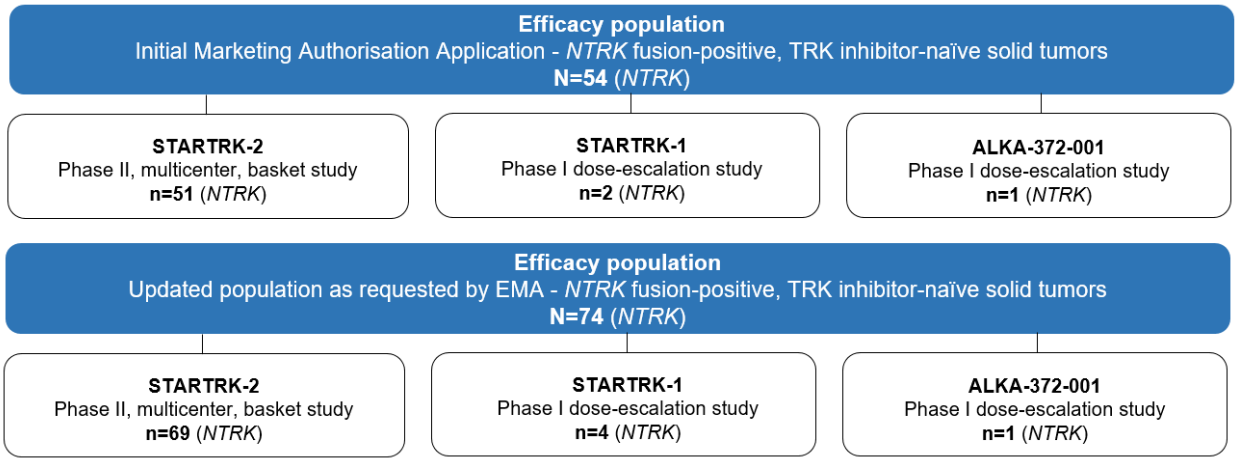
6.2 Main characteristics of included studies

Entrectinib

Data on entrectinib in solid tumours with NTRK gene fusion is described in an integrated analysis of the ALKA-372-001, STARTRK-1 and STARTRK-2 [27,28,63]. In the pooled analysis the activity of entrectinib in patients with metastatic or locally advanced or unresectable or CNS NTRK fusion-positive solid tumours has been evaluated. Safety data in the integrated analysis is characterised in the context of all available data in adult patients [27,28,63].

ALKA-372-001 is 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 NTRK1, NTRK2, NTRK3, ROS1, or ALK molecular alterations. STARTRK-2 is an open-label, multicenter, 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. The design of the integrated analysis is visualised in Figure 3.

Figure 3. Integrated analysis design of NTRK fusion-positive patients



Two efficacy datasets are available for NTRK-fusion positive adult patients treated with entrectinib [28]. The initial population (n=54) was submitted to EMA in the marketing authorisation application. Patients were enrolled up to 30 November 2017 and had at least 6 months of follow-up. All harboured NTRK fusion gene (NTRK 1/2/3) and had metastatic or locally advanced NTRK fusion-positive solid tumours. Presence of NTRK fusions were evaluated using either local molecular profiling or central RNA-NGS. An updated dataset was submitted as per Committee for Medicinal Products for Human Use (CHMP) request. A population of 74 patients (aged ≥18 years) was efficacy-evaluable in the integrated analysis, where 19 patients had CNS disease at baseline and 55 patients had no baseline CNS disease. This dataset also had a minimum of 6 months follow-up. The integrated analysis included patients from 12 different tumour types, covering both high and low frequencies. The included tumour types was breast, cholangiocarcinoma, CRC, gastrointestinal other, gynaecological, neuroblastoma, neuroendocrine tumours, NSCLC, pancreatic, mammary analogue secretory carcinoma of the salivary gland (MASC), sarcoma, thyroid. Sarcomas (22%), NSCLC (18%) and MASC (18%) were the most frequently represented tumour types. The most frequently represented gene fusions were of NTRK3 in 56.8%, followed by NTRK1 in 44.6%, while gene fusions of NTRK2 were rarer with 2.7% (2/74). Key demographic and baseline disease characteristics of both dataset of the adult NTRK patients in the integrated analysis is presented in Table 5.

Table 5. Demographics and baseline disease characteristics				
	Population		**Entrectinib** (Initial overall population, n=54) [63]	**Entrectinib** (Updated overall population, n=74) [28]
Demographics	Age	Median (ranger), years ≥65 years, n (%)	57.5 (21-83) 20 (37.0)	57 (21-83) 26 (35.1)
	Sex, n (%)	Female	32 (59.7)	39 (52.7)
	Race, n (%)	White Asian Black or African american Not reported	43 (79.6) 7 (13.0) 0 4 (7.4)	52 (70.3) 13 (17.6) 2 (2.7) 7 (9.5)
	ECOG PS, n (%)	0 1 2	23 (42.6) 25 (46.3) 6 (11.)	30 (40.5) 34 (45.9) 10 (13.5)
	History of smoking, n (%)		23 (43.4)	29 (40.3)
Baseline Disease Characteristics	tumour type (high level), n (%)	Breast Cholangiocarcinoma CRC GI other Gynecological Neuroblastoma Neuroendocrine NSCLC Pancreatic MASC Sarcoma Thyroid Others	6 (11.1) 1 (1.9) 4 (7.4) 0 2 (3.7) 0 3 (5.6) 10 (18.5) 3 (5.6) 7 (13.0) 13 (24.1) 5 (9.3) -	6 (8.1) 1 (1.4) 7 (9.5) 1 (1.4) 2 (2.7) 1 (1.4) 4 (5.4) 13 (17.6) 3 (4.1) 13 (17.6) 16 (21.6) 7 (9.5) -
	NTRK gene fusion, n (%)	NTRK1 NTRK2 NTRK3	22 (40.7) 1 (1.9) 31 (57.4)	30 (40.5) 2 (2.7) 42 (56.8)
	Median time since diagnosis, months (range)		21.4 (2.1-433.1)	21.0 (2.1-433.1)
	Disease stage at initial diagnosis, n (%)	 0 I (A/B) II (A/B)	(n=53)[a] 1 (1.9) 6 (11.3) 8 (14.8)	(n=73)[a] 2 (2.7) 7 (9.6) 12 (16.4)

e r i s t i c s		III (A/B/C) IV unknown	12 (22.6) 21 (39.6) 5 (9.4)	15 (20.3) 30 (41.1) 7 (9.6)
	Metastatic disease	any site, n (%) bone, n (%) brain, n (%) liver, n (%) lung, n (%) lymph nodes, n (%) skin, n (%) other, n (%)	52 (96.3) 17 (31.5) 12 (22.2) 21 (38.9) 33 (61.1) 30 (55.6) 3 (5.6) 15 (27.8)	72 (97.3) 20 (27.0) 19 (25.7) 28 (37.8) 45 (60.8) 39 (52.7) 4 (5.4) 25 (33.8)
	No of prior systemic therapies [c], n (%)	0 1 2 3 4 >4	14 (25.9) 15 (27.8) 16 (29.6) 4 (7.4) 4 (7.4) 1 (1.9)	20 (27.0) 21 (28.4) 20 (27.0) 6 (8.1) 4 (5.4) 3 (4.1)
	Previous therapy, n (%)	Any systemic treatment[c] Surgery Radiotherapy	48 (88.9) 43 (79.6) 36 (66.7)	64 (86.5) 61 (82.4) 47 (63.5)
	Baseline CNS lesions by INV, n		12	19
	Prior radiotherapy to brain, n (%)		8 (66.7)[e]	13 (68.4)

In addition to the integrated analyses of the tumour agnostic setting, some abstract have been published with data on single cancer types. For MASC and thyroid there are published abstracts on the initial dataset (n=54) and for GI cancers and NSCLC, abstracts was been published for the updated dataset (n=74) [64-67].

[redacted]

For GI, NSCLC, [redacted] median OS and PFS was reached, for the other cancer types it was not estimable. GI cancer covers 7 (58%) CRC patients, 3 (24%) pancreatic patients, 1 (8%) cholangiocarcinoma and 1 (8%) others (adenocarcinoma of upper GI tract) patient [67]. [redacted]

For the GI, NSCLC, [redacted] populations, outcome data will be presented in the clinical questions. For ORR, detailed information on the single cancer types are also published in entrectinib EPAR [28].

Please see Table 6 for information on the different single cancer types.

Table 6. Demographics and baseline disease characteristics

Population		**MASC n=7** (Overall population, n=54) [64]	**Thyroid n=5** (Overall population, n=54) [65]	**Gastrointestinal cancers n= 12** (Overall population, n=74) [67]	**NSCLC n=13** (Overall population, n=74) [66]	[redacted]	[redacted]
Age	Median (ranger), years	55 (42-70)	60 (51-78)	59.3 (31-75)	60 (46-77)	[redacted]	[redacted]
Sex, n (%)	Female	3 (43)	4 (80)	6 (50)	-	[redacted]	[redacted]
ECOG PS, n (%)	0 1 2	7 (100)[a] - -	2 (40) 3 (60)	11 (92)[a] - 1 (8)	- - -	[redacted]	[redacted]
NTRK gene fusion, n (%)	NTRK1 NTRK2 NTRK3	- - 7 (100)	1 (20) - 4 (80)	8 (67) - 4 (33)	- - -	[redacted]	[redacted]
CNS lesions present, n (%)		1 (14)	3 (60)	0	9 (69.2)[b]	[redacted]	[redacted]
No of prior systemic therapies, n (%)	0 1 ≥2	4 (57) 0 3 (43)	2 (40) 1 (20) 2 (40)	4 (33) 2 (17) 6 (50)	- - -	[redacted]	[redacted]
Prior systemic therapy, n (%)	Chemotherapy TKI inhibitor Immunotherapy Hormone medication Radioiodine Surgery Radiotherapy	4 (57) 2 (29) - 1 (14) - - -	1 (20) 3 (60) 1 (20) - 1 (20) - -	11 (92) 3 (25) - - - 8 (67) 3 (25)	13 (100) 1 (7.7) 6 (46.2) - - - -	[redacted]	[redacted]
Prior radiotherapy to brain, n (%)		0	3 (60)	-	5 (38.5)	[redacted]	[redacted]

[a]reported for ECOG PS 0-1; [b] reported as CNS metastases at baseline

Patients were included in the integrated analysis if they had 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 Eastern Cooperative Oncology Group (ECOG) performance status 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
- history of tyrosine kinase inhibitor-induced pneumonitis
- peripheral neuropathy grade 2 or worse

Please also refer to Appendix 10.3 for main characteristics of the included studies

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.

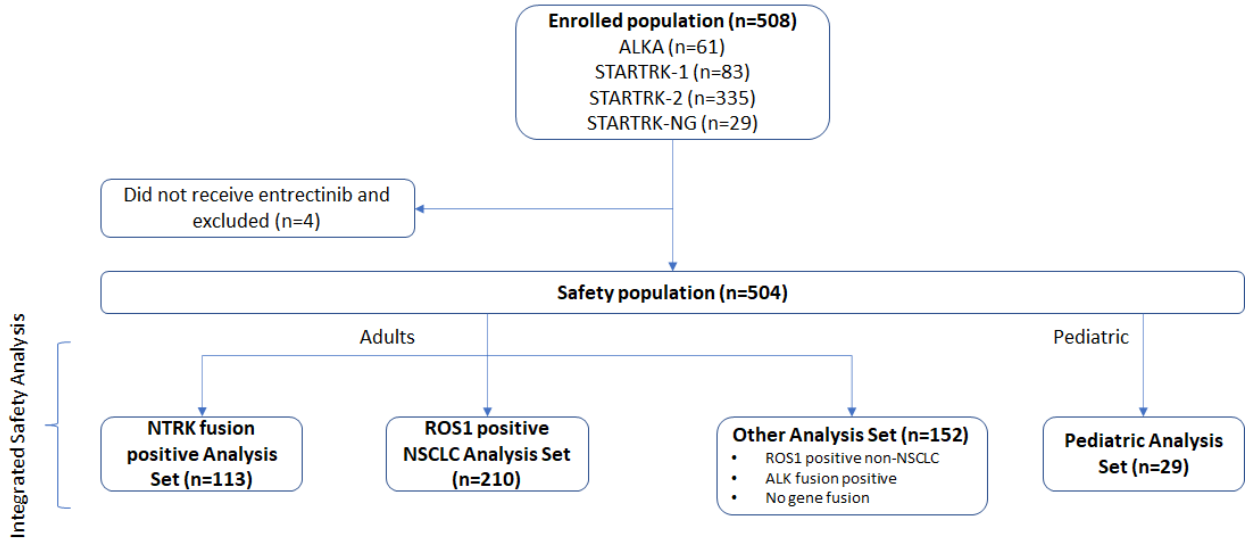
Adult analysis sets:

- 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 (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
- Updated pediatric analysis set (n=32).

Figure 4. Patient Population and Analysis Sets for Integrated Safety Analysis



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 pediatric patients. If data is available on the NTRK- fusion positive analysis set from ALKA, STARTRK-1, and STARTRK-2, this 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 pediatric patients).

Paediatric population

For the pediatric efficacy population described in STARTRK-NG, the initial dataset included 29 patients of whom 7 had NTRK-positive fusions (aged from 4 months to 9 years), the rest had other fusions (3 patients had ALK and 5 patients ROS1) or where non-fusion positive (n=15, either not detected or test not available) [28]. Of those 7 NTRK-fusion positive patients, 6 were efficacy-evaluable (one had to short follow-up). The pediatric patients primarily had NTRK3 gene fusions. All achieved an objective response by BICR and DOR was 1.8-9.3 months. Two patients had locally advanced and the remaining 5 had metastatic disease. 18 (56.3%) of patients had metastatic disease and 15 (43.8%) had locally advanced disease. 27 (84.4%) had received prior treatment for their cancer, including surgery, radiotherapy, or systemic therapy [28]. The most common cancers included in the analysis were: neuroblastoma (N=13), inflammatory myofibroblastic tumours (N=3), glioblastoma (N=3), infantile sarcoma (N=2), ganglioneuroblastoma (N=2). The median duration of exposure for all paediatric patients was 5.57 months (range: 0.2 months to 29.8 months) [28].

Two additional children with NTRK-fusion positive solid tumours were included in a compassionate use program [28]. A 6 years old male with high grade astrocytoma and a 1.5 years old male with infantile fibrosarcoma.

The two paediatric safety populations of n=29 and n=32 are described in the section above.
In an updated abstract from ASCO 2020 by Desai et al. 34 patients (4.9 months to 20 years old; median age 7 years) have been evaluated for response to treatment with entrectinib [68]. Although 34 patients were evaluated, 14 were fusion-positive (including NTRK 1/2/3, ROS1 and ALK) and 20 had non-fusion tumours. Of the 14 fusion positive patients, 5 patients had NTRK-fusion positive CNS tumours and 3 patients had NTRK-positive fusion in solid tumours.

It should be noted that no efficacy data is avaliable for the final paediatric indication from EMA with patients aged 12 to 18 years [28]. EMA assessed that the pharmacokinetic simulations performed for adolescents within BSA 1.1-1.5 m2 showed that the exposure is within those obtained in adult patients. Activity in adolescents is considered established based on the extrapolation of the data from adults with NTRK-fusion positive solid tumours

6.2.1 Comparators

As there are no established standard of care for NTRK-fusion positive patients the following sections will describe comparators for entrectinib in NTRK-fusion positive patients.

Known NTRK status

The literature search on NTRK fusions only revealed literature that describes the integrated analysis for entrectinib [63]. In addition to this, two additional publications were added for the adult population via hand search. The first is a publication by Bennett et al. and explores an intrapatient analysis as a potential approach to derive comparative evidence [2]. This analysis was described in a poster presented on ISPOR 2019. Data from the 54 patients from STARTRK-2 who have received at least one prior systemic therapy for metastatic disease were included. The outcome is best response to therapy by line of prior systemic therapy and time to next treatment.

Of the 54 patients included, 31 patients had received prior systemic treatment. 21 patients had documented progression on the most prior treatment. Of the 31 patients with prior therapy there were 16 responses (Partial Responses (PR) or Complete Responses (CR)) to entrectinib compared to 4 responses on most recent prior therapy. For the 21 with documented progression on prior therapy there were 11 responses on entrectinib compared to 2 responses on most recent prior therapy. Median time to next treatments (TTNT) and median PFS were similar for entrectinib and longer than estimated median TTNT in most recent prior therapy [2].

The second publication is by Rosen et al. and is a retrospective analysis of individual patient-level data from a prospective genomic screening program at a single centre [5]. The study includes more than 26,312 patients, where 76 patients had confirmed NTRK fusions. For these patients overall response rate, recurrence-free survival, progression-free survival, and overall survival was reported. Patients received treatment with chemotherapy, immunotherapy and TRK inhibitors. No adverse events were reported in this publication. Primary endpoint for the study is frequency of “actionable” oncogenic mutations and

secondary endpoints are: 1) to determine the impact of molecular profiling results performed in the CLIA-setting (Clinical Laboratory Improvement Amendments) on the treatment of patients, 2) interrogate the mechanisms and 3) To explore the genetic mechanisms of tumourgenesis.

As mentioned, among the 26,312 patients screened in Rosen et al., 76 had NTRK fusions (prevalence of 0.28%) [5]. NTRK fusions was observed in 17 different tumours. Of the 76 NTRK-fusion positive patients 51 had advanced or recurrent NTRK-fusions positive disease, 35 (69%) received chemotherapy, 12 (24%) received immunotherapy and 38 (75%) received TRK inhibitors. ORR for first-line therapy (excluding TRK inhibitors) was 46.7%; for chemotherapy-containing regimens (all treatment lines) was 62.5%; and for TRK inhibitors (all treatment lines) was 64.7%. For patients with NTRK fusion-positive tumours, median relapse-free survival in patients treated with curative intent was 3.5 years, median PFS on first-line therapy for advanced disease was 9.1 months, and median OS (all patients) was 19.8 years [5].

Experimental treatment - The CoPPO trial

As described above very limited literature was found on patients with known NTRK fusion status. In the protocol for entrectinib in NTRK-fusion positive patients the scientific committee mentions that some patients have exhausted all standard treatment options and may be included in experimental treatment trials. It is assumed by Roche that the outcome on experimental treatment in a phase 1 setting is also relevant to describe in order to understand the expected prognosis of patients with incurable cancer and an actionable target without any standard of care.
A Danish publication by Tuxen et al. was added via hand search [4]. The study explored matched treatment based on either gene mutations or RNA expression in the Copenhagen Prospective Personalized Oncology (CoPPO) trial. This prospective, single-center, single-arm open-label study included patients with advanced solid cancers and exhausted treatment options referred to a phase I unit. Primary endpoint is progression-free survival and secondary endpoints include the percentage of patients allocated to treatment guided by the genomic profile and response rate according to RECIST1.1 in patients receiving molecular profiling–guided therapy. Eligibility criteria were: exhausted treatment options, life expectancy of ≥3 months, normal organ function, measurable disease by RECIST1.1, ECOG PS of 0 or 1, age ≥ 18 years, and lesions accessible for biopsy. Both WES-DNA and RNA were analyzed.

A total of 591 patients were included in the CoPPO study and 500 patients (85%) were eligible for participation and subjected to biopsy. A molecular profile was achieved in 460 biopsied patients (92%). WES was achieved in 458 patients and 2 patients were subjected to a targeted panel due to lack of tumour DNA. SNP array was performed in 440 patients. RNA was sufficient for RNA sequencing and expression array in 447 patients. Overall, complete genomic profiles consisting of WES, SNP array, RNA sequencing, and expression array were achieved in 435 biopsied patients (87%). A potentially actionable target was proposed in 352 patients (70%) and 101 patients (20%) received treatment matched to their molecular profile. In total, 101 patients were allocated to treatment based on 29 different targets.

PFS and ORR was evaluable in all 101 patients receiving matched treatment and median PFS was 12 weeks (95% CI: 9.9–14.4). Objective responses (RECIST1.1) in the group of 101 patients treated according to their molecular profiles included 15 patients (15%; 95% CI: 9%–24%) with partial response (PR) and no complete responses (CR). Stable disease as the best response was achieved in 38 patients (38%) and progressive disease (PD) was observed in 33 patients (33%). The remaining 16 patients (16%) were not evaluated at the predefined evaluation time mainly because of early clinical deterioration (12%). Intention-to-treat analysis revealed a response rate of 2.5% (15 responders of 591 screened patients).

Table 7. Demographics and baseline disease characteristics

	Population		**Rosen et al.** (Overall population, n=76) [5]	**CoPPO trial** (population with matched treatment, n=101) [4]
Demographics	Age	Median (range), years ≥65 years, n (%)	52 (0-78)	60 (27-86)
	Sex, n (%)	Female	47 (61.8)	58 (57)
	Race, n (%)	White Asian Black or African american Not reported	-	-
	ECOG PS, n (%)	0 1 2	-	39 (39) 62 (61) 0 (0)
	History of smoking, n (%)			-
Baseline Disease	tumour type (high level), n (%)	Breast Cholangiocarcinoma CRC GI other Gynecological Neuroblastoma Neuroendocrine NSCLC Pancreatic MASC Sarcoma Thyroid Others	- - 8 (10.5) - - 4 (5.3) - 6 (7.9) 4 (5.3) - 9 (11.8) 10 (13.2) 35 (46.1)*	13 (13) - 25 (25) 1 (1) 8 (8) 1 (1) 3 (3) 7 (7) 6 (6) - 1 (1) - 36 (36)*
	NTRK gene fusion, n (%)	NTRK1 NTRK2 NTRK3	-	None

Characteristics	Median time since diagnosis, months (range)		-	-
	Disease stage at initial diagnosis, n (%)	0 I (A/B) II (A/B) III (A/B/C) IV unknown	- - 34 (58.6)[b] - 24 (41.4) -	-
	Metastatic disease	any site, n (%) bone, n (%) brain, n (%) liver, n (%) lung, n (%) lymph nodes, n (%) skin, n (%) other, n (%)	24 (41.4)	-
	No of prior systemic therapies [c], n (%)	0 1 2 3 4 >4	-	Median (range) 3 (1-11)
	Previous therapy, n (%)	Any systemic treatment[c] Surgery Radiotherapy	57 (75)[d] 65 (87.8)[d] 33 (47.1)[d]	-
	Baseline CNS lesions by INV, n		-	-
	Prior radiotherapy to brain, n (%)		-	-

Best supportive care in patients with unknown NTRK status

Based on the literature search string provided in the protocol from the Medicines Council, Roche examined the available literature for studies containing a BSC arm. Although the identified literature was for patients with unknown NTRK fusion status, the study population had to be within scope of the entrectinib indication. The included studies contains data on patients in later lines of therapy with no other identified driver mutation.

The literature search resulted in 28 articles with BSC in late line treatment. Studies were clustered according to their tumour type, and median OS and PFS, ORR as well as Health-Related Quality of Life (HRQoL) was extracted from each study.

CLC and NSCLC were the two largest groups with 11 and 10 articles respectively. These will be presented individually below. The additional articles on other cancer types will be presented together in the "others" section. A full overview of the BSC analysis and its results can also be found in Appendix 10.4.

The analysis of the 28 articles should be seen as a supplementary comparison as clustering available data of BSC arms might help provide an overview of the prognosis for patients who have exhausted their treatment options and are receiving palliative care. Due to the number of studies, their heterogeneity, as well as possible limitations regarding comparability to an NTRK fusion-positive population, it was not deemed feasible or useful for the analysis to compare entrectinib and the BSC studies separately. Such analyses would be complex both to carry out and to synthesise in a meaningful way as it would have to account for differences in tumour types, prognosis, study design, reporting methods as well as general patient characteristics (age, gender, race, ECOG, etc.).

Median OS, Median PFS, ORR, and HRQoL will be presented where available.

For all the medians reported, we will calculate an overall median (1. Quartile; 3. Quartile) for the relevant tumour types and one collected overall median across tumour types.

CRC

11 studies presenting relevant outcome data on CRC was included. Median OS was reported between 2.8 - 7.4 months and median PFS between 1.68 - 2.63 months. Based on the reported data, the following CRC median values (1. quartile; 3. quartile) were calculated on the basis for the reported medians: 4.9 (4.5; 6.1) months median OS, 1.8 (1.7-1.89) months median PFS, and a median ORR of 1.35% (0.0%; 2.44%).

Table 8. Median OS, Median PFS, and ORR for BSC in colorectal cancer

Publication	Population	Median OS, months	Median PFS, months	ORR, %
Rao et al., 2004 [69]	n=133	6.08*	2.63*	0
Van Cutsem et al., 2007 [70]	n=232	N/A	1.68	0
Sorbye et al., 2009 [71]	n=244	2.8	N/A	N/A
Grothey et al., 2013 [42]	n=255	5	1.7	0.40
Caballero-Baños, M et al. , 2016 [72]	n=24	4.7	2.3	4.20
Grothey, A et al., 2018 [73]	n=42	6.14*	1.86*	2.38
Jonker, D. J. et al., 2018 [74]	n=144	4.8	N/A	N/A
Kim, T. W. et al., 2018 [75]	n=128 (Wild Type RAS cohort)	6.9	1.7	2.30
	n=114 (Wild Type RAS, Wild Type BRAF cohort)	7.4	1.8	N/A

Van Cutsem, E. et al., 2018 [76]	n=35 (USA cohort)	4.3	1.7	N/A
	n=132 (EU cohort)	4.9	1.7	N/A
Chen, E. X. et al., 2020 [77]	n=61	4.1	1.9	0
* converted from weeks to months (Number of weeks per month =4.348214286); N/A - not available				

Besides the outcomes data presented in Table 9, HRQoL was reported in 3 out of the 11 articles [42,69,70]. 2 of the 3 reported QoL using QLQ-C30 and data will be presented in the QoL section [42,69].

NSCLC

10 studies presenting relevant outcome data on NSCLC was included. Median OS was reported between 1.95 - 8.5 months and median PFS between 0.5 - 7 months. Based on the reported data, the following NSCLC median (1. quartile; 3. quartile) were calculated on the basis for the reported medians: 5.1 (3.7; 8) months median OS and 1.8 (1.39-2.32) months median PFS. One trial reported ORR (1.3% ORR).

Table 9. Median OS, Median PFS, and ORR for BSC in Non-Small Cell Lung Cancer

Publication	Population	Median OS, months	Median PFS, months	ORR, %
Agteresch, HJ. et al., 2000 [78]	n=30	4.7	N/A	N/A
Ranson, M. et al., 2000 [79]	n=78	4.8	0.5	N/A
Roszkowski, K. et al., 2000 [80]	n=70	5.7	2.05	N/A
Thatcher, N. et al., 2005 [81]	n=563	5.1	N/A	1.3
Parikh, P. M. et al., 2011 [82]	n=53	3.7	1.38	N/A
Belani, C. P. et al., 2012 [83]	n=115 (Non-East Asian population)	8.5	1.8	N/A
Lee, S. M. et al., 2012 [84]	n=320	3.6	2.6	N/A
Paz-Ares, L. et al., 2015 [85]	n=353	8.3	1.4	N/A
Mulvenna, P. et al., 2016 [86]	n=269	1.95*	N/A	N/A
Satyanarayan, S. et al., 2016 [87]	n=49	8	7	N/A
* converted from weeks to months (Number of weeks per month =4.348214286); N/A - not available				

Besides the outcomes data presented in the table above, HRQoL was reported in 3 out of the 10 articles [79,80,86]. Only Roszkowski et al. reported QoL using QLQ-C30 [80].

Others

The remaining 8 studies present relevant outcome data on the following cancer types: GIST, pancreatic cancer, sarcoma, glioblastoma, and melanoma. Based on the reported data, medians and outcome intervals were created.

For GIST, median OS was only reported in one study with 12.9 months. The overall median PFS was 1.60 (1.25-1.95) months and no ORR was reported. For pancreatic cancer the median OS was reported between 2.3-2.76 months and the overall median (1. quartile; 3. quartile) was 2.7 (2.5; 2.73) months. Median PFS was only reported for one trial (1.41) months and ORR was not reported. For sarcoma, glioblastoma and melanoma see Table 11, as only one trial was included for each of these cancer types.

Table 10. Table 8. Median OS, Median PFS, and ORR for BSC in other cancer types

Publication	Cancer type	Population	Median OS, months	Median PFS, months	ORR, %
Demetri G et al., 2013 [88]	GIST	n=66	N/A	0.9	1.5
Mir O et al., 2016 [89]	GIST	n=41	12.9	2.3	N/A
Ciuleanu, T. E. et al., 2009 [90]	Pancreatic	n=155	2.76*	1.41*	N/A
Pelzer, U. et al., 2011 [91]	Pancreatic	n=23	2.3	N/A	N/A
Tröger, W. et al., 2013 [92]	Pancreatic	n=110	2.7	N/A	N/A
Le Cesne, A. et al., 2016 [93]	Sarcoma	n=51	10.8	1.4	N/A
Socha, J et al., 2016 [94]	Glioblastoma	n=47	6.9*	3.68*	N/A
Hofmann, M et al. 2011 [95]	Melanoma	n=24	4.5*	N/A	N/A

* converted from weeks to months (Number of weeks per month =4.348214286); N/A - not available

HRQoL was only reported in the melanoma trial using QLQ-C30 [95].

Conclusion

Based on the studies described above, it can be concluded that BSC shows a relatively low median OS and median PFS in various cancer types, with an overall median OS at 4.9 (3.9; 6.90) months, overall median PFS at 1.8 (1.48; 2.24) months and overall median ORR at 1.4% (0.0%; 2.38%). These results will be used in the clinical questions to give a perspective on what could be expected on BSC in patients with unknown NTRK status.

7 Clinical questions

7.1 What is the clinical benefit of entrectinib compared to best supportive care in adult patients with NTRK gene fusion-positive solid tumours?

7.1.1 Presentation of the relevant study and results

The following sections contain a comparative analysis of entrectinib versus placebo or best supportive care, 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 and safety in NTRK-fusion positive solid tumours.

Overall, there is no direct comparison available between entrectinib and BSC and no studies on BSC in NTRK fusion-positive patients were identified. To compare the data of entrectinib to treatment outcomes on BSC and in adult patients who have exhausted satisfactory treatment options, the analysis will use three sources of comparative evidence as well as a supplementary analysis of the prognosis on BSC in later lines of therapy.

The three sources of comparative evidence are:

- The intrapatient analysis compares entrectinib with the most prior treatment [2,3]
- The study by Rosen et al. on treatment outcomes in TRK fusion-positive patients [5]
- The CoPPO trial on patients receiving matched therapy in a phase I setting [4]

For the supplementary analysis on the prognosis in patients receiving BSC, results will be presented for OS, QoL, ORR and PFS.

Individual evaluations of the studies show indications of important differences in study populations 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.

Differences and limitations in the trials

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

In the intrapatient analysis, a limitation is the use of TTNT as a proxy for PFS [2]. Although it can be expected that patients will typically end their treatment in the event of progression, some variance between TTNT and the true PFS of the most recent prior therapy could be expected. Differences in local SoC may also influence the TTNT/PFS of the most recent prior therapy. As the intrapatient analysis is performed on the same patient group, the outcome data is however compared with balanced baseline characteristics.

For the study by Rosen et al. there are some precautions and limitations that should be kept in mind [5]. The publication does not report on ECOG PS, number of prior lines of therapies, or CNS metastasis at baseline. In the study, 58.6% of patients were in stage II (A/B) or better compared to only 28% in the integrated analysis of entrectinib. 41.4% had metastatic disease in Rosen et al. compared to 97.3% in the integrated analysis. 75% had previously received any systemic treatment in Rosen et al. while this proportion was 86.5% in the integrated analysis. Based on these differences, it would be expected that the population in Rosen et al. would have a better performance than in the entrectinib population.

In the CoPPO trial there are also some precautions and limitations that should be kept in mind when comparing to the integrated analysis of entrectinib [4]. The publication did not report disease stage at diagnosis, metastatic disease (incl. CNS metastasis at baseline), or previous therapies. Number of prior therapies were only reported as median and range, but not for the individual lines. There were no patients in ECOG PS 2, while there was 61% in ECOG PS 1 compared to 45.9% in the entrectinib integrated analysis.

For both Rosen et al. and CoPPO there are also major differences in the frequencies of the included tumour types, compared to the entrectinib population.

One of the main limitations of the supplementary comparative analysis in BSC is the lack of knowledge of NTRK-fusion status and other biomarkers in general. The knowledge regarding targetable driver mutations have developed a lot, and in some of the earlier publications, biomarkers were not tested to the same degree as is done today. Another important limitation is the heterogeneity of the included BSC studies, there were significant differences in cancer types, baseline characteristics and reported outcomes.

7.1.2 Overall survival - Critical outcome

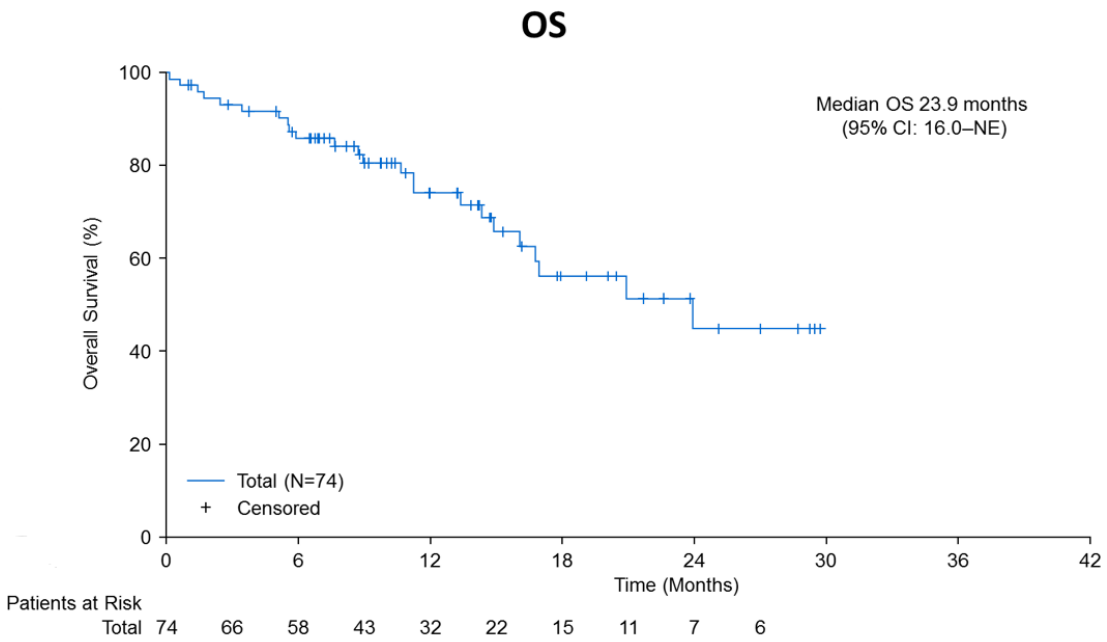
The scientific committee requests data on three parameters for OS with the following clinical differences deemed to be relevant:

- Median OS - a difference of 3 months
- OS-rate at 24 months - a difference of 10% points
- Proportion of patients with pCR or outcome of radical surgery - a narrative assessment

Median OS and OS-rate at 24 months

In the 74 patients included at the time of primary integrated efficacy analysis, the median OS was 23.9 months (95% CI: 16.0, NE). Data is however still immature with <35% of patients experiencing an event at the CCOD [28]. 24 patients (32.4%) had died at the time of the updated dataset.

Figure 5. Overall survival for NTRK-fusion positive patients [96]



Data on the median OS for certain specific tumour types has been assessed and published in posters. This includes MASC, thyroid cancer, NSCLC, and gastrointestinal cancers. Due to the sample sizes in each tumour type, the tumour-specific OS data should be interpreted with caution.

For MASC and thyroid cancer, data was reported from the initial dataset (n=54). Median OS was not estimable at the time of the publication [64,65]. For NSCLC (n=13), median OS was 14.9 months (95% CI, 5.9-NE). For NSCLC with CNS metastasis at baseline (n=9), median OS was 8.9 months (95% CI, 5.6-NE) and for NSCLC without CNS metastasis at baseline (n=3) median OS was not estimable (95% CI, 14.9-NE) [66].

For the overall subgroup with gastrointestinal cancer (n=12), median OS was 16.0 months (95% CI, 11.2-NE) [67]. Data was also reported for specific GI cancers. For cholangiocarcinoma (n=1) and "GI cancer-other" (n=1) the median OS was not estimable. For CRC (n=7), the median OS was 16.0 months (95% CI, 2.4-NE) and for pancreatic cancer (n=3) the median OS was 13.4 months (95% CI, 13.4-NE) [67].

[redacted]

With OS data for entrectinib not yet mature, the OS-rate after 2 years cannot be estimated. At the latest CCOD with median 14.2 months follow-up 50 patients (67.6 %) were still alive [28].
Extrapolated 2-year OS estimates can be found in the health economic technical document.

Comparator studies
OS as an endpoint was also assessed in the study by Rosen et al. but was only analyzed as time from initial diagnosis to death, which limits comparability [5]. The follow-up time in survivors was 3.1 years (range: 0.1-22.5) and the median OS was 19.82 years (95% CI: 19.12-NR).

Overall, it is not possible to compare the median OS from entrectinib and Rosen et al., due to the way OS was analyzed in Rosen et al. The results of the BSC analysis could be used to assess the prognosis of a cancer patient who has exhausted all available treatment alternatives and who is a candidate for either experimental treatment or palliative care. From this perspective, the results indicate a relatively poor prognosis after emptying standard of care. Naïve comparisons against entrectinib data should be undertaken with caution, as the data is based on data from multiple different studies on varying patient populations, treatment practices, study designs, and unknown NTRK fusion status. Should the results of this analysis however be indicative of the prognosis for a patient with no satisfactory treatment option, the median OS of entrectinib of 23.9 months could however be regarded as impressive for the patients that harbor NTRK-fusion positive tumour.
Median OS was also analysed based on the BSC literature found via the literature search. Across all included tumour types, the median OS varied from 1.95-12.9 months. The overall median OS for BSC with unknown NTRK status was 4.9 (3.9; 6.90)months. For the subgroups in BSC, overall median OS was 4.9 (4.5; 6.11)months in CRC, 5.1 (3.7; 8) months in NSCLC and 2.7 (2.5; 2.73)months for pancreatic cancer. A complete overview of the reported median OS values can be found in Tables 9, 10, 11 and in Appendix 10.4.

Proportion of patients with pCR or outcome of radical surgery
There are no reports of either pathologic complete response or outcome of radical surgery for the NTRK-fusion positive population [28,63].

Conclusion
Based on the presented OS data, entrectinib has demonstrated a median OS of 23.9 months (95% CI: 16.0, NE) and 50 patients (67.6 %) were still alive after median 14.2 months follow-up. It was only possible to describe OS in the supplementary analysis of BSC without known NTRK status which showed an overall median OS of 4.9 (3.9; 6.90) months varying from 1.95-12.9 months. Based on these results, entrectinib

demonstrates a difference that is above the minimal clinically relevant difference of 3 months compared to BSC. Additionally, for the overlapping subgroups for entrectinib and BSC, entrectinib shows a clinically minimal relevant difference in NSCLC, CRC and pancreatic cancer again for NTRK-fusions positive patients. The limitations of the comparative approach should be taken into account when assessing the results of this analysis. The BSC analysis may, however, provide an indication of the treatment outcomes and prognosis when using BSC in later lines.

Table 11. Overview of the reported OS data

	Drug (study population, N)	Median OS (95% CI, Months)
Narrative comparison	**Entrectinib, overall** (Integrated analysis, n=74) [28]	23.9 (16.0, NE)
	Rosen et al., overall [5] (Rosen et al., n=15)	19.82 years (19.12-NR)[a]
	Best supportive care (Overall median OS)	4.9
	Matched treatment [4] (CoPPO trial, n=101)	N/A

[a] only analyzed as time from initial diagnosis to death; NE - not estimable; N/A - Not available

7.1.3 Quality of life - Critical outcome

The scientific committee requests data on quality of life and states that a mean difference of 10 points from baseline (using the QLQ-C30 questionnaire) is relevant.

Entrectinib

PROs were only evaluated in STARTRK-2 (n=51), and were thus not included in the integrated efficacy analysis. The completion rates for QLQ-C30 were high at baseline (94.1%) and the completion rate remained high (≥80%) at most study visits. Completion rate was 55% at the end of treatment (EOT) visit. At baseline, patients reported moderate-to-high functioning scores for QLQ-C30. While receiving entrectinib, patients tended to maintain or improve on high baseline HRQoL (mean changes ranging from -4.17 to 9.72 on the global health status). For functional scales (e.g., physical functioning, role functioning), patients continued to report moderate-to high scores at most study visits, with a trend towards clinical improvement, with the exception of cognitive functioning, which while maintaining overall its high

baseline value, trended towards some worsening over time above the threshold of 10-points (worst mean change score of -11.11 at Cycle 20 Day 1). Patients with NSCLC (n=9) and those with mCRC (n=3) reported low symptom burden at baseline at and at most study visits throughout the study [28].

In addition to the earlier data, updated QoL data was presented at ESMO [97]. The mean score in global health status was 68.6 at baseline with a mean change from baseline at cycle 13 of +5.3. Furthermore, for physical functioning, mean scores were 74.8 at baseline with a mean change from baseline at cycle 13 of +6.3. Role functioning was 66.9 at baseline with a mean change from baseline at cycle 13 of +12.3 and cognitive functioning was 83.9 at baseline with maintenance (0.0) at cycle 13. This was assessed in the efficacy-analysis population which included all patients who received ≥1 dose of entrectinib during the selected cut-off dates and had measurable disease at baseline (n=71) [97].

Comparator studies

Quality of life has not been reported for any of the comparator studies and it is therefore not possible to compare entrectinib PRO data to any of these studies [2,4,5].

BSC in patients with unknown NTRK status

4 of the 28 included articles on BSC in patients with unknown NTRK status included EORTC QLQ-C30 data [42,69,80,95]. Rao et al. and Roszkowski et al. solely reported HRQoL as a comparison between BSC and the active arm and it is therefore not possible to describe the HRQoL for BSC alone [69,80]. Both studies reported no significant difference between the two arms.

For Grothey et al. QLQ-C30 was reported at baseline and end of treatment. In the BSC arm, the global QLQ-C30 score was 64.7 at baseline and 51.9 by the end of treatment [42]. This result was similar in the intervention arm.

Hofmann et al. reports HRQoL at baseline and after 8 weeks for the BSC arm after 8 weeks all functions where similar or had decreased besides physical function that had a slight increase. A reduction in global health status was found after 8 weeks [95].

Conclusion

Based on the limited and spare reporting of HRQoL in the comparative studies and the lack of a comparator with known NTRK status, it was not possible to determine whether there is a minimal clinical relevant difference. However entrectinib did show a minimal patient treatment burden and reported improvement in or maintenance of day-to-day functioning, HRQoL.

It is noteworthy that a positive mean change of 5.3 in global health status scores was reported [97]. Comparisons to studies on BSC in patients with unknown NTRK status can involve limitations, however none of these reported a positive mean change in global scores.

7.1.4 Objective response rate - Important outcome

The scientific committee requests data on objective response rate. No minimal clinically relevant difference has been determined. Instead, the protocol proposes a narrative description.

Entrectinib

ORR was achieved in 63.5% of the patients with the lower limit of the 95% CI excluding 30 % (95% CI: 51.5%, 74.4%) demonstrating a clinically meaningful effect for entrectinib (Table 13). Out of the 74 patients, 5 patients archived CR, 42 had PR and 6 patients had documented disease progression [28].

Table 12. Objective response and best overall response, BICR assessment (efficacy evaluable analysis [28,63]

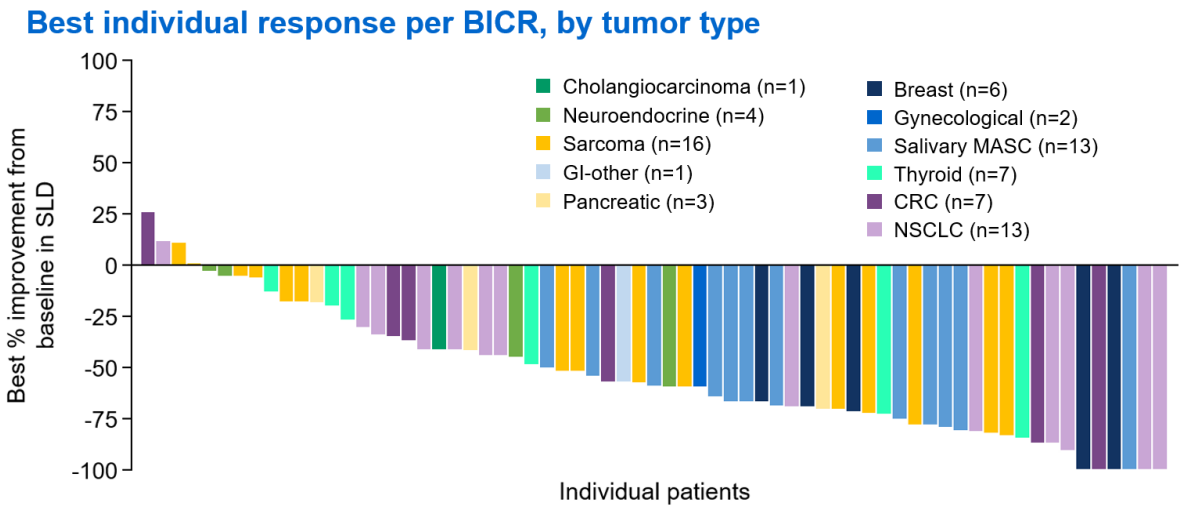
	Patients, n (%)	Patients, n (%)
N	54 (100)	74 (100)
Responders	31 (57.4)	47 (63.5)
95% CI for response rate	(43.2, 70.8)	(51.5, 74.4)
Complete Response (CR)	4 (7.4)	5 (6.8)
Partial response (PR)	27 (50.0)	42 (56.8)
Stable Disease (SD)	9 (16.7)	9 (12.2)
Non-CR/PD	3 (5.6)	3 (4.1)
Missing or unevaluable	7 (13.0)	9 (12.2)

Best Overall Response is derived per RECIST 1.1. Not Evaluable/Not Done category includes patients having on-study scans that could not be evaluated and patients who discontinued prior to obtaining adequate scans to evaluate or confirm response. SD and non CR/PD must be observed study day 35 or later, otherwise they count as NE. Objective response is defined as PR or CR confirmed by repeat imaging at least 28 days following first documentation of response. Otherwise, the patient is considered to be a non-responder. Patients were categorized as having non-CR/non-PD if they had non-target lesions (as assessed by BICR), but had measurable disease at baseline as assessed by Investigator.

ORR has also been measured for the specific tumour types (see Figure 6 and Table 14). It is also available for specific disease histologies. For NSCLC the ORR in Adenocarcinoma was 89% (8/9); Squamous cell carcinoma ORR 0% (0/2) and in NSCLC not otherwise specified 50% (1/2). In sarcoma the ORR in

angiosarcoma was 0% (0/1); chondrosarcoma 0% (0/1); follicular dendritic cell sarcoma 0% (0/1); MPNST 0% (0/1); cervical adenosarcoma 100% (1/1); endometrial stromal sarcoma 100% (1/1); GIST 100% (2/2); Spindle cell 50% (2/4); Sarcoma other 75% (3/4). For thyroid cancer, the ORR in papillary thyroid was 25% (1/4); thyroid other 66.7% (2/3) [28].

Figure 6. Best individual response per BICR, by tumour type [96].



Patients with missing SLD percent change are excluded from the plot. SLD, sum of longest diameters. GI, gastrointestinal. CRC, colorectal cancer. NSCLC, non-small-cell lung cancer. MASC, mammary analogue secretory carcinoma.

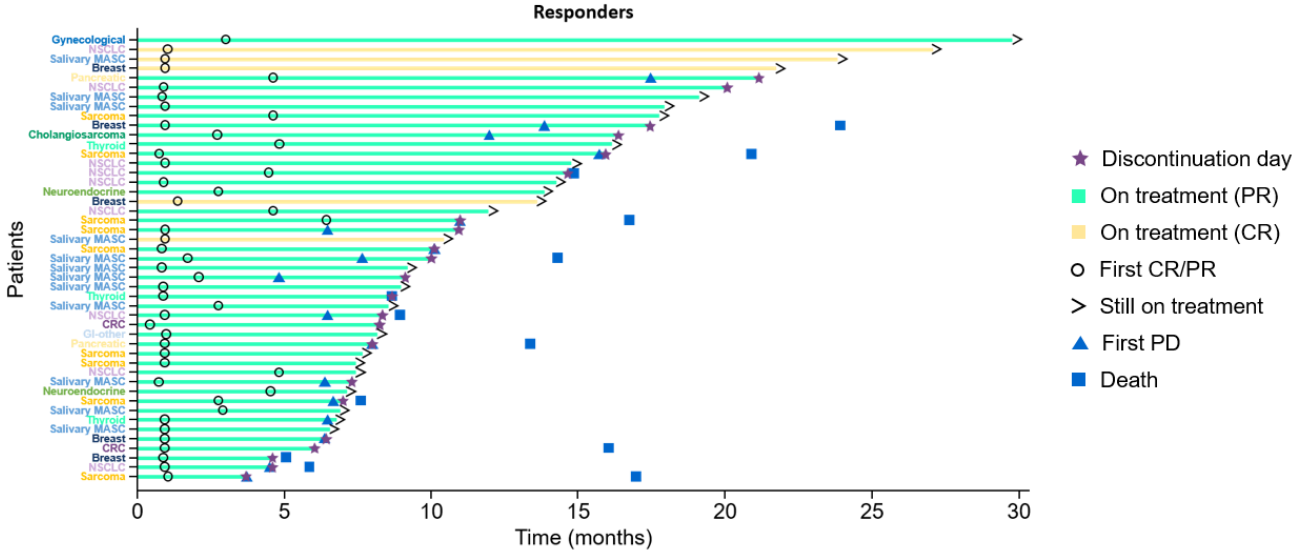
Table 13. ORR (BICR assessment) by tumour type in the NTRK efficacy evaluable population (CCOD october 2018) [28]

Tumour type	Patients (n = 74)	ORR, n (%)(95% CI)	DOR, range (months)
Sarcoma	16	9 (56.3) (29.9, 80.3)	2.8, 15.1
Non-small cell lung cancer	13	9 (69.2) (38.6, 90.9)	1.4*, 25.9*
Salivary (MASC)	13	12 (92.3) (64.0, 99.8)	2.8, 22.1*
Breast cancer (secretory)	4	4 (100) (39.8, 100)	5.5, 20.2*
Breast cancer (non-secretory)	2	NE, PR NA	4.2
Thyroid cancer	7	3 (42.9) (9.9, 81.6)	5.6, 10.9*
Colorectal cancer	7	2 (28.6) (3.7, 71)	7.9*, 15.2
Neuroendocrine cancers	4	2 (50.0) (6.8, 93.2)	1.9*, 9.2*
Pancreatic cancer	3	2 (66.7) (9.4, 99.2)	7.1, 12.9
Ovarian cancer	1	Non CR/PD NA[a]	26.0*
Endometrial carcinoma	1	PR NA	26.0*
Cholangiocarcinoma	1	PR NA	9.3
Gastrointestinal cancer (other)	1	PR NA	5.6*
Neuroblastoma	1	NE NA	NA

*Censored; [a]Patients were categorized as having non-CR (complete response)/non-PD(progressive disease) if they had non-target lesions (as assessed by BICR), but had measurable disease at baseline as assessed by Investigator.
ORR: Objective Response Rate; DOR: Duration of Response; MASC: mammary analogue secretory carcinoma; NA: not applicable due to small number or lack of response; CR: complete response; PR: partial response; PD: progressive disease; NE: not estimable.*

Across cancer types most patients that responded to entrectinib achieved a rapid time to response for most patients within the first 5 months, see Figure 7.

Figure 7. Time on treatment for responders [96]



Rosen et al.

In the study by Rosen et al. [5], ORR was presented for different populations. For first-line therapy, across all classes of therapy excluding TRK inhibitors, 7 out of 15 patients had objective responses, resulting in an ORR of 46.7% (95% CI: 21.3, 73.4). For the 44 patients with best overall response, 1 (2.3%) patient had CR, 6 (13.6%) had PR, 2 (4.5%) had SD and 6 (13.6%) had PD. The last 29 (65.9%) patients had unknown responses.

24 patients received chemotherapy containing-regimens and 15 had objective response and the ORR was 62.5% (95% CI: 40.6–81.2). For the 35 patients with best overall response, 4 (11.4%) patients had CR, 11 (31.4) had PR, 4 (11.4%) had SD and 5 (14.3%) had PD. The last 11 (31.4%) patients had unknown responses. 1 out of 9 patients had objective response and ORR was 11.1% (95% CI: 0.3–48.2) [5].

For the 12 patients that received immunotherapy, including two MSI-H colorectal cancers, the best overall response was only reported as 1 (8.3%) CR, 3 (25%) SD, 5 (41.6%) PD and 3 (25%) unknown. Only one

patient with MSI-H colorectal cancer achieved a complete response lasting 3.5 years that was ongoing at the time of data cut [5].

Lastly, for the patients receiving TRK inhibitor therapy, 23 out of 34 patients had objective response and the ORR was 64.7% (95% CI: 46.5–80.3). For the 38 patients with best overall response 6 (15.8%) CR, 17 (44.7%) PR, 9 (23.7%) SD, 2 (5.3%) had PD and 4 (10.5%) had unknown response [5].

There are several precautions that should be taken when comparing these data with entrectinib. Firstly, the patient demographics are only listed for the overall population and not specified for the different subgroups. Important factors like ECOG PS, prior lines of therapy, and CNS metastasis are not reported in the Rosen et al. publication [5]. The composition of tumour types also differ between the two populations which can affect the results.

Intrapatient analysis

Response was also evaluated in the intrapatient analysis. Of the 31 patients with prior therapy, 16 patients had responses (PR or CR) compared to 4 responses on the previous line of therapy. This translates to an ORR of 51.6% on entrectinib compared to an ORR of 12.9% in the most recent line of therapy.

In the 21 patients with documented progression on prior therapythere were 11 responses compared to 2 responses on the previous line of therapy. The ORR is therefore 52.4% in entrectinib compared to 9.5% in the most recent line of therapy [2].

[redacted]

CoPPO trial

In the CoPPO trial, objective responses were observed in 15 patients (14,9%, 95% CI, 9-24%) with PR and none with CR [4]. 38 patients (38%) had SD as the best response and 33 patients (33%) had progessive disease.

BSC without known NTRK-fusion status

Only 9 out of the 27 included BSC trials reported ORR for BSC without known NTRK status. In these 9 studies the overall median ORR was 1.4% (0.0%; 2.38%) and results ranged between 0 and 4.2%.

Conclusion

Entrectinib shows a clinically relevant response rate of 63.5% across the various tumour types. When comparing this to the comparator studies, the response rate is markedly higher for entrectinib than what has otherwise been reported. As discussed, there are limitations when performing naïve treatment comparisons in this setting. However, it is worth noting that:

- Based on the intrapatient analysis, treatment with entrectinib results in higher response rates compared to the most recent line of therapy [2]. This is significant as the response to treatment is normally expected to decrease as patients receive additional treatment lines.
- For the population with known NTRK status in Rosen et al. similar numerical values for ORR in chemotherapy and TKIs are seen, but as mentioned above the lack of baseline characteristics like ECOG PS, prior lines of therapy, CNS metastases makes the comparability of these studies difficult and should be done with caution. Despite this, the first-line therapy (excluding TKIs) only showed an ORR of 46.70% [5].
- The ORR of entrectinib is higher than that reported in the CoPPO trial (difference of 48.6%). This is interesting as the overall setting is relatively similar, as the patients in the CoPPO trial represent patients from different tumour types who have exhausted their available treatment options and who have instead been assigned a treatment relevant for their specific target mutation [4].
- The BSC analysis also reflects patients who have exhausted available treatment options, however, the relatively limited response rate should likely be seen in the context of BSC being a palliative treatment. The reported ORRs between 0-4.2% for BSC in later lines shows the unmet need for this population. Although NTRK-positive fusions are rare, detection of this fusion offers patients a clinical minimal relevant response and tumour shrinkage with entrectinib.

Table 14. Overview of the reported ORR data

	Drug (study population, N)	ORR % (95% CI, Months)
Narrative comparison	**Entrectinib [63]** (Integrated analysis, n=54)	57.4% (43.2, 70.8)
	Entrectinib [28] (Integrated analysis, n=74)	63.5% (51.5, 74.4)
	Intrapatient analysis [2] Entrectinib Documented progression (n=21)	52.4%

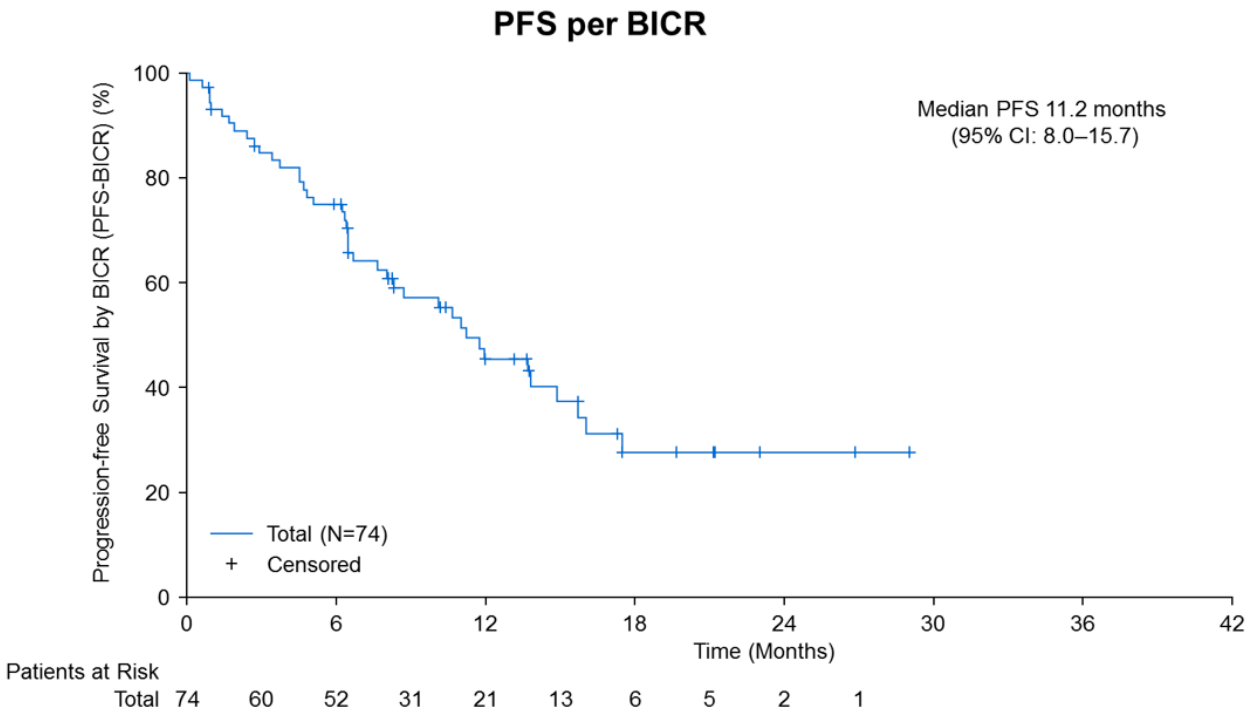
	Intrapatient analysis [2] Most recent prior therapy Documented progression (n=21)	9.5%
		
		
	First-line therapy[a] [5] (Rosen et al., n=15)	46.7% (21.3, 73.4)
	Chemotherapy containing-regimens[b] [5] (Rosen et al., n=24)	62.5% (40.6, 81.2)
	TRK inhibitor therapy[c] [5] (Rosen et al., n=34)	67.6% (49.5, 82.6)
	Matched treatment [4] (CoPPO trial, n=101)	15% (9, 24)
	Best supportive care[d]	1.4%
[a]across all classes of therapy excluding TRK inhibitors; [b]The best response across all lines of therapy received for advanced disease; [c]including entrectinib and larotrectinib; [d]based on reported ORR		

7.1.5 Progression-free survival - Important outcome

The scientific committee requests data on PFS defined as either the median difference in PFS or the difference in the proportion of progression-free survival after 12 months. It is further stated that the minimal clinically important differences are considered to be 3 months or 10% respectively.

PFS has been reported in the integrated analysis for both the initial MAA datacut (n=54, CCOD=31 May 2018) and for the Day 120 dataset where an additional 20 patients had been included (n=74, CCOD=31 Oct 2018). In the Day 120 dataset, the most recent datacut, the median PFS was reported as 11.2 (8.0, 15.7). This is consistent with the MAA dataset, where a median PFS of 11.2 months (8.0, 14.9) was also reported.

Figure 8. Progression-free survival per BICR for NTRK-fusion positive patients [96].



The median PFS has also been assessed for certain tumour types. For MASC and thyroid cancer, data was reported from the initial dataset (n=54). PFS was however not estimable at the time of analysis [64,65].

For NSCLC (n=13), median PFS was 14.9 months (95% CI, 4.7, NE) [66].

For gastrointestinal cancers (n=12) the overall PFS was 7.1 months (2.4, 16.0). PFS was also reported for cholangiocarcinoma (n=1, 12.0 months), CRC (n=7, 2.4 months, 1.0, 16.0), and pancreatic cancer (n=3, 8.0 months (6.2, 17.5) [67].

[redacted]

In terms of comparative data, PFS has been assessed in the intrapatient analysis, Rosen et al., the CoPPO trial, and the literature analysis of best supportive care.

Intrapatient analysis

In the intrapatient analysis, the PFS of entrectinib was compared to the expected PFS of the most recent prior therapy using intrapatient data. To estimate the expected PFS of the previous line of therapy, the analysis used Time To Next Treatment (TTNT) as a proxy for PFS.

The analysis included patients from STARTRK-2 who had received at least one prior systemic therapy for metastatic disease. The analysis used STARTRK-2 patients exclusively due to differences in eCRF design for other studies included in the ISE. Of the 51 efficacy evaluable patients, 31 had received prior therapy. 21 of those patients had documented[1] progression on prior therapy while 10 did not. Results were presented for both the total group of patients with prior therapy and those with documented progression on prior therapy [2].

[redacted]

For prior therapies, TTNT was defined as time from start of therapy to start of the next line of therapy/start of entrectinib. If the start date day was missing, the 1st of the given month was used instead. For entrectinib, TTNT is defined as the treatment duration i.e. time from start of entrectinib therapy to end of entrectinib therapy. Using the treatment duration for entrectinib could be considered as a conservative approach, as patients who are still undergoing treatment with entrectinib are censored for this analysis [2].

To test the validity of TTNT as a proxy for PFS, it is relevant to compare the TTNT and the PFS for entrectinib. Overall, the median PFS and median TTNT were similar with 14.8 months median TTNT vs. 13.7 months median PFS in the prior therapy group of 31 patients (10.0 months median TTNT vs. 8.7 months median PFS in the documented progression group of 21 patients) [2].

[1] Patients with documented progression included reason for discontinuation of primary resistance (no response to therapy - 9 patients), progressive disease (7 patients), or “other reason” combined with non missing data for progression (5 patients)

[redacted]

When comparing TTNT for entrectinib to TTNT for the most recent prior therapy, the entrectinib TTNT was longer in both groups. In the overall group of 31 patients, the difference was 10.2 months (14.8 months vs. 4.6 months) and in the group with documented progression the difference was 6 months (10.0 vs. 4.0) [2].

[redacted]

To sum up the results, the intrapatient analysis of TTNT suggests that despite treatment with entrectinib taking place in a later line of therapy, patients tended to have longer treatment durations compared to their most recent prior therapy [2]. As disease progression most likely will lead to treatment cessation and a switch to the next line of treatment it could indicate that patients have had improved PFS on entrectinib compared to their most recent prior therapy. Depending on the exact relationship between PFS and TTNT, the difference could surpass the minimal clinically relevant difference of 3 months.

Table 15. TTNT and PFS of entrectinib and most recent prior therapy [2]

Subgroup	Treatment	Median (95% CI) TTNT	Median (95% CI) PFS (BICR)
Patients with prior therapy (N=31)	Most recent prior therapy	4.6 months (3.5, 8.0)	NA
Patients with prior therapy (N=31)	Entrectinib	14.8 (10.0, NA)	13.7 (7.7, NA)
Documented progression on prior therapy (N=21)	Most recent prior therapy	4.0 (2.9, 7.0)	NA
Documented progression on prior therapy (N=21)	Entrectinib	10.0 (6.4, NA)	8.7 (6.2, NA)

[redacted]

[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

Rosen et al.

PFS was assessed for NTRK-fusion positive patients in the study by Rosen et al [5]. As the study included patients from the time of their initial diagnosis, analyses were carried out on both recurrence-free survival (RFS) and PFS. PFS were assessed in patients who developed advanced disease or with de novo metastatic disease (n=51). The analysis excluded patients who had received curative first-line treatment and remained disease-free (n=13), who had never been treated with systemic therapy for incurable disease (n=4), or if records were inadequate (n=8). PFS was defined as time from date of first-line therapy for advanced disease until radiologic progression (n=37), changing therapies to start a clinical trial (n=2), or changing medical therapies for other reasons (n=4).

For patients who developed recurrent or advanced disease, median PFS was 9.1 months (4.8, 13.1) on their first line of therapy. It should be noted that the definition of first line therapy was not specified for this endpoint. PFS was not either reported in others specific therapies or lines of treatment [5].

CoPPO Trial

In the CoPPO trial, median PFS was the primary endpoint of the study. PFS was evaluated in all 101 patients that received matched treatment. The median PFS was 12 weeks (9.9, 14.4) [4].

BSC analysis

PFS was also one of the outcomes in the BSC analysis based on the literature search. The overall median PFS across all included studies was 1.8 (1.48; 2.24) months. For the subgroups in BSC, overall median PFS was 1.8 (1.7; 1.89) months in CRC, 1.8 (1.39; 2.32) months in NSCLC and 1.6 (1.25; 1.95) months for GIST. A complete overview of the reported median OS values can be found in Tables 9, 10, 11 and in Appendix 10.4. The studies reported varying median PFS values, however, nearly all studies reported a median PFS of best supportive care below 4 months. The exception to this was a study by Satyanarayan et al. in NSCLC, which reported a median PFS of 7 months [87]. Despite the limitations of this analysis, the studies indicate that patients progress relatively early after initiating BSC.

Conclusion

Overall, the median PFS of entrectinib in the integrated analysis was reported as 11.2 (8.0, 15.7) at the most recent datacut (n=74). When comparing this to the comparative data sources, this is the longest median PFS reported. Results indicate that:

- The treatment length of entrectinib is longer than that of the most recent line of therapy. Given that treatment within cancer is typically halted by the time of progression, this could imply a longer time until progression for entrectinib. Depending on the validity of TTNT as a proxy for PFS the difference likely exceeds the minimal clinically relevant threshold of 3 months [2,3].
- The progression-free survival of entrectinib is longer than that observed in the study by Rosen et al. on NTRK patients but without exceeding the minimal clinically relevant threshold of 3 months. However, PFS was only reported on first line therapy [5].
- Progression-free survival of entrectinib is longer than that observed in the CoPPO trial. This is a noteworthy result as the CoPPO trial results might reflect the typical PFS results when providing a targeted treatment after exhausting available treatment lines [4].
- The progression free survival of entrectinib is longer than that observed in the literature analysis of BSC. The overall median PFS of 1.8 (1.48; 2.24) months indicates that patients progress relatively fast after initiating palliative care.

Table 16. Overview of the reported PFS data

	Drug (study population, N)	Median PFS (95% CI, Months)
Narrative comparison	**Entrectinib [63]** (Integrated analysis, n=54)	11.2 (8.0, 14.9)
	Entrectinib [28] (Integrated analysis, n=74)	11.2 (8.0, 15.7)
	Intrapatient analysis [2] Entrectinib (Documented progression on prior therapy, n=21)	8.7 (6.2, NE)
	Intrapatient analysis [2] Most recent prior therapy (Documented progression on prior therapy, n=21)	4.0 (2.9, 7.0)[b]
	[redacted]	[redacted]

	[redacted]	
	[redacted]	[redacted]
	Rosen et al. [5] (TRK fusion-positive patients)	9.1 (4.8, 13.1)
	Matched treatment [4] (CoPPO trial, n=101)[a]	12 weeks (95% CI: 9.9, 14.4)
	Best supportive care **(**overall median PFS)	1.8 months
[a] results reported as weeks in study [b]TTNT used as proxy for PFS in the intrapatient analysis		

7.1.6 Grade 3-4 related AEs – Important outcome

The scientific committee requests data on the proportion of grade 3-4 adverse events and states that a difference of 5% is clinically relevant.

In the initial integrated safety dataset (n=355), 61.1% of the patients experienced grade ≥3 AEs [28]. In the updated integrated safety data (n=504) 61.1% of the patients also experienced grade ≥3 AEs [28]. When looking only at the adult population in the updated integrated safety analysis, 218 (63.2%) patients between 18 and 64 years (n=345) and 74 (56.9%) patients ≥65 years (n=130) experienced grade 3-5 AEs [28]. When adding these numbers together, 292 (61.5%) patients ≥18 years (n=475) experienced grade ≥3 AEs.

The qualitative description of grade ≥3 AEs has been presented in the EPAR for the CCOD of May 31 2018 for an overall safety population of 355 patients and 68 adult NTRK-fusion positive patients [28]. This dataset is used in this application, as there are no published data of grade 3-4 adverse events in the updated integrated safety dataset (n=504). AEs were only reported at grade 3-5 and with an incidence above 2% in one of the study baskets (ROS1-positive NSCLC adults, other adults and paediatrics are not presented here, therefore for some or all the baskets presented in Table 19, the AE could also be presented if the incidence is lower than 2.0%).

An overview of grade 3-5 adverse events with a frequency of ≥2% can be seen in Table 19. No treatment-related grade 5 AEs were reported in the integrated analysis.

The most frequently reported 3-5 adverse events grade 3-5 events for the overall population (in ≥2% of patients) were anaemia (10.7%), increased weight (6.5%), dyspnoea (6.2%), and fatigue (4.2%) , pneumonia (3.9%), pulmonary embolism (3.7%), AST increased (3.4%), hypoxia (3.4%), ALT increased (3.1%), pleural effusion (3.1%), hypophosphatemia (2.8%), syncope (2.5%), neutrophil count decreased (2.5%), neutropenia (2.5%), urinary tract infection (2.3%) as well as diarrhea, hypotension, hypokalaemia, hyponatraemia and lipase increased (all at 2.0% each). For the overall population in this dataset (N=355), grade 5 AEs occurred in 20 (5.6%) patients and for the NTRK population (n=68) it was 6 (8.8%) patients. Investigator assessed that none of them were related to entrectinib [28]. Ten of the 20 Grade 5 AEs were respiratory AEs, the majority of which (9 of 10) were reported in patients with lung cancers or lung metastasis in the context of disease progression or deterioration of underlying cancers. Overall, there were no patterns with respect to the type of Grade 5 AEs reported, and the majority of Grade 5 AEs were reported in the context of worsening of underlying disease or complications of the underlying malignancy [28].

Table 17. Grade 3-5 adverse events in patients treated with entrectinib with an incidence of at least 2% in the overall safety population (CCOD 31 May 2018) [28]

		NTRK safety population (n=68), n(%)	Total adult (n=339)	Total safety population for Rozlytrek (n=355), n(%)
overall	Total number of pts with >=1 event	50 (73.5 %)	209 (61.7)	217 (61.1 %)
Investigations	Total number of pts with >=1 event	13 (19.1)	59 (17.4)	65 (18.3)
	weight increase	9 (13.2)	23 (6.8)	23 (6.5)
	AST increased	2 (2.9)	11 (3.2)	12 (3.4)
	ALT increased	3 (4.4)	10 (2.9)	11 (3.1)
	neutrophil count decreased	0	6 (1.8)	9 (2.5)
	lipase increased	0	7 (2.1)	7 (2.0)
	amylase increased	0	6 (1.8)	6 (1.7)
	lymphocyte count decreased	0	3 (0.9)	5 (1.4)
	platelet count decreased	0	1 (0.3)	4 (1.1)
	weight decreased	0	0	2 (0.6)
	gamma-glutamyltransferase increased	0	0	1 (0.3)
	white blood cell count increased	0	0	1 (0.3)
Respiratory, thoracic and mediastinal disorders	Total number of pts with >=1 event	11 (16.2)	50 (14.7)	53 (14.9)
	dyspnoea	4 (5.9)	19 (5.6)	22 (6.2)
	pulmonary embolism	3 (4.4)	13 (3.8)	13 (3.7)

	hypoxia	5 (7.4)	10 (2.9)	12 (3.4)
	pleural effusion	3 (4.4)	11 (3.2)	11 (3.1)
	acute respiratory failure	2 (2.9)	3 (0.9)	3 (0.8)
	respiratory failure	0	3 (0.9)	3 (0.8)
	pulmonary oedema	0	2 (0.6)	3 (0.8)
	cough	0	0	1 (0.3)
Blood and lymphatic system disorders	Total number of pts with >=1 event	15 (22.1)	43 (12.7)	46 (12.4)
	anaemia	13 (19.1)	35 (10.3)	38 (10.7)
	neutropenia	2 (2.9)	9 (2.7)	9 (2.5)
	febrile neutropenia	0	1 (0.3)	2 (0.6)
Nervous system disorders	Total number of pts with >=1 event	9	42 (12.4)	44 (12.4)
	syncope	3 (4.4)	8 (2.4)	9 (2.5)
	hypersomnia	0	0	1 (0.3)
Infections and infestations	Total number of pts with >=1 event	11 (16.2)	42 (12.4)	43 (12.1)
	pneumonia	4 (5.9)	14 (4.1)	14 (3.9)
	urinary tract infection	1 (1.5)	8 (2.4)	8 (2.3)
	sepsis	2 (2.9)	7 (2.1)	7 (2.0)
	lung infection	0	3 (0.9)	4 (1.1)
	device related infection	0	1 (0.3)	2 (0.6)
Metabolism and nutrition disorders	Total number of pts with >=1 event	10 (14.7)	42 (12.4)	43 (12.1)
	hypophosphatemia	3 (4.4)	9 (2.7)	10 (2.8)
	hypokalaemia	0	7 (2.1)	7 (2.0)
	hyponatraemia	1 (1.5)	7 (2.1)	7 (2.0)
	hyperglycaemia	1 (1.5)	6 (1.8)	6 (1.7)
	hyperuricemia	2 (2.9)	6 (1.8)	6 (1.7)
	hypoalbuminemia	1 (1.5)	5 (1.5)	5 (1.4)
	hypocalcaemia	1 (1.5)	4 (1.2)	4 (1.1)
	decreased appetite	0	0	1 (0.3)
General disorders and administration site conditions	Total number of pts with >=1 event	11 (16.2)	30 (8.8)	30 (8.5)
	fatigue	8 (11.8)	15 (4.4)	15 (4.2)
	asthenia	0	4 (1.2)	(1.1)
Musculoskeletal and	Total number of pts with >=1 event	6 (8.8)	20 (5.9)	21 (5.9)

connective tissue disorders				
	back pain	0	5 (1.5)	5 (1.4)
	myalgia	0	3 (0.9)	3 (0.8)
	pain in extremity	0	0	1 (0.3)
Gastrointestinal disorder	Total number of pts with >=1 event	2 (2.9)	17 (5.0)	19 (5.4)
	diarrhoea	1 (1.5)	7 (2.1)	7 (2.0)
	abdominal pain	0	1 (0.3)	2 (0.6)
	constipation	0	1 (0.3)	2 (0.6)
	dysphagia	0	0	1 (0.3)
	oesophageal stenosis	0	0	1 (0.3)
Vascular disorders	Total number of pts with >=1 event	4 (5.9)	18 (5.3)	18 (5.1)
	hypotension	2 (2.9)	7 (2.1)	7 (2.0)
	hypertension	1 (1.5)	5 (1.5)	5 (1.4)
Cardiac disorders	Total number of pts with >=1 event	6 (8.8)	13 (3.8)	14 (3.9)
	pericardial effusion	1 (1.5)	3 (0.9)	4 (1.1)
	cardio-respiratory arrest	2 (2.9)	2 (0.6)	2 (0.6)
Psychiatric disorders	Total number of pts with >=1 event	3 (4.4)	13 (3.8)	13 (3.7)
Injury, poisoning and procedural disorders	Total number of pts with >=1 event	2 (2.9)	12 (3.5)	13 (3.7)
	femur fracture	0	0	1 (0.3)
Skin and subcutaneous tissue disorders	Total number of pts with >=1 event	0	6 (1.8)	6 (1.7)
	rash	0	3 (0.9)	3 (0.8)
Renal and urinary disorders	Total number of pts with >=1 event	0	5 (1.5)	5 (1.4)
	acute kidney injury	0	3 (0.9)	3 (0.8)
Hepatobiliary disorders	Total number of pts with >=1 event	0	3 (0.9)	3 (0.8)
Adverse event that appear in this table, if the incidence in any study basket was equal to or above 2%. data on ROS1 NSCLC adults, Other adults and pediatics patients are not shown in this table, but AE could be presented based on their incidence.				

In addition to this data, all adverse reactions grade ≥3 for the updated integrated safety population is available in appendix 10.5

Comparators

Neither the intrapatient analysis, Rosen et al. or the CoPPO trial reported on grade 3-4 AEs or safety in general and it was therefore not possible to compare it to entrectinib [2,4,5]. Patients in these studies received either chemotherapy, immunotherapy and/or TKIs and it would therefore be expected that they would experience AEs that are similar to what is reported and observed elsewhere.

For the BSC population without known NTRK status it is generally seen that fewer patients experience at least one grade 3-4 AE than in the entrectinib group. However for the patients receiving either entrectinib or BSC that do experience a grade 3-4 AE, the differences in frequencies for the given AEs are comparable. There are also differences in the type of AEs reported and this could be explained by the different therapies included in BSC (e.g. analgesics, antibiotics, steroids)

Conclusion

Due to the lack of safety reporting in the primary comparative studies it is not possible to determine whether there is a minimal clinical relevant difference. For patients without known NTRK status receiving BSC had as expected fewer patients experiencing at least one grade 3-4 AE.

The most common grade 3-4 AEs for entrectinib was anemia, weight increase and dyspnea.

7.1.7 Narrative description of the AE profile - Important outcome

As described, the safety population for entrectinib is based on the integrated analysis. The safety profile of entrectinib will be described based on the total safety population of 504 adult and pediatric patients where available. The entrectinib EPAR and SmPC contains the most recent safety data [27,28].

Of the 504 adult patients, most received all their planned doses of entrectinib with few missed doses. The median duration of exposure was 5.5 months, corresponding to a median of 7 cycles, although some patients were able to receive entrectinib for up to 42 months.

Entrectinib was generally well tolerated with a manageable safety profile. Almost all patients experienced at least 1 adverse event (99,1% of patients). The most frequently reported AEs (≥ 25% of patients) were constipation (43.4%), fatigue (43.4%), dysgeusia (42.5%), dizziness (38.9%), diarrhoea (38.1%), anaemia (35.4%), oedema peripheral (31.9%), blood creatinine increased (29.2%), nausea (28.3%), and weight increased (26.5%).

Most of the AEs that required intervention were managed with either dose interruption (45.8% of patients) or dose reduction (26% of patients). AEs leading to discontinuation of entrectinib were reported in 9.1% of patients from the updated integrated safety population (n=504) [28].

An overview of the safety profile in both NTRK fusion-positive tumours and the overall safety population can be seen in Table 20.

Table 18. Summary of adverse events in the safety population [27,28]

	NTRK fusion-positive adults (n=68)	Overall safety population (n=355)	Overall safety population (n=504)
Any Adverse Events	68 (100%)	353 (99.4)	499 (99)
Related Adverse Events	61 (89.7%)	325 (91.5)	-
Grade ≥3 Adverse Events	50 (73.5%)	217 (61.1)	308 (61.1)
Related Grade ≥3 Adverse Events	29 (42.6%)	110 (31.0)	-
Adverse Events Leading to Death	6 (8.8%)	20 (5.6)	24 (4.8)
Serious Adverse Events	32 (47.1%)	137 (38.6)	
Adverse Events Leading to Discontinuation of Trial Drug	9 (13.2%)	30 (8.5)	46 (9.1)

Most AEs that required intervention were managed with either dose interruption (45,9% of patients) or dose reduction (26.0% of patients). Grade 3-4 AEs were experienced by 61.1% of patients. Overall, the rate of discontinuations due to AEs was low at 9.1% and no pattern or cluster of AEs leading to discontinuation could be identified. For the AEs deemed related to the treatment the discontinuation rate was 3.9%.

SAEs occurred in 38,6% of patients. The most frequently reported SAEs (≥ 2% of patients) were pneumonia (3,9%), dyspnea (3,7%), pleural effusion (3,4%), pulmonary embolism (2,3%), and pyrexia (2,0%). A smaller proportion of pediatric patients experienced SAEs compared to adults. Please see 7.2.6 narrative description of the pediatric population.

Among the 504 patients who received entrectinib across clinical trials, 130 (25.8%) patients were 65 years or older and 34 (6.7%) were 75 years or older. The overall safety profile of entrectinib in the elderly patients is similar to the safety profile observed in patients younger than 65 years of age. Adverse reactions occurring more frequently in the elderly compared to patients less than 65 years old were dizziness (48.5% vs 36.6%), blood creatinine increased (31.5% vs 23.3%), and hypotension (21.5% vs 14.7%), ataxia (23.8% vs 12.8%).
For a summary of the adverse events, please see Appendix 10.5

Summary of the safety profile for Rozlytrek
The safety of entrectinib has been evaluated in 504 adult and pediatric patients in 4 clinical studies. Even though 99.0 % of the patients experienced at least one AE (all grade), entrectinib was well tolerated and had a manageable safety profile.

EMA 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 [27,28].

Comparators
As mentioned in section 7.1.6. neither Rosen et al., the intrapatient analysis or the CoPPO trial reported on safety in general and it was therefore not possible to make a narrative description of the safety profiles and compare it to entrectinib [2,4,5]. In the Rosen et al. and CoPPO publications we know that patients have received chemotherapy, immunotherapy and/or TKIs and would therefore expect that these patients would have safety profiles similar to other comparable therapies [4,5].

It is difficult to make a narrative description of the safety profile of BSC because of the heterogeneity of the both the pharmaceuticals (e.g. antibiotics, analgesics, corticosteroids) and other potential interventions (e.g radiation) that could be included. But it is possible to make a general drug-class description.

Antibiotics
Depending on the cancer and related infections, different antibiotics could be relevant. Adverse events to this drug-class could include the following:

- **Diarrhea**
- **Nausea**

- **Rash**
- **Myalgia**

Analgesics

Depending on the cancer and related pain different analgesics therapy are relevant and could include paracetamol, NSAID, opioids, corticosteroids,, tricyclic antidepressants or antidepressants of the SNRI type and gabapentin/pregabalin [98]. Adverse events on these drug-classes could include:

- **Gastrointestinal and/or cardiac side effects** for NSAID
- **Development of tolerance** to opioids
- **Drug dependence** to opioids both mentally and physically
- **withdrawal symptoms** at discontinuation for opioids and antidepressants
- **Anticholinergic adverse events** for antidepressants

Corticosteroids

Systemic use of glucocorticoids for immunosuppressive therapy AEs typically fall under one of these categories [99]:

- **Inhibition of hypothalamic-pituitary-adrenal cortex function**, so that the adrenal cortex's own production of glucocorticoids is reduced or possibly removed altogether.
- **Iatrogenic hypercorticism** including osteoporosis, aseptic bone necrosis, cushingoid fat distribution, atrophy of the skin, striae cutis, purpura, thrombotic tendency, psychiatric symptoms in the form of insomnia, restlessness, sometimes euphoria and in predisposed patients regular psychoses, of microbial infections (especially tuberculosis), dysregulated diabetes mellitus, hypertension, hypokalaemia, growth retardation in children, myopathy, posterior subcapsular cataract, glaucoma.

- **Pseudotumour cerebri** Is a symptom picture seen in children, which is manifested by headache, vomiting, diplopia and stasis paper. This symptom picture is seen by variations in dose, possibly in connection with discontinuation of glucocorticoid therapy.

- **Steroid pseudorheumatism** consists of diffuse muscle and joint pain that is not affected by non-steroidal antirheumatic drugs, as well as mental instability, fatigue and fatigue. The symptoms are also seen in patients who do not have rheumatic disease. The symptom complex occurs partly with a permanent and rather high dosage of glucocorticoids, partly in connection with the discontinuation of glucocorticoid treatment.

- **Inhibition of inhibition of GH (in children inhibited height growth), LH/FSH and TSH.** Protein synthesis is inhibited in the extrahepatic tissue and protein catabolism is increased, so long-term systemic glucocorticoid treatment in pharmacological doses leads to poor and delayed wound healing, skin atrophy, striae, telangiectasias, vascular fragility with ecchymoses, myopathy and muscle atrophy. The effect on bones is pronounced. Glucocorticoids increase bone loss through

an inhibition of estrogen, testosterone, adrenal androgen and growth hormone. Bone loss is also increased via a direct inhibition of bone formation (osteoblasts). Bone resorption (osteoclasts) increases directly and indirectly, calcium absorption decreases and calcium excretion increases, leading to a decrease in β-calcium and an increase in β-parathyroid hormone.

- **Inhibition of height growth in children and inhibition of LH / FSH and TSH.** Glucocorticoids inhibit height growth in children. Prolonged treatment with glucocorticoid in pharmacological doses causes osteoporosis. Luteinizing hormone is inhibited by pharmacological doses of glucocorticoids, which may lead to hypogonadism. TSH and GH can also be inhibited by pharmacological doses of glucocorticoids.

- **Glucose and lipid metabolism.** The glucose concentration in the blood increases due to stimulated gluconeogenesis in the liver and inhibited insulin-stimulated glucose uptake into the cells. Glucocorticoids cause increased lipolysis, hypercholesterolemia, and rearrangement of fat deposits from the extremities to the truncus.

- **Impact on the hematopoietic system.** In the hematopoietic tissue, eosinopenia is characteristic, presumably due to both increased destruction and decreased formation. Granulocytosis seen during glucocorticoid therapy is likely to be primarily due to inhibited emigration of granulocytes from the bloodstream. Furthermore, glucocorticoids increase the number of erythrocytes.

Conclusion on the narrative description of the safety profiles

Given the heterogeneity of BSC it is difficult to compare the two treatments. In this narrative comparison it can be concluded that there are differences in the safety profiles of entrectinib and BSC. This is due to the large difference in drug-classes and mode of action for these. It should also be noted that there is a difference in the aim of the two treatments. The treatment goal of entrectinib is life-prolonging and the treatment goal for BSC is palliation.

With treatments aiming on life-prolongation there is generally a greater willingness to accept adverse events and entrectinib has been demonstrated to be well tolerated with a manageable safety profile.

7.1.8 Time to CNS-progression - Less important outcome

The scientific committee requests data on time to CNS progression in both patients with CNS metastasis at baseline as well as in patients that progress in CNS while on entrectinib treatment.

Entrectinib

Of the patients (n=74) included in the updated dataset, 27 (36.5%) had a CNS event. Time to CNS progression for entrectinib was 16.8 months (95% CI; 14.3, not estimable). It should be noted that patients

without CNS lesions present at baseline per the investigator assessment were not required to have scheduled brain scans every 8 weeks [28].

Efficacy by baseline CNS disease status has been described based on the initial dataset (n=54). 11 patients in the NTRK efficacy evaluable population had baseline CNS disease, while 43 had no baseline CNS disease (by BICR).

For patients with CNS metastasis at baseline, time to CNS progression was not reported. However Intracranial ORR was collected for this population. ORR was consistent with 54.5% (23.4, 83.3) in patients with CNS disease and 58.1% (42.1, 73.0) in patients without CNS disease. The PFS in this subset of patients was 14.3 months (5.1, NE) [28].

An updated analysis of CNS efficacy was presented recently on ESMO in an abstract by John et al. [100]. The analysis included 16 patients with baseline CNS disease by BICR with 8 patients with measurable CNS metastases. The IC-ORR was 62.5% (5/8, 1 CR and 4 PR) in the measurable set and 50% in the full analysis set (8/16, 4 CR and 4 PR). Median IC PFS was 10.1 months (2.8-NE) in the measurable set and 8.9 months (5.9-14.3) in the full analysis set.

Comparators
There was not published any data on time to CNS progression for any of the comparative studies [2,4,5].

Conclusion
Entrectinib shows 16.8 months of time to CNS progression on the population without CNS-metastasis at baseline. In the new updated analysis, entrectinib shows 10.1 months median IC-PFS in the measurable subgroup and 8.9 months in the overall group.

7.2 What is the clinical benefit of entrectinib compared to best supportive care for paediatric patients (age 12-18) with NTRK gene fusion-positive solid tumours?

7.2.1 Presentation of the relevant study and results

The following section will use the results of the integrated analysis of STARTRK-2 and STARTRK-NG unless stated explicitly stated otherwise. There are no comparative studies and data for all outcomes will be presented in a narrative manner. There are generally two data sets relevant to this application. The initial dataset from EMA MAA includes 7 NTRK-fusion positive patients and the updated data including 5 patients with NTRK-fusion positive CNS tumors and 3 patients with NTRK-fusion positive solid tumors [28,68].X

As mentioned in the presentation of the paediatric efficacy data in section 6.2, no efficacy data is available for patients aged between 12 to 18 years [28]. EMA assessed that the pharmacokinetic simulations

performed for adolescents within BSA 1.1-1.5 m2 showed that the exposure is within those obtained in adult patients. Activity in adolescents is considered established based on the extrapolation of the data from adults with NTRK-fusion positive solid tumours.

The safety data is presented on either n=29 or n=32.

7.2.2 Overall survival - Critical outcome

The scientific committee requests data on three parameters for OS with the following clinical differences deemed to be relevant:

- Median OS - a difference of 3 months
- OS-rate at 24 months - a difference of 10% points
- Proportion of patients with pCR or outcome of radical surgery - a narrative assessment

Median OS

Median overall survival has not been reported for the pediatric population.

OS-rate at 24 months

With OS data not yet mature the OS-rate after 2 years cannot be estimated.

Proportion of patients with pCR or outcome of radical surgery

There are no reports of either pathologic complete response or outcome of radical surgery for the paediatric population in general or for the NTRK-fusion positive population [28].

Conclusion

Median OS in the pediatric population has not yet been reported and it is therefore not possible to conclude anything regarding this outcome.

7.2.3 Quality of life - critical outcome

The scientific committee requests data on quality of life and states that a mean difference of 4,5 points from baseline (using the PedsQL questionnaire) is relevant.

Quality of life is not reported separately for the pediatric population treated with entrectinib.

7.2.4 Objective response rate - Important outcome

The scientific committee requests data on objective response rate. No minimal clinically relevant difference has been determined. Instead, the protocol proposes a narrative description.

Entrectinib

Of the 6 eligible pediatric subjects in the initial dataset, all achieved an objective response by BICR (2 CR and 4 PR), with DOR ranged between 1.8 and 9.3 months [28].

Of the 34 eligible paediatric subjects at the 1 July 2019 data-cut the objective response rate (defined as the total number of CR and PR) in fusion-positive patients (including ALK, ROS1 and NTRK) was 86% (12/14) versus 5% (1/20) in non-fusion patients [68]. Showing the importance of being fusion positive. For the NTRK-fusion positive population the 5 patients with CNS tumours achieved 3 CR, 1 PR and 1 PD, and for the 3 patients with solid tumours 2 had CR and 1 PR [68].

Conclusion

Although the available efficacy results in paediatric patients appear promising, they have been obtained in a very heterogeneous and small population so they have to be interpreted with caution, and it is difficult to draw conclusions based on such limited data [28]. Although the data for the paediatric patients are limited, the results for ORR are quite positive with 7 of 8 experienced CR or PR and one with a PD.

7.2.5 Progression-free survival - Important outcome

The scientific committee requests data on PFS defined as either the median difference in PFS or the difference in the proportion of progression-free survival after 12 months. It is further stated that the minimal clinically important differences are considered to be 3 months or 10% respectively.

Entrectinib

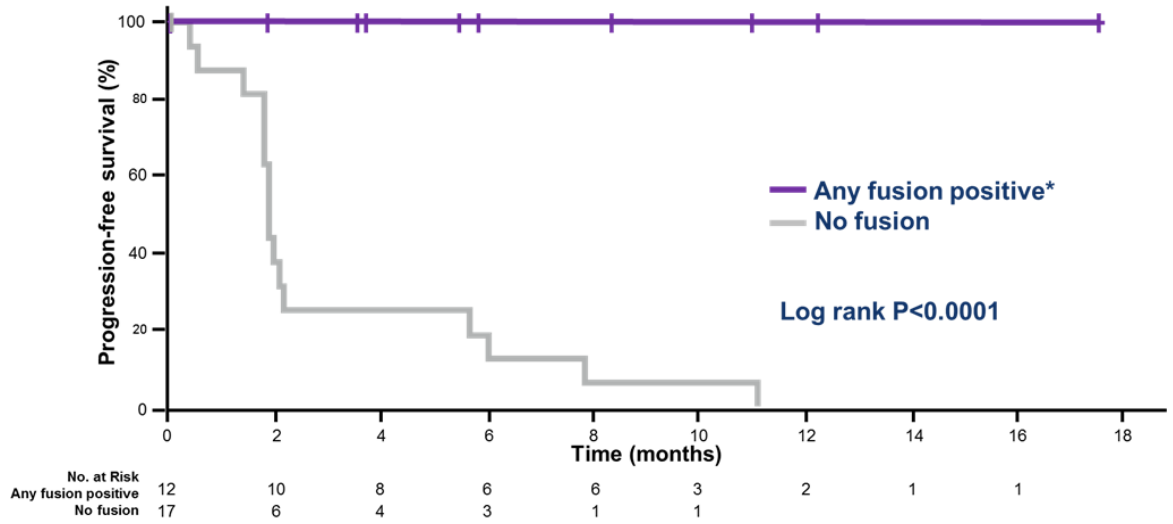
For the initial dataset of 7 NTRK-fusion positive patients median PFS was not reported [28].

For the STARTRK-NG population data are presented as fusions positive (including ALK, ROS1 and NTRK fusions) and as no fusion population. Beneath are results from two different data cuts.

At the 1 July 2019 data-cut median PFS was 17.5 months (95% CI 7.4–NE) in fusion-positive paediatric patients versus 1.9 months (1.8–5.7; p=0.0002) in non-fusion patients [68]. As mentioned, it should be noted that the fusion positive population includes ALK, ROS1 and NTRK.

Data from an earlier dataset was used to show the difference in the progress in the KM curves for the fusion positive population and patients with no fusions. Figure 9 contains the KM curve for investigator-assessed PFS as per the CCOD of October 31 2018 [101]. It should be noted that the figure shows data for all fusion positive pediatric patients and not only for NTRK-fusion positive. The figures shows the importance in identifying patients that harbour fusion positive solid tumours.

Figure 9. KM curve for PFS (IA) in fusion and non-fusion-positive paediatric patients [101]



Conclusion

Based on the available data entrectinib shows a long and relevant median PFS for all fusion positive patients enrolled. The median PFS shown in the paediatric population is longer than the median PFS in adults.

7.2.6 Grade 3-4 related AEs and narrative description for the pediatric population – Important outcome

The scientific committee requests data on the proportion of grade 3-4 adverse events and states that a difference of 5% is clinically relevant. As well as a narrative description of the safety profile for the pediatric population.

Entrectinib grade 3-4 AEs

The overall safety profile of entrectinib in the paediatric and adolescent populations is similar to the safety profile in adults [27].

In the paediatric safety population (n=29) of the updated integrated safety population (n=504), 16 patients <18 experienced grade ≥3 AEs [28]. For the updated paediatric safety dataset (n=32) it was reported that 21 (65.6%) patients grade ≥3 AEs [28].

Adverse reactions and laboratory abnormalities of Grade 3 or 4 severity occurring more frequently (at least a 5% increased incidence) in paediatric patients compared to adult patients were neutropenia (28.1% vs. 3.4%), weight increased (21.9% vs 6.9%), headache (6.3% vs 0.6%) and bone fractures (12.5% vs 1.9%)

[27]. For the adolescent population safety data were limited, but similar to the adult population. Neutropenia and headache was reported as Grade ≥3 adverse reactions [27].

In the updated dataset, the following treatment related AEs and grade 3-4 AEs were reported (please see Table 21) [68]. There are no qualitative description of paediatric grade 3-4 AEs available besides this data.

Table 19. Treatment related and grade 3-4 adverse events in pediatric patients treated with entrectinib [68]

AEs	Treatment related AEs, n	Grade 3-4, n
Weight increased	14	5
Elevated creatinine	13	0
Anemia	13	0
Nausea	11	0
AST increased	10	1
ALT Increased	10	1
Decreased neutrophils	9	6
Bone fractures	7	0

Please see Section 7.1.6 for description of grade 3-4 related AEs in the integrated safety population.

Entrectinib narrative description of the AE profile

Overall, the safety profile for paediatric population was similar to the adult population. In paediatric patients the safety of entrectinib was based on an extrapolation of data from adult patients in the integrated analysis as well as data from 32 paediatric patients included in the STARTRK-NG trial and 2 patients included in STARTRK-2. 2 of the patients were less than 2 years old, 23 patients were 2-11 years old, 7 patients were 12-17 years old [27]. There are limited safety data in adolescents, however the safety profile in adolescents is similar to the overall safety profile of entrectinib [28].

An overview of the safety profile in the paediatric safety population can be seen in Table 22 [28].

Table 20. Summary of Adverse Events in the pediatric safety population [28]

	Overall paediatric safety population (n=29)	Overall padiatric safety population (n=32)
Any Adverse Events, n (%)	29 (100)	32 (100)
Serious Adverse Events, n (%)	10 (34.5)	14 (43.8)
Grade ≥3 Adverse Events, n (%)	16 (55.2)	21 (65.6)
Adverse Events leading to discontinuation, n (%)	2 (6.9)	3 (9.4)

Adverse Events Leading to dose reduction, n (%)	10 (34.5)	11 (34.4)
Adverse Events Leading to dose interruption, n (%)	12 (41.4)	15 (46.9)
Adverse Events Leading to Death, n (%)	0	0

For a detailed description of the adverse events for paediatric patients, please see Appendix 10.6.

Summary of the safety profile for Rozlytrek

Overall, the available safety data in the paediatric setting are limited, since only 32 subjects who received entrectinib were aged <18 years. Most importantly, only 14/32 paediatric patients had tumours with NTRK 1/2/3 or ROS1 gene fusions, and 7/32 were aged ≥12 and <18 years, as per the claimed indication. The longer median exposure (5.6 months, up to 11.7 months for "on-target" subjects) in the updated analysis allowed, however, for a better characterisation of entrectinib toxicity in younger patients. In this regard, despite some uncertainty due to poor numbers, lack of direct controls and clinical heterogeneity, the paediatric safety profile of entrectinib appears to be overall in line with that observed in adults. Some differences (e.g. a higher incidence of haematological, liver, renal and ocular toxicity, and a greater risk of bone fractures and weight increase) can, however, be noted [28].

EMA 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 [28].

Conclusion

The overall safety profile for adults and paediatrics are similar, but some AEs are seen more often in the paediatric population which includes neutropenia, weight increased, headache and bone fractures. In the updated dataset the most frequent grade 3-4 AEs was weight increase and decreased neutrophils.

8 Other considerations

8.1 Growth modulation index

In the Medicines Council's protocol for the assessment of entrectinib in the NTRK-indication, the scientific committee requested an analysis on the included patients in the trial that compares the PFS and ORR data of entrectinib to the previous line of treatment (known as a growth modulation index).

This analysis has been done for entrectinib in the intrapatient analysis and has been described throughout this application. Results for ORR and PFS have been described in clinical question 1.

[redacted]

[redacted]

8.2 NTRK-Fusion Testing

NTRK fusion testing has been described in section 4.2.

8.3 Prognostic value of NTRK-fusions

The prognostic value of NTRK-fusions still needs to be researched further. This subject has been discussed in Section 5.

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10 Appendices

10.1 Literature search – Inclusion and exclusion criteria and search strings

Table 21. Inclusion and exclusion criteria

	Inclusion criteria	Exclusion criteria
Population	Patients ≥ 12 years of age with locally advanced or metastatic solid cancer, where all other satisfactory treatment options are exhausted.	Other types of populations than the demanded ones Other target mutation than NTRK fusions. Exclusively Asian population
Interventions	Entrectinib Placebo eller best supportive care (BSC)	Other types of intervention than the demanded ones
Outcomes	At least one relevant for protocol (OS, QoL, ORR, PFS, AEs)	Outcomes out of PICO scope
Design	Prospective, randomised clinical trials Prospective/ observational studies Full text only Including outcomes of relevance	Conference abstract, review, case reports Studies that do not report at least one of the critical or important effect measures Retrospective studies
Language	English, Scandinavian	Other language
Publication date	Not specified	Not earlier than 2000
Human/animal	Human only	Veterinary (not human)

Figure 10. Search string for Search 1 (05-07-2020)

Search	Actions	Details	Query	Results	Time
#33	•••	›	Search: **#32 NOT #27**	90	12:13:55
#32	•••	›	Search: **#13 AND #31**	124	12:13:40
#31	•••	›	Search: **#28 OR #29 OR #30**	3,966,412	12:13:27
#30	•••	›	Search: **Registries[mh]**	95,811	12:13:14
#29	•••	›	Search: **observational[tiab] OR case control[tiab] OR cohort[tiab] OR cohorts[tiab] OR follow-up[tiab] OR longitudinal[tiab] OR prospective [tiab] OR retrospective[tiab] OR cross sectional[tiab] OR database[tiab] OR registry[tiab] OR nationwide[tiab]**	2,969,493	12:13:00
#28	•••	›	Search: **Observational Study[pt] OR Epidemiologic Studies[mh:noexp] OR Case Control Studies[mh] OR Cohort Studies[mh] or Cross-Sectional Studies[mh]**	2,502,612	12:12:47
#27	•••	›	Search: **#13 AND #26**	80	12:12:26
#26	•••	›	Search: **#14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25**	4,952,115	12:12:13
#25	•••	›	Search: **Comparative Study[pt] OR Multicenter Study[pt]**	2,085,268	12:11:59
#24	•••	›	Search: **Clinical Trial[pt] OR Clinical Trials as Topic[mesh:noexp]**	984,778	12:11:46
#23	•••	›	Search: **single blind*[tiab] OR double-blind*[tiab] OR triple-blind*[tiab]**	168,729	12:11:34
#22	•••	›	Search: **open-label[tiab]**	42,539	12:11:22
#21	•••	›	Search: **trial[ti] OR study[ti]**	1,568,536	12:11:11
#20	•••	›	Search: **comparative[tiab] AND (trial[tiab] OR study[tiab])**	196,420	12:11:01
#19	•••	›	Search: **multicenter[tiab] OR multi-center[tiab] OR multicentre[tiab] OR multi-centre[tiab]**	154,091	12:10:48
#18	•••	›	Search: **enrolled[tiab]**	299,216	12:10:35

#17	•••	›	Search: **phase 1*[tiab] OR phase 2*[tiab] OR phase 3*[tiab] OR phase I* [tiab]**	208,059	12:10:23
#16	•••	›	Search: **control group*[tiab] OR control arm[tiab]**	461,296	12:10:11
#15	•••	›	Search: **controlled trial[tiab] OR controlled study[tiab]**	171,698	12:09:55
#14	•••	›	Search: **randomized[tiab] OR randomised[tiab] OR randomly[tiab] OR placebo[tiab] OR sham*[tiab] OR dummy*[tiab]**	1,045,262	12:09:43
#13	•••	›	Search: **#8 NOT #12**	413	12:09:30
#12	•••	›	Search: **#9 OR #10 OR #11**	11,198,859	12:09:17
#11	•••	›	Search: **Case Reports[pt] OR Comment[pt] OR Editorial[pt] OR Letter[pt] OR Guideline[pt] OR Review[pt] OR Systematic Review[pt] OR case report[ti] OR review[ti]**	6,478,910	12:09:04
#10	•••	›	Search: **animal*[ti] OR murine[ti] OR mouse[ti] OR mice[ti] OR rat[ti] OR rats[ti] OR rodent[ti]**	1,527,672	12:08:50
#9	•••	›	Search: **Animals[mh] NOT Humans [mh]**	4,714,751	12:08:38
#8	•••	›	Search: **#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7**	788	12:08:22
#7	•••	›	Search: **TRK[tiab] AND (fusion[tiab] OR fusions[tiab]) AND (cancer[tiab] OR cancers[tiab])**	138	12:08:10
#6	•••	›	Search: **TRK[tiab] AND (fusion[tiab] OR fusions[tiab]) AND proteins [tiab]**	62	12:07:58
#5	•••	›	Search: **TRK[tiab] AND (fusion[tiab] OR fusions[tiab]) AND positive[tiab]**	82	12:07:46
#4	•••	›	Search: **neurotrophi*[tiab] AND tropomyosin receptor kinase*[tiab] AND (fusion[tiab] OR fusions[tiab])**	39	12:07:34
#3	•••	›	Search: **neurotrophi*[tiab] AND (TRK[tiab] OR TRKA[tiab] OR TRKB[tiab] OR TRKC[tiab]) AND (fusion[tiab] OR fusions[tiab])**	154	12:07:23
#2	•••	›	Search: **(NTRK[tiab] OR NTRK1[tiab] OR NTRK2[tiab] OR NTRK3[tiab]) AND (fusio…[tiab] OR fusions[tiab])**	589	12:07:09
#1	•••	›	Search: **entrectinib[nm] OR entrectinib[tiab] OR Rozlytrek*[tiab] OR NMS-E628[tiab] OR RXDX-101[tiab]**	111	12:06:38

Figure 11. Search string for Search 2 (21-06-2020)

#1	entrectinib:kw	Limits	4
#2	(entrectinib or Rozlytrek* or "NMS E628" or "RXDX 101"):ti,ab	Limits	8
#3	((NTRK OR NTRK1 OR NTRK2 OR NTRK3) NEAR/5 (fusion OR fusions)):ti,ab	Limits	6
#4	neurotrophi*:ti,ab AND (TRK OR TRKA OR TRKB OR TRKC):ti,ab AND (fusion OR fusions):ti,ab	Limits	3
#5	neurotrophi*:ti,ab AND (tropomyosin NEXT receptor NEXT kinase*):ti,ab AND (fusion OR fusions):ti,ab	Limits	0
#6	TRK:ti,ab AND (fusion OR fusions):ti,ab AND positive:ti,ab	Limits	2
#7	TRK:ti,ab AND (fusion OR fusions):ti,ab AND proteins:ti,ab	Limits	0
#8	TRK:ti,ab AND (fusion OR fusions):ti,ab AND (cancer OR cancers):ti,ab	Limits	4
#9	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8	Limits	16
#10	("conference abstract" OR review):pt	Limits	173437
#11	NCT*:au	Limits	190433
#12	("clinicaltrials.gov" OR trialsearch):so	Limits	327385
#13	#10 OR #11 OR #12	Limits	500968
#14	#9 NOT #13	Limits	2

Figure 12. Search string for Search 3 (02-07-2020)

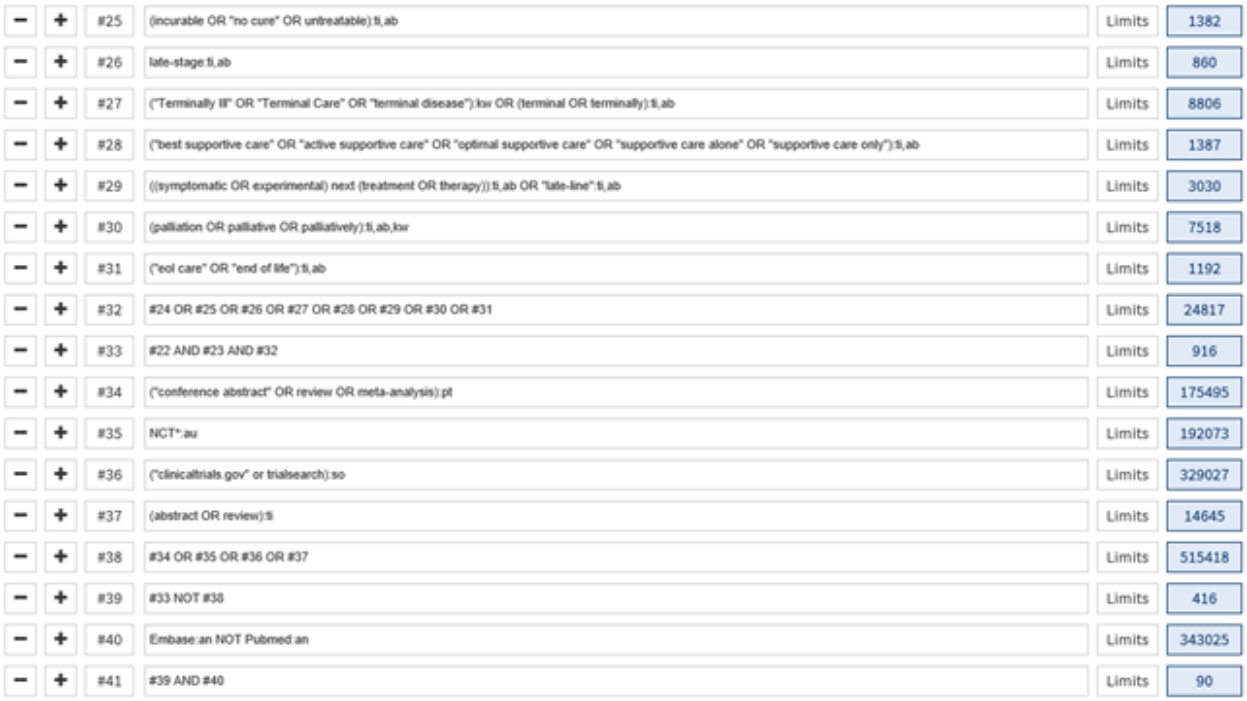
Search	Actions	Details	Query	Results	Time
#38	•••	›	Search: **#36 NOT #37**	429	07:43:25
#37	•••	›	Search: **Case Reports[pt] OR Comment[pt] OR Editorial[pt] OR Guideline [pt] OR Letter[pt] OR Meta-Analysis[pt] OR News[pt] OR Observational Study[pt] OR Review[pt] OR Systematic Review[pt] OR case report[ti] OR meta-analysis[tiab] OR review[ti] OR Retrospective Studies[mh] OR retrospective[ti] OR systematic review[tiab]**	7,569,323	07:43:10
#36	•••	›	Search: **#33 AND #34 AND #35**	692	07:42:56
#35	•••	›	Search: **English[la]**	26,468,008	07:42:44
#34	•••	›	Search: **(Randomized Controlled Trial[pt] OR Controlled Clinical Trial[pt] OR randomized[tiab] OR randomised[tiab] OR placebo[tiab] OR randomly[tiab] OR random allocation[tiab] OR trial[ti]) NOT (Animals [mh] NOT Humans [mh])**	1,104,817	07:42:28
#33	•••	›	Search: **#22 AND #23 AND #32**	4,322	07:42:12
#32	•••	›	Search: **#24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31**	610,253	07:42:00
#31	•••	›	Search: **eol care[tiab] OR end of life[tiab]**	23,511	07:41:48
#30	•••	›	Search: **Palliative Care[mh] OR palliation[tiab] OR palliative[tiab] OR palliatively[tiab]**	94,745	07:41:37
#29	•••	›	Search: **symptomatic treatment[tiab] OR symptomatic therapy[tiab] OR experimental treatment[tiab] OR late-line[tiab]**	11,345	07:41:25
#28	•••	›	Search: **best supportive care[tiab] OR active supportive care[tiab] OR optimal supportive care[tiab] OR supportive care alone[tiab] OR supportive care only[tiab]**	2,723	07:41:12
#27	•••	›	Search: **Terminally Ill[mh] OR Terminal Care[mh] OR (terminal[tiab] NOT terminal half-life[tiab]) OR terminally[tiab]**	464,500	07:41:02
#26	•••	›	Search: **late stage[tiab]**	22,099	07:40:50
#25	•••	›	Search: **incurable[tiab] OR "no cure"[tiab] OR untreatable[tiab]**	17,034	07:40:40
#24	•••	›	Search: **treatment resistant[tiab] OR treatment resistance[tiab] OR chemotherapy resistant[tiab]**	13,402	07:40:28

#23	•••	>	Search: **metastatic[ti] OR metastasis[ti] OR metastases[ti] OR advanced [ti] OR recurrent[ti] OR refractory[ti]**	383,966	07:40:17
#22	•••	>	Search: **#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21**	451,692	07:40:07
#21	•••	>	Search: **glioblastoma[ti] OR glioma[ti] OR astrocytoma[ti] OR oligodendroglioma[ti] OR primary cerebral lymphoma[ti]**	44,060	07:39:54
#20	•••	>	Search: **primary[ti] AND (CNS[ti] OR central nervous system[ti] OR brain [ti]) AND (cancer[ti] OR tumour[ti] OR tumor[ti] OR lymphoma[ti])**	2,713	07:39:42
#19	•••	>	Search: **(pancreatic[ti] OR pancreas[ti]) AND (cancer[ti] OR carcinoma[ti] OR adenocarcinoma[ti])**	39,138	07:39:29
#18	•••	>	Search: **congenital mesoblastic nephroma[ti]**	200	07:39:16
#17	•••	>	Search: **breast[ti] AND secretory[ti] AND (carcinoma[ti] OR carcinomas [ti])**	136	07:39:03
#16	•••	>	Search: **(appendiceal[ti] OR appendix[ti]) AND (cancer[ti] OR carcinoma [ti])**	464	07:38:51
#15	•••	>	Search: **(bile duct*[ti] OR biliary duct*[ti]) AND (carcinoma[ti] OR cancer [ti])**	1,894	07:38:37
#14	•••	>	Search: **cholangiocarcinoma[ti]**	7,510	07:38:25
#13	•••	>	Search: **melanoma[ti]**	65,658	07:38:14
#12	•••	>	Search: **NSCLC[ti] OR non-small cell lung cancer[ti] OR nonsmall cell lung cancer[ti]**	40,752	07:38:02
#11	•••	>	Search: **lung[ti] AND (adenocarcinoma[ti] OR carcinoma[ti])**	21,601	07:37:48
#10	•••	>	Search: **GIST[ti]**	1,511	07:37:36
#9	•••	>	Search: **gastrointestinal stromal[ti] AND (tumor[ti] OR tumour[ti] OR tumors[ti] OR tumours[ti])**	5,801	07:37:26
#8	•••	>	Search: **(thyroid[ti] OR parathyroid[ti]) AND (cancer[ti] OR carcinoma[ti] OR adenocarcinoma[ti])**	31,883	07:37:17

#7	•••	›	Search: **(bowel[ti] OR colon[ti] OR colonic[ti] OR colorectal[ti] OR rectal [ti] OR rectum[ti] OR sigmoid[ti] OR intestinal[ti]) AND (cancer[ti] OR carcinoma[ti] OR adenocarcinoma[ti])**	125,983	07:37:06
#6	•••	›	Search: **(salivary[ti] OR parotid[ti] OR submandibular[ti] OR sublingual [ti]) AND (gland[ti] OR glands[ti]) AND (masc[ti] OR cancer[ti] OR carcinoma[ti] OR adenocarcinoma[ti])**	3,078	07:36:54
#5	•••	›	Search: **MASC[ti] OR mammary analogue secretory carcinoma[ti]**	143	07:36:41
#4	•••	›	Search: **bone cancer[ti] OR bone sarcoma[ti] OR Ewing sarcoma[ti] OR osteosarcoma[ti]**	16,157	07:36:09
#3	•••	›	Search: **angiosarcoma[ti] OR hemangiosarcoma[ti] OR chondrosarcoma [ti] OR fibromyxosarcoma[ti] OR fibrosarcoma[ti] OR infantile fibrosarcoma[ti] OR myxofibrosarcoma[ti] OR leiomyosarcoma[ti] OR liposarcoma[ti] OR malignant mesenchymoma[ti] OR malignant mesenchymal tumor[ti] OR neurofibrosarcoma[ti] OR rhabdomyosarcoma[ti] OR synovial sarcoma[ti] OR spindle cell sarcoma [ti]**	28,941	07:35:50
#2	•••	›	Search: **(soft tissue[ti] OR soft-part[ti] OR connective tissue[ti]) AND (sarcoma[ti] OR sarcomas[ti] OR cancer[ti] OR cancers[ti])**	7,271	07:35:39
#1	•••	›	Search: **solid[ti] AND (tumor[ti] OR tumors[ti] OR tumour[ti] OR tumours[ti])**	11,277	07:35:26

Figure 13. Search string for Search 4 (05-07-2020)

#1	solid:ti AND (tumor OR tumors OR tumour OR tumours):ti	Limits	1324
#2	(soft tissue OR soft-part OR connective tissue):ti AND (sarcoma OR sarcomas OR cancer OR cancers):ti	Limits	716
#3	(angiosarcoma OR hemangiosarcoma OR chondrosarcoma OR fibromyxosarcoma OR fibrosarcoma OR infantile fibrosarcoma OR myxofibrosarcoma OR leiomyosarcoma OR liposarcoma OR "malignant mesenchymoma" OR "malignant mesenchymal tumor" OR neurofibrosarcoma OR rhabdomyosarcoma OR synovial next sarcoma OR spindle next cell next sarcoma):ti	Limits	274
#4	(bone next cancer OR bone next sarcoma OR "Ewing sarcoma" OR osteosarcoma):ti	Limits	462
#5	(MASC OR "mammary analogue secretory carcinoma"):ti	Limits	3
#6	(salivary OR parotid OR submandibular OR sublingual):ti AND (gland OR glands):ti AND (masc OR cancer OR carcinoma OR adenocarcinoma):ti	Limits	71
#7	(bowel OR colon OR colonic OR colorectal OR rectal OR rectum OR sigmoid OR intestinal):ti AND (cancer OR carcinoma OR adenocarcinoma):ti	Limits	13085
#8	(thyroid OR parathyroid):ti AND (cancer OR carcinoma OR adenocarcinoma):ti	Limits	709
#9	"gastrointestinal stromal":ti AND (tumor OR tumour OR tumors OR tumours):ti	Limits	241
#10	GIST:ti	Limits	169
#11	lung:ti AND (adenocarcinoma OR carcinoma):ti	Limits	925
#12	(NSCLC OR "non-small cell lung cancer" OR "nonsmall cell lung cancer"):ti	Limits	8086
#13	melanoma:ti	Limits	3418
#14	cholangiocarcinoma:ti	Limits	222
#15	(bile next duct* OR biliary next duct*):ti AND (carcinoma OR cancer):ti	Limits	58
#16	(appendiceal OR appendix):ti AND (cancer OR carcinoma):ti	Limits	5
#17	breast:ti AND secretory:ti AND (carcinoma OR carcinomas):ti	Limits	0
#18	congenital next mesoblastic next nephroma:ti	Limits	0
#19	(pancreatic OR pancreas):ti AND (cancer OR carcinoma OR adenocarcinoma):ti	Limits	3227
#20	primary:ti AND (CNS OR "central nervous system" OR brain):ti AND (cancer OR tumour OR tumor OR lymphoma):ti	Limits	168
#21	(glioblastoma OR glioma OR astrocytoma OR oligodendroglioma OR "primary cerebral lymphoma"):ti	Limits	2072
#22	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21	Limits	34890
#23	(metastatic OR metastasis OR metastases OR advanced OR recurrent OR refractory):ti	Limits	59554
#24	((treatment OR chemotherapy) next (resistant OR resistance)):ti,ab	Limits	2865



#25	(incurable OR "no cure" OR untreatable):ti,ab	Limits	1382
#26	late-stage:ti,ab	Limits	860
#27	("Terminally Ill" OR "Terminal Care" OR "terminal disease"):kw OR (terminal OR terminally):ti,ab	Limits	8806
#28	("best supportive care" OR "active supportive care" OR "optimal supportive care" OR "supportive care alone" OR "supportive care only"):ti,ab	Limits	1387
#29	((symptomatic OR experimental) next (treatment OR therapy)):ti,ab OR "late-line":ti,ab	Limits	3030
#30	(palliation OR palliative OR palliatively):ti,ab,kw	Limits	7518
#31	("eol care" OR "end of life"):ti,ab	Limits	1192
#32	#24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31	Limits	24817
#33	#22 AND #23 AND #32	Limits	916
#34	("conference abstract" OR review OR meta-analysis):pt	Limits	175495
#35	NCT*:au	Limits	192073
#36	("clinicaltrials.gov" or trialsearch):so	Limits	329027
#37	(abstract OR review):ti	Limits	14645
#38	#34 OR #35 OR #36 OR #37	Limits	515418
#39	#33 NOT #38	Limits	416
#40	Embase:an NOT Pubmed:an	Limits	343025
#41	#39 AND #40	Limits	90

10.2 Literature search – Prisma Flow Diagrams

Figure 14. Prisma Flow Diagram for Search 1

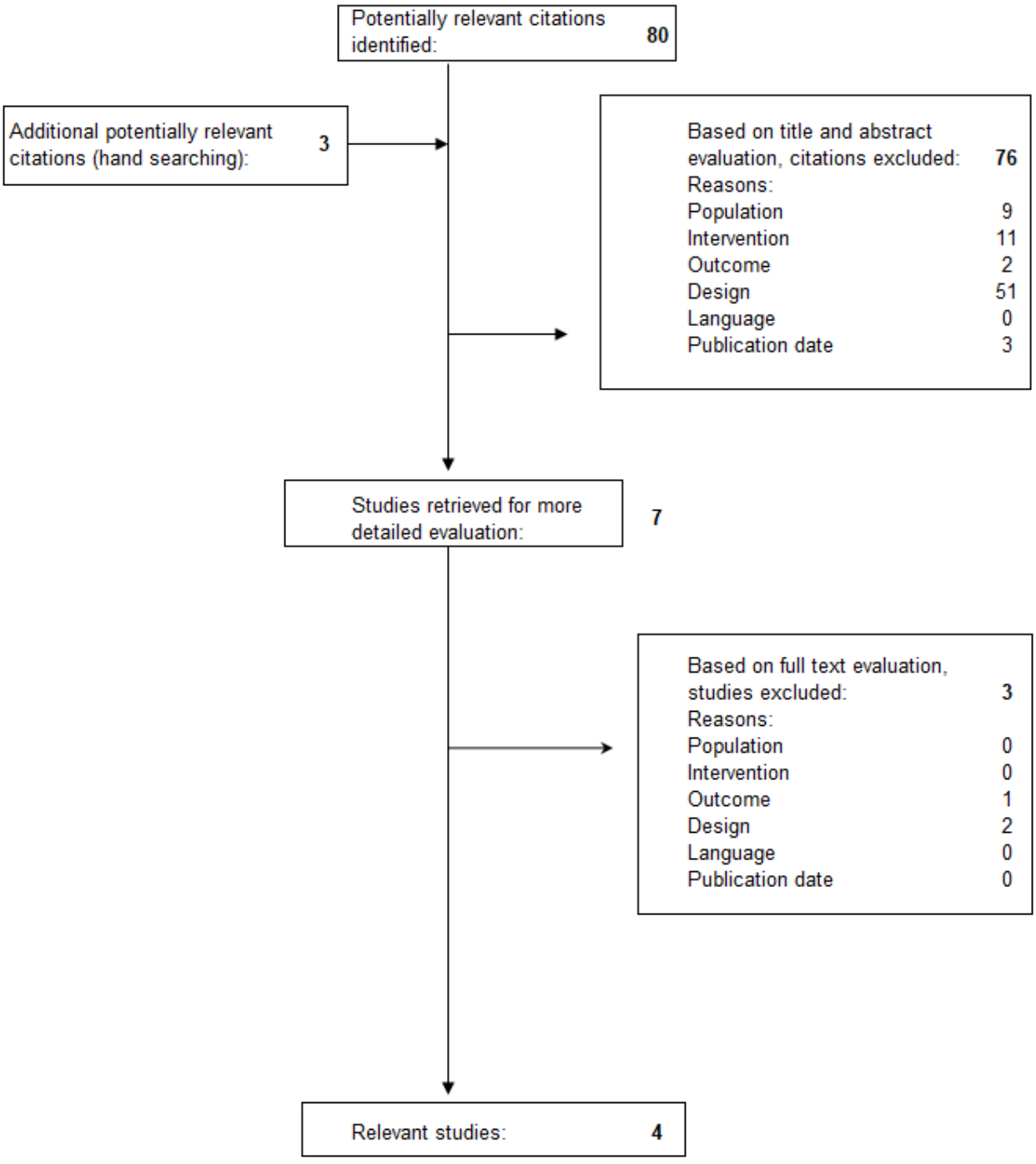


Figure 15. Prisma Flow Diagram for Search 1b

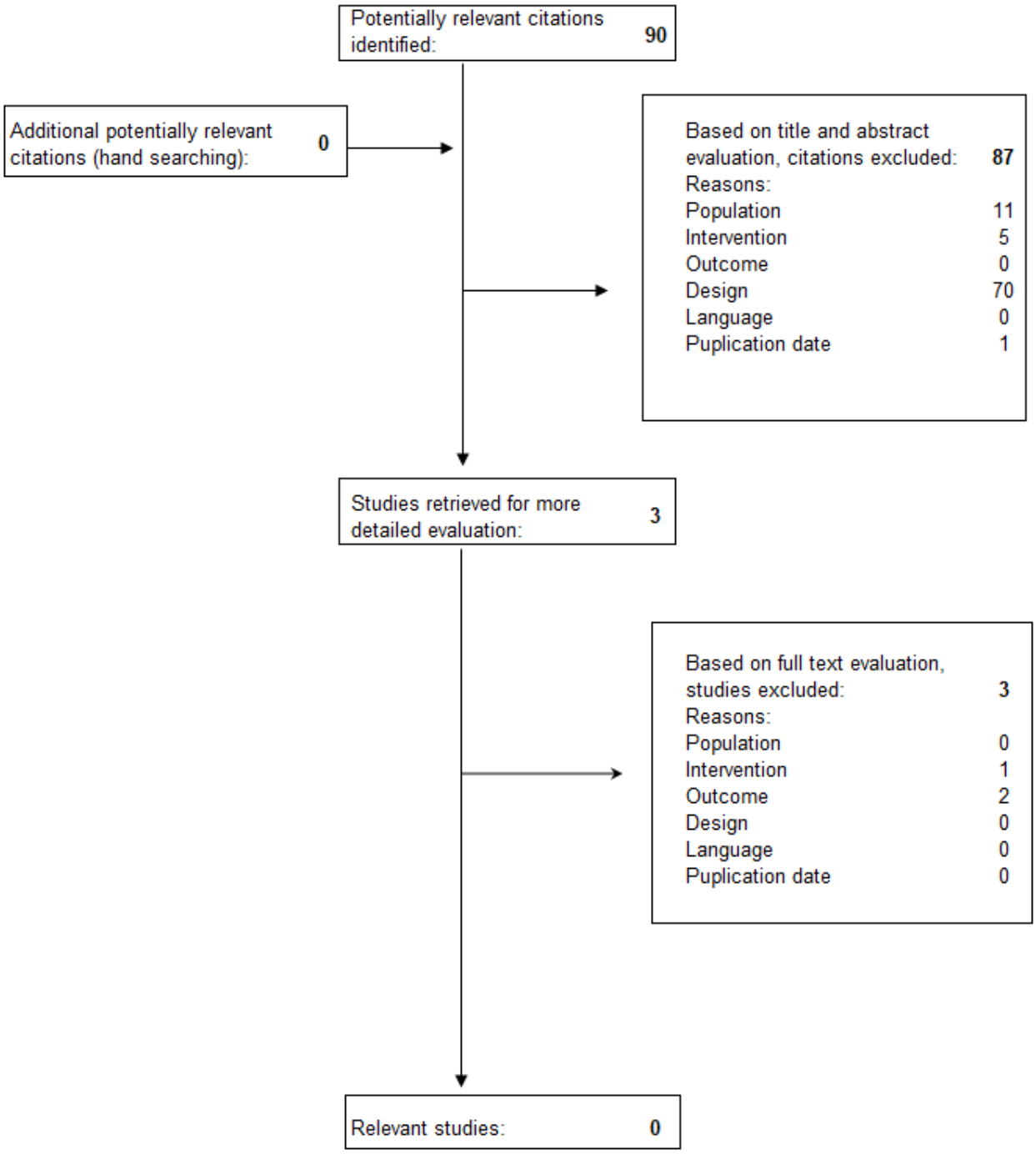


Figure 16. Prisma Flow Diagram for Search 2

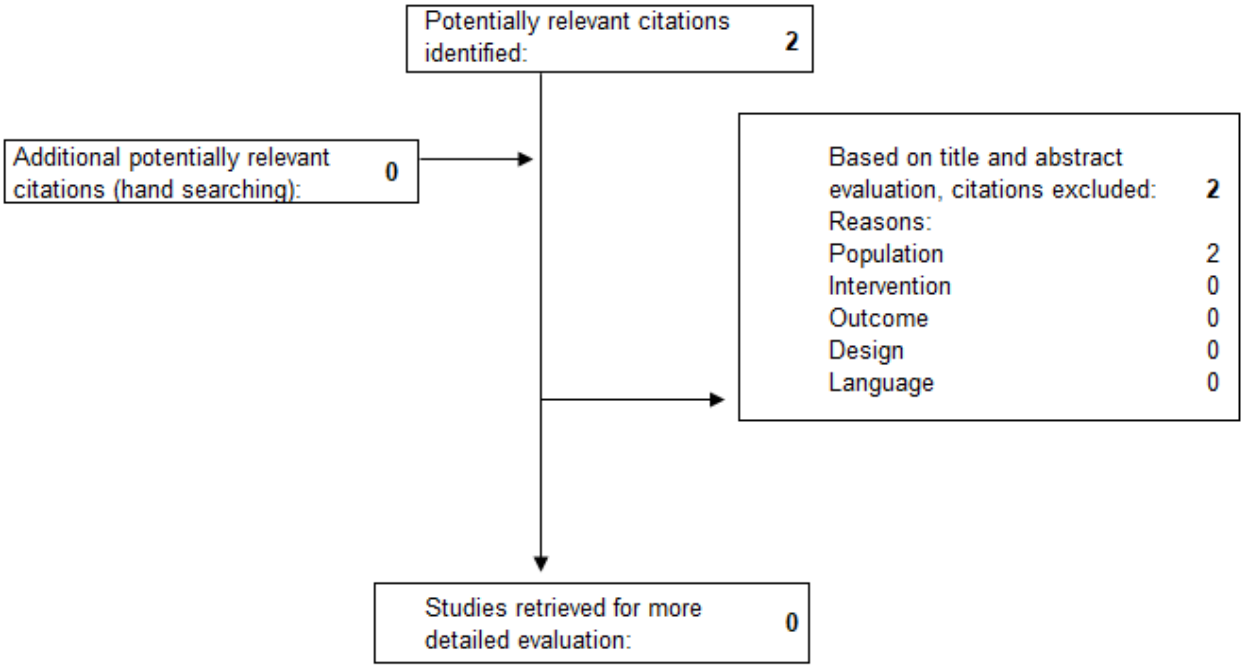


Figure 17. Prisma Flow Diagram for Search 3

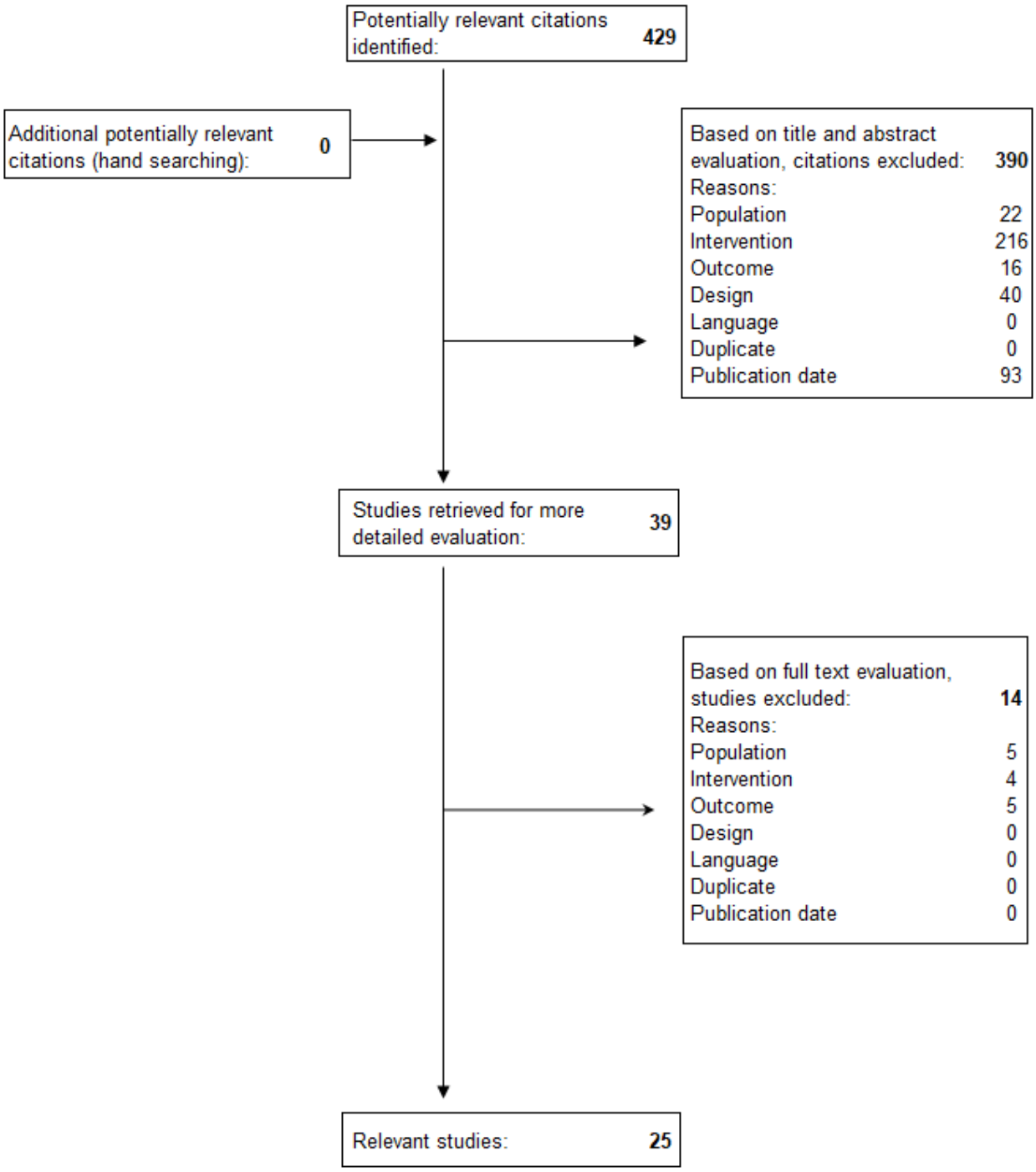


Figure 18. Prisma Flow Diagram for Search 4

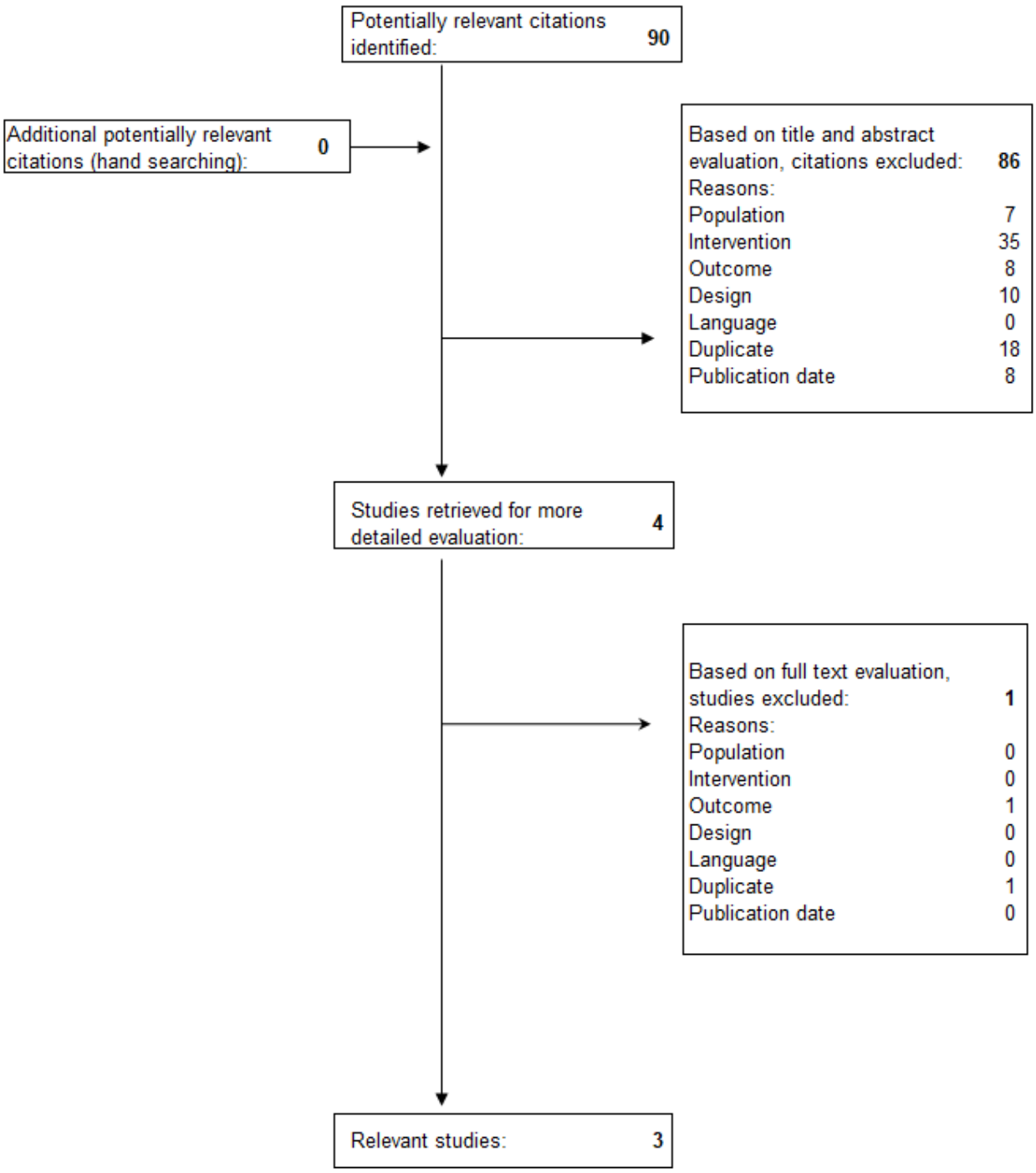


Table 22. Overview of excluded full text articles

Author	Journal and year	Title	Reason	Search
Alvarez-Breckenridge, C., Miller, J. J., Nayyar, N., Gill, C. M., Kaneb, A., D'Andrea, M., Le, L. P., Lee, J., Cheng, J., Zheng, Z., Butler, W. E., Multani, P., Chow Maneval, E., Ha Paek, S., Toyota, B. D., Dias-Santagata, D., Santagata, S., Romero, J., Shaw, A. T., Farago, A. F., Yip, S., Cahill, D. P., Batchelor, T. T., Iafrate, A. J. and Brastianos, P. K.	NPJ Precis Oncol, 2017	Clinical and radiographic response following targeting of BCAN-NTRK1 fusion in glioneuronal tumor	Design: Case description	Search 1
Drilon, A., Siena, S., Ou, S. I., Patel, M., Ahn, M. J., Lee, J., Bauer, T. M., Farago, A. F., Wheler, J. J., Liu, S. V., Doebele, R., Giannetta, L., Cerea, G., Marrapese, G., Schirru, M., Amatu, A., Bencardino, K., Palmeri, L., Sartore-Bianchi,	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)	Previous analysis of entrectinib data	Search 1

A., Vanzulli, A., Cresta, S., Damian, S., Duca, M., Ardini, E., Li, G., Christiansen, J., Kowalski, K., Johnson, A. D., Patel, R., Luo, D., Chow-Maneval, E., Hornby, Z., Multani, P. S., Shaw, A. T. and De Braud, F. G.				
Sigal, D., Tartar, M., Xavier, M., Bao, F., Foley, P., Luo, D., Christiansen, J., Hornby, Z., Maneval, E. C. and Multani, P.	J Natl Compr Canc Netw, 2017	Activity of Entrectinib in a Patient With the First Reported NTRK Fusion in Neuroendocrine Cancer	Design: Case report	Search 1
NS, I. Jzerman, Drabbe, C., den Hollander, D., Mohammadi, M., van Boven, H., Desar, I. M. E., Gelderblom, H., Grünhagen, D. J., Reyners, A. K. L., van Noesel, M. M., Mathijssen, R. H. J., Steeghs, N. and van der Graaf, W. T. A.	Cancers (Basel,) 2020	Gastrointestinal Stromal Tumours (GIST) in Young Adult (18-40 Years) Patients: A Report from the Dutch GIST Registry	Study did not include any relevant interventions (entrectinib or BSC)	Search 1b

Pekova, B., Sykorova, V., Dvorakova, S., Vaclavikova, E., Moravcova, J., Katra, R., Astl, J., Vlcek, P., Kodetova, D., Vcelak, J. and Bendlova, B.	Thyroid, 2020	RET, NTRK, ALK, BRAF and MET fusions in a large cohort of pediatric papillary thyroid carcinomas	Study did not include any of the outcomes in the protocol	Search 1b
Ross, D. S., Liu, B., Schram, A. M., Razavi, P., Lagana, S. M., Zhang, Y., Scaltriti, M., Bromberg, J. F., Ladanyi, M., Hyman, D. M., Drilon, A., Zehir, A., Benayed, R., Chandarlapaty, S. and Hechtman, J. F.	Ann Oncol, 2020	Enrichment of kinase fusions in ESR1 wild-type, metastatic breast cancer revealed by a systematic analysis of 4854 patients	Study did not include any of the outcomes in the protocol	Search 1b
Temel, J. S., Greer, J. A., Muzikansky, A., Gallagher, E. R., Admane, S., Jackson, V. A., Dahlin, C. M., Blinderman, C. D., Jacobsen, J., Pirl, W. F., Billings, J. A. and Lynch, T. J.	N Engl J Med, 2010	Early palliative care for patients with metastatic non-small-cell lung cancer	Does not include BSC arm and is in an early setting	Search 3

Asmis, T. R., Powell, E., Karapetis, C. S., Jonker, D. J., Tu, D., Jeffery, M., Pavlakis, N., Gibbs, P., Zhu, L., Dueck, D. A., Whittom, R., Langer, C. and O'Callaghan, C. J.	Ann Oncol, 2011	Comorbidity, age and overall survival in cetuximab-treated patients with advanced colorectal cancer (ACRC)--results from NCIC CTG CO.17: a phase III trial of cetuximab versus best supportive care	OS only reported as a hazard ratio	Search 3
Koch, A., Bergman, B., Holmberg, E., Sederholm, C., Ek, L., Kosieradzki, J., Lamberg, K., Thaning, L., Ydreborg, S. O. and Sörenson, S.	Eur J Cancer, 2011	Effect of celecoxib on survival in patients with advanced non-small cell lung cancer: a double blind randomised clinical phase III trial (CYCLUS study) by the Swedish Lung Cancer Study Group	Intervention: Only palliative chemo included	Search 3
Belani, C. P., Brodowicz, T., Ciuleanu, T. E., Krzakowski, M., Yang, S. H., Franke, F., Cucevic, B., Madhavan, J., Santoro, A., Ramlau, R., Liepa, A. M., Visseren-Grul, C., Peterson, P., John, W. J. and Zielinski, C. C.	Lancet Oncol, 2012	Quality of life in patients with advanced non-small-cell lung cancer given maintenance treatment with pemetrexed versus placebo (H3E-MC-JMEN): results from a randomised, double-blind, phase 3 study	Outcome: No relevant outcomes. PRO reported via LCSS.	Search 3

Miller, V. A., Hirsh, V., Cadranel, J., Chen, Y. M., Park, K., Kim, S. W., Zhou, C., Su, W. C., Wang, M., Sun, Y., Heo, D. S., Crino, L., Tan, E. H., Chao, T. Y., Shahidi, M., Cong, X. J., Lorence, R. M. and Yang, J. C.	Lancet Oncol, 2012	Afatinib versus placebo for patients with advanced, metastatic non-small-cell lung cancer after failure of erlotinib, gefitinib, or both, and one or two lines of chemotherapy (LUX-Lung 1): a phase 2b/3 randomised trial	Population: Outcomes reported for EGFR-positive patients	Search 3
Yoshino, T., Mizunuma, N., Yamazaki, K., Nishina, T., Komatsu, Y., Baba, H., Tsuji, A., Yamaguchi, K., Muro, K., Sugimoto, N., Tsuji, Y., Moriwaki, T., Esaki, T., Hamada, C., Tanase, T. and Ohtsu, A.	Lancet Oncol, 2021	TAS-102 monotherapy for pretreated metastatic colorectal cancer: a double-blind, randomised, placebo-controlled phase 2 trial	Population: Japanese patients	Search 3
Kim, T. W., Elme, A., Kusic, Z., Park, J. O., Udrea, A. A., Kim, S. Y., Ahn, J. B., Valencia, R. V., Krishnan, S., Bilic, A., Manojlovic, N., Dong, J., Guan, X., Lofton-Day, C., Jung, A. S. and Vrdoljak, E.	Br J Cancer, 2016	A phase 3 trial evaluating panitumumab plus best supportive care vs best supportive care in chemorefractory wild-type KRAS or RAS metastatic colorectal cancer	Outcome: Previous analysis of included study	Search 3

Rodriguez, P. C., Popa, X., Martínez, O., Mendoza, S., Santiesteban, E., Crespo, T., Amador, R. M., Fleytas, R., Acosta, S. C., Otero, Y., Romero, G. N., de la Torre, A., Cala, M., Arzuaga, L., Vello, L., Reyes, D., Futiel, N., Sabates, T., Catala, M., Flores, Y. I., Garcia, B., Viada, C., Lorenzo-Luaces, P., Marrero, M. A., Alonso, L., Parra, J., Aguilera, N., Pomares, Y., Sierra, P., Rodríguez, G., Mazorra, Z., Lage, A., Crombet, T. and Neninger, E.	Clin Cancer Res, 2016	A Phase III Clinical Trial of the Epidermal Growth Factor Vaccine CIMAvax-EGF as Switch Maintenance Therapy in Advanced Non-Small Cell Lung Cancer Patients	Intervention: early treatment line	Search 3
Khosravi, A., Esfahani-Monfared, Z., Seifi, S. and Khodadad, K.	Tanaffos, 2017	Prospective Randomized Phase II Parallel Study of Vinorelbine Maintenance Therapy versus Best Supportive Care in Advanced Non-Small Cell Lung Cancer	Intervention: Early treatment line	Search 3

Longo-Muñoz, F., Argiles, G., Tabernero, J., Cervantes, A., Gravalos, C., Pericay, C., Gil-Calle, S., Mizuguchi, H., Carrato-Mena, A., Limón, M. L. and Garcia-Carbonero, R.	Clin Transl Oncol, 2017	Efficacy of trifluridine and tipiracil (TAS-102) versus placebo, with supportive care, in a randomized, controlled trial of patients with metastatic colorectal cancer from Spain: results of a subgroup analysis of the phase 3 RECOURSE trial	Outcome: Results described elsewhere in included article on the RECOURSE trial	Search 3
Xu, R. H., Li, J., Bai, Y., Xu, J., Liu, T., Shen, L., Wang, L., Pan, H., Cao, J., Zhang, D., Fan, S., Hua, Y. and Su, W.	J Hematol Oncol, 2017	Safety and efficacy of fruquintinib in patients with previously treated metastatic colorectal cancer: a phase Ib study and a randomized double-blind phase II study	Population: Asian	Search 3
Liao, X., Li, H., Liu, Z., Liao, S., Li, Q., Liang, C., Huang, Y., Xie, M., Wei, J. and Li, Y.	Medicine (Baltimore), 2018	Clinical efficacy and safety of apatinib in patients with advanced colorectal cancer as the late-line treatment	Population: Asian	Search 3
Lozanovski, V. J., Polychronidis, G., Gross, W., Gharabaghi, N., Mehrabi, A., Hackert, T., Schemmer, P. and Herr, I.	Invest New Drugs, 2020	Broccoli sprout supplementation in patients with advanced pancreatic cancer is difficult despite positive effects-results from the POUDER pilot study	Outcome: No data on palliative treatment	Search 3

Ou, J., Zhu, X., Chen, P., Du, Y., Lu, Y., Peng, X., Bao, S., Wang, J., Zhang, X., Zhang, T. and Pang, C. L. K.	J Adv Res, 2020	A randomized phase II trial of best supportive care with or without hyperthermia and vitamin C for heavily pretreated, advanced, refractory non-small-cell lung cancer	Population: Asian	Search 3
Galun, D., Troger, W., Reif, M., Schumann, A., Stankovic, N. and Milicevic, M.	Annals of oncology., 2012	Mistletoe extract therapy versus no antineoplastic therapy in patients with locally advanced or metastatic pancreatic cancer: a randomized clinical phase III trial on overall survival	Results of this study have been described for a later datacut in an included article.	Search 4

10.3 Main characteristics of included studies

Table 23. Main study characteristics of ALKA-372-001	
Trial name	ALKA-372-001
NCT number	EudraCT nr: 2012-000148-88 (Not registered in Clinicaltrials.gov)
Objective	ALKA-372-001: First-in-human dose-escalation study.
Publications – title, author, journal, year	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); Drilon et al; Cancer discov; 2017.
Study type and design	Phase I, first-in-human, multicenter, open-label, ascending-dose study
Follow-up time	Not reported

Population (inclusion and exclusion criteria)	Consenting adult (age≥18) patients with histologically or cytologically confirmed diagnosis of advanced/metastatic solid tumours with ALK positive alterations (per original protocol) or ALK negative patients with TRKA, TRKB, TRKC, or ROS1 genetic alterations (ALK negative patients with TRKA or ROS1 genetic alterations only up to protocol amendment 5) in patients for whom no alternative effective standard therapy was available, standard therapy was considered unsuitable, or had been refused (per protocol amendment 8), were eligible for the study. Other main selection criteria included: ECOG PS ≤2; life expectancy of at least 3 months; baseline laboratory data indicating acceptable hematologic status, liver and renal function; resolution of any acute toxic effects (excluding alopecia) of any prior anticancer therapy (NCI CTCAE v 4.03 grade ≤1 or to the baseline laboratory values); tissue available for analysis. Patients with controlled asymptomatic CNS involvement were eligible in absence of therapy with anticonvulsant (from protocol amendment 8, non-enzyme-inducing anti-epileptic drugs were allowed). Steroids at stable dose (≤4 mg/day dexamethasone or equivalent) for at least 2 weeks were allowed. Prior cancer therapy was allowed including crizotinib, ceritinib (added with protocol amendment 6) and other investigational drugs. From protocol amendment 8 onwards, prior TRK, ROS1, or ALK (all other than NSCLC patients only) inhibitors were no longer allowed in patients who had tumours harboring those respective molecular alterations.
Intervention	Rozlytrek was administered orally in three dose schedules: ● Schedule A (n=19): 100, 200, 400, 800, 1200, or 1600 mg/m^2 once daily (fasted) 4-days on, 3-days off schedule x 3 weeks followed by 7-day rest in a 4-week cycle. ● Schedule B (n=32): 200, 400 mg/m^2 or 600 mg con-tinuous once daily (fed) in a 4-week cycle; ● Schedule C (n=6): 400 or 800 mg/m^2 once daily (fed) in a continuous 4-days on, 3-days off schedule in a 4-week cycle.

	As of 30 Nov 2017, 58 patients were enrolled, and 57 received entrectinib. The study is ongoing. Two patients were still receiving treatment at the CCOD.
Baseline characteristics	Tumour molecular characterization performed before starting treatment with entrectinib showed the presence of a TRKA/B/C, ROS1, or ALK molecular alterations in all treated patients except for one patient who had SCLC without genetic alterations of interest but enrolled in the study with a waiver.
Primary and secondary endpoints	Primary endpoint: ● First cycle dose-limiting toxicities (DLTs) and maximum tolerated dose (MTD). Secondary endpoints: ● Overall safety profile of entrectinib ● PK parameters ● Objective tumour response as measured using RECIST v1.1 as determined by investigator (DOR, SD duration, PFS and OS were exploratory analyses). On treatment tumour assessment was repeated at the end of every even (i.e. end of cycle 2, 4, 6 etc., per the original protocol) or odd cycle (per protocol amendment 6) and at the end of last treatment cycle, if more than 4 weeks had passed from last tumour imaging. For patient treated for longer than 12 cycles, assessment was performed every 3 cycles (per protocol amendment 6). Patients with responding tumours (CR or PR) were required to have the response confirmed at least 4 weeks after the 1st documentation of response. Amendment 8 allowed a blinded independent central review of imaging for retrospective (ongoing patients) and prospective (newly enrolled patients).
Method of analysis	58 patients with advanced/ metastatic solid tumours with TRKA/B/C, ROS1, or ALK positive genetic alterations were enrolled, 57 received entrectinib, 54 patients were evaluable for DLT and 54 for efficacy. Efficacy analyses were carried out on treated and evaluable patients. Point estimates with 95% confidence intervals (CIs) are calculated for efficacy endpoints (ORR, DOR, SD duration, PFS, and OS). Time-to-event endpoints

	were summarized using the Kaplan-Meier method. No formal significance testing was performed. Missing data were not imputed.
Subgroup analyses	NA

Table 24. Main study characteristics of STARTRK-1	
Trial name	STARTRK-1
NCT number	NCT02097810
Objective	Safety and tolerability of entrectinib via standard dose escalation scheme and determine the recommended Phase 2 dose. Safety and efficacy will be assessed in the dose expansion portion of the study.
Publications – title, author, journal, year	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); Drilon et al; Cancer discov; 2017.
Study type and design	Phase I, single-arm, multicenter, open-label, dose escalation and expansion, ascending-dose study with dose escalation 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.
Follow-up time	Not reported
Population (inclusion and exclusion criteria)	Patients with locally advanced or metastatic cancer with a detectable molecular alteration in targets of interest may be eligible for enrollment (TrkA (coded by the gene NTRK1), TrkB (coded by the gene NTRK2), TrkC (coded by the gene NTRK3), ROS1 (coded by the gene ROS1), and ALK (coded by the gene ALK). Key Inclusion Criteria:

	● Histologically or cytologically confirmed diagnosis of locally advanced or metastatic solid tumors that have a NTRK1, NTRK2, NTRK3, ROS1, or ALK molecular alteration. ● Measurable disease according to RECIST version 1.1. ● Prior cancer therapy is allowed, including crizotinib, ceritinib, and investigational drugs. ● Prior radiotherapy is allowed ● Patients with controlled asymptomatic central nervous system involvement are allowed. ● Resolution of all acute toxic effects (excluding alopecia) of any prior anti-cancer therapy to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 4.03 Grade less than or equal to 1. ● Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≤ 2. ● Adult patients age 18 years or older. ● Life expectancy of at least 3 months. Key Exclusion Criteria: ● Current participation in another therapeutic clinical trial. ● Prior treatment with entrectinib. ● History of prolonged QTc interval (e.g., repeated demonstration of a QTc interval > 450 milliseconds). ● History of additional risk factors for torsade de pointes (e.g., family history of long QT syndrome). ● Known active infections (bacterial, fungal, viral including HIV positivity). ● Gastrointestinal disease (e.g., Crohn's disease, ulcerative colitis, or short gut syndrome) or other malabsorption syndromes that would impact on drug absorption. ● Known interstitial lung disease, interstitial fibrosis, or history of tyrosine kinase inhibitor-induced pneumonitis. ● Peripheral neuropathy ≥ Grade 2.
Intervention	Oral entrectinib entrectinib (PO once daily in a continuous daily dosing regimen for 28 consecutive days).

<table>
<tr><td>Baseline characteristics</td><td>
<table>
<tr><th>Molecular Characterization of Tumour, n (%)</th><th>Overall (N=76)</th></tr>
<tr><td>TRKA</td><td>11 (4,5)</td></tr>
<tr><td>TRKB</td><td>3 (3,9)</td></tr>
<tr><td>TRKC</td><td>9 (11,8)</td></tr>
<tr><td>ROS1</td><td>24 (31,6)</td></tr>
<tr><td>ALK</td><td>24 (31,6)</td></tr>
<tr><td>NA</td><td>5 (6,6)</td></tr>
</table>
</td></tr>
<tr><td>Primary and secondary endpoints</td><td>Primary endpoints:
Dose-Limiting Toxicity (DLT)
Maximum Tolerated Dose (MTD)
Recommended Phase 2 Dose (RP2D)
Overall Response Rate (ORR) in Dose Expansion
Secondary endpoints:
Plasma Concentrations of Entrectinib
Disease Control per RECIST v1.1 as assessed by Investigator.
Duration of Response per RECIST v1.1 as assessed by Investigator.
Overall Survival (OS)
Progression-Free Survival (PFS)</td></tr>
<tr><td>Method of analysis</td><td>The DLT analysis set (dose escalation) included 14 patients. The safety analysis set included 76 patients and the efficacy analysis set included 68 patients.

Summary statistics were used to present data, with 95% confidence intervals (CIs). Time-to-event endpoints (PFS, OS, and DOR) were calculated from start date to the date of the applicable event and were reported in months. PFS and OS were to be analyzed in all treated patients (ie, the safety analysis set), however, these analyses were performed using the efficacy analysis set to align all efficacy endpoints for the same population. Time-to-event endpoints were summarized using the Kaplan Meier estimates. No formal significance</td></tr>
</table>

	testing was performed. Missing data were not imputed except for partially missing dates.
Subgroup analyses	NA

Table 25. Main study characteristics of STARTRK-2	
Trial name	STARTRK-2
NCT number	NCT02568267
Objective	To determine the efficacy and safety 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)
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
Study type and design	Open label phase II basket study in each patient population basket of solid tumors that harbor an NTRK1/2/3, ROS1, or ALK gene rearrangement.
Follow-up time	The median duration of follow-up was 12,9 months (IQR 8,77–18,76).

Population (inclusion and exclusion criteria)	Inclusion criteria: ● Adult patients (≥18 years) who signed consent form with histologically- or cytologically confirmed locally advanced or metastatic solid tumor that harbors an NTRK1/2/3, ROS1, or ALK gene rearrangement that is predicted to translate into a fusion protein with a functional TRKA/B/C, ROS1, or ALK kinase domain, respectively, without a concomitant second oncodriver (e.g. epidermal growth factor receptor, KRAS) as determined by Ignyta's CAP/CLIA laboratory or by any nucleic acid-based diagnostic testing method performed at a local CLIAcertified ● or equivalently-accredited diagnostic laboratory. ● Measurable disease as assessed locally using the RECIST v1.1 (patients with non-measurable disease were eligible for enrollment in the "non-evaluable" basket). ● Patients with CNS involvement, including leptomeningeal carcinomatosis, which is either asymptomatic or previously-treated and controlled, are allowed. Seizure prophylaxis is allowed with non-EIAEDs only. Patients requiring steroids must be at stable or decreasing doses for at least 2 weeks prior to the start of entrectinib treatment. ● Prior anticancer therapy is allowed (excluding approved or investigational TRK, ROS1, or ALK (non-NSCLC patients only) inhibitors in patients who have tumors that harbor those respective gene rearrangements). Prior radiotherapy is allowed if more than 14 days have elapsed since the end of treatment. Patients who received brain irradiation must have completed whole brain radiotherapy at least 14 days prior and/or stereotactic radiosurgery at least 7 days prior to the start of entrectinib treatment. ● ECOG performance status ≤2 and minimum life expectancy of at least 4 weeks ● Adequate liver function (AST and ALT≤3.0×ULN; ≤5.0×ULN if liver metastases are present; total serum bilirubin ≤2.0×ULN; patients with a known history of Gilbert's syndrome and/or isolated elevations of indirect bilirubin are eligible). ● Females of childbearing potential must have a negative serum pregnancy test during Screening and must not be breastfeeding or intending to become pregnant during the study. ● Ability to swallow entrectinib intact without chewing, crushing, or opening the capsules. Key Exclusion Criteria: ● History of other previous cancer that would interfere with the determination of safety or efficacy of entrectinib with respect to the qualifying solid tumor malignancy. ● Incomplete recovery from any surgery.

	● Any condition (in the past 3 months) that would interfere with the determination of safety or efficacy of entrectinib: myocardial infarction, unstable angina, coronary/peripheral artery bypass graft, symptomatic congestive heart failure, cerebrovascular accident or transient ischemic attack, stroke, symptomatic bradycardia, or uncontrolled arrhythmias requiring medication. ● History of non-pharmacologically induced prolonged QTc interval (e.g., repeated demonstration of a QTc interval ≥500 milliseconds from ECGs performed at least 24 hours apart). ● History of additional risk factors for torsade de pointes (e.g., family history of long QT syndrome). ● Peripheral neuropathy Grade ≥2. ● Known active infections (bacterial, fungal, or viral, including HIV positive). ● Active gastrointestinal disease (e.g., Crohn's disease, ulcerative colitis, or short gut syndrome) or other malabsorption syndromes that would reasonably impact drug absorption. ● Known interstitial lung disease, interstitial fibrosis, or history of tyrosine kinase inhibitor-induced pneumonitis.
Intervention	Entrectinib 600 mg once-daily in repeated 4-week cycle (n=72).
Baseline characteristics	Please see table of the integrated efficacy analysis of ALKA, STARTRK-1 and STARTRK-2 in 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	Each study basket was considered an independent study. All efficacy analyses were performed for the Efficacy Evaluable Analysis Population (EE) populations of NTRK fusion-positive solid tumors and ROS1-positive NSCLC, unless otherwise specified.

	ORR was reported as the proportion of responders along with the corresponding 2-sided 95% Clopper-Pearson exact confidence interval (CI). Clinical Benefit Rate (CBR) was reported as the proportion of patients achieving the clinical benefit with corresponding 2-sided 95% Clopper-Pearson exact CI. Intracranial Tumor Response (IC-ORR): were reported as the proportion of patients achieving intracranial tumor response on the total number of patients with brain metastases at baseline, with corresponding 2-sided 95% Clopper-Pearson exact confidence interval. Time to Event data (DOR, TTR, PFS, time to CNS progression, IC-PFS, and OS) were summarized by median, 25th, and 75th percentiles estimated using the Kaplan-Meier method. The associated 95% CIs were calculated using the method of Brookmeyer and Crowley (1982) and Klein and Moeschberger (1997). Landmark analyses (e.g., duration rates at 6 months, 9 months, 12 months, and 18 months) were provided with their corresponding 95% CIs calculated using the method of Kalbfleisch and Prentice (1980). Median follow-up was estimated using the reverse Kaplan-Meier method (Schemper and Smith. 1996). Depending on available sample size (n >=5). Exploratory analyses to assess concordance between BICR and Investigators assessments of response, and sensitivity analyses of ORR-BICR for the full EA were carried out. NTRK efficacy evaluable analysis set n=72 Patients evaluable for safety n=332
Subgroup analyses	Subgroup analyses of safety and efficacy were performed by Age, Sex, Race, Region, ECOG, Number of Lines of Prior Anticancer Therapies, Prior Treatment, Types of prior treatment, Prior radiation, Extracranial vs. intracranial solid tumors.

Table 26. Main study characteristics of STARTRK-NG	
Trial name	STARTRK-NG
NCT number	NCT02650401
Objective	The Phase 1 study evaluating the effect of Rozlytrek in children, adolescent, and young adult patients. The study consisted of a dose escalation phase (Phase I) in patients with relapsed or refractory extracranial solid tumors, with or without mo-lecular alterations (Part A), plus expansion parts (Phase Ib) in patients with primary brain tumors harboring NTRK1/2/3, ROS1, or ALK molecular alterations (Part B), neuroblastoma (Part C), other non-

	neuroblastoma, extracranial solid tumors harboring NTRK1/2/3, ROS1, or ALK gene fusions (Part D) and an exploratory cohort of patients who were otherwise eligible but unable to swallow cap-sules (Part E).
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
Study type and design	Phase I/Ib, multicenter, 5-part, open-la-bel, dose escalation and expansion study.
Follow-up time	Not reported
Population (inclusion and exclusion criteria)	Inclusion Criteria: ● Disease status: ○ Phase 1 portion (closed): Participants must have measurable or evaluable disease, as defined by RECIST v1.1 ○ Phase 2 portion: ■ Part B: Participants must have measurable or evaluable disease, as defined by RANO ■ Part C (closed): Participants must have measurable or evaluable disease, as defined by RECIST v1.1 ± Curie Scale ■ Part D: Participants must have measurable or evaluable disease, as defined by RECIST v1.1 ■ Part E (closed): Participants must have measurable or evaluable disease, as defined by RECIST v1.1 ± Curie Scale or RANO ● Tumor type: ○ Phase 1 portion: Part A: Relapsed or refractory extracranial solid tumors ○ Phase 2 portion ■ Part B: Primary brain tumors with NTRK1/2/3 or ROS1 gene fusions; gene fusions are defined as those predicted to translate into a fusion protein with a functional TRKA/B/C or ROS1 kinase domain, without

	a concomitant second oncodriver as determined by a nucleic acid-based diagnostic testing method ■ Part D: Extracranial solid tumors (including NB) with NTRK1/2/3 or ROS1 gene fusions; gene fusions are defined as those predicted to translate into a fusion protein with a functional TRKA/B/C or ROS1 kinase domain, without a concomitant second oncodriver as determined by a nucleic acid-based diagnostic testing method ● Histologic/molecular diagnosis of malignancy at diagnosis or the time of relapse ● Archival tumor tissue from diagnosis or, preferably, at relapse ● Performance status: Lansky or Karnofsky score ≥ 60% and minimum life expectancy of at least 4 weeks ● Prior therapy: Participants must have a disease that is locally advanced, metastatic, or where surgical resection is likely to result in severe morbidity, and who have no satisfactory treatment options for solid tumors and primary CNS tumors that are neurotrophic tyrosine receptor kinase (NTRK) or ROS1 fusion-positive ● Participants must have recovered from the acute toxic effects of all prior chemotherapy, immunotherapy, or radiotherapy prior to enrollment ● Adequate organ and neurologic function ● Females of childbearing potential must have a negative serum pregnancy test during screening and be neither breastfeeding nor intending to become pregnant during study participation. Agreement to remain abstinent or use use combined contraceptive methods prior to study entry, for the duration of study participation and in the following 90 days after discontinuation of study treatment. ● For male participants with a female partner of childbearing potential or a pregnant female partner: Agreement to remain abstinent or use a condom during the treatment period and for at least 3 months after the last dose of study drug Exclusion Criteria: ● Receiving other experimental therapy ● Known congenital long QT syndrome ● History of recent (3 months) symptomatic congestive heart failure or ejection fraction ≤50% at screening

	● Known active infections ● Familial or personal history of congenital bone disorders, bone metabolism alterations or osteopenia ● Receiving Enzyme Inducing Antiepileptic Drugs (EIAEDs) within 14 days of first dose. ● Prior treatment with approved or investigational TRK or ROS1 inhibitors ● Known hypersensitivity to entrectinib or any of the other excipients of the investigational medicinal product ● Patients with NB with bone marrow space-only disease ● Incomplete recovery from acute effects of any surgery prior to treatment. ● Active gastrointestinal disease or other malabsorption syndromes that would impact drug absorption. ● Other severe acute or chronic medical or psychiatric condition or lab abnormality that may increase the risk associated with study participation, drug administration or may interfere with the interpretation of study results.
Intervention	A total of 17 patients were screened during Phase 1 portion of the study and 1 patient failed screening due to withdrawal of consent. A total of 16 patients were enrolled (3 patients at 250 mg/m2; 3 patients at 400 mg/m2; 7 patients at 550 mg/m2; and 3 patients at 750 mg/m2). Only 3 patients had gene fusions (EML4-NTRK3, TFG-ROS1, DCTN1-ALK). Only those 3 subjects achieve an objective response. Phase I part A (dose escalation): Entrectinib was administered orally with food, once daily, in repeated 4-week cycles. The doses levels were: 250 mg/m2, 400 mg/m2, 550 mg/m2, 750 mg/m2. (F2B formulation was administered in the first dose level, F1 for the subsequent dose levels). Phase Ib part B, C, D: Entrectinib doses at the pediatric RP2D determined in Part A. Phase Ib part E: entrectinib initially dosed at a -1 dose level de-escalation from the RP2D established in Part A. In part E, entrectinib should be mixed with age-appropriate soft food or liquid and consumed with fat-containing food.

	According to protocol version 6, in Parts B and D Phase 2 Portion two formulations will be used (i.e., F06 and F1) based upon the patient's ability to swallow. An age-appropriate formulation will be introduced in the future. The recommended dose of 300 mg/m2 with F06 for pediatric patients who can swallow intact capsules.
Baseline characteristics	Please see table of the integrated efficacy analysis of ALKA, STARTRK-1 and STARTRK-2 in Table 5.
Primary and secondary endpoints	Primary: ● MTD or RP2D Secondary: ● Safety ● ORR ● DOR ● PFS ● PK of Rozlytrek in plasma ● TTR, CBR ● intracranial tumor response ● TTR, CNS-PFS
Method of analysis	No formal statistical hypothesis testing for Phase 1 (Part A) portion was planned. Efficacy, PK, and safety data were summarized using descriptive statistics.
Subgroup analyses	Not reported

Table 27. Main study characteristics of Doebele et al. 2020 Integrated analysis of three phase 1-2 trials	
Trial name	ALKA-372-001, STARTRK-1 and STARTRK-2
NCT number	EudraCT 2012-000148-88, NCT02097810 and NCT02568267

Objective	To determine the ORR of entrectinib, as assessed by blinded independent central review (BICR), in each patient population basket of solid tumors that harbor an NTRK1/2/3, ROS1, or ALK gene rearrangement.
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
Study type and design	An integrated efficacy and safety analysis of patients with metastatic or locally advanced solid tumours harbouring oncogenic NTRK1, NTRK2, and NTRK3 gene fusions in three phase 1 or 2 clinical trials (ALKA-372-001, STARTRK-1, and STARTRK-2). Study designs of each trial are described above under the individual trials.
Follow-up time	The median follow-up was 12,9 months (IQR: 8,77-18,76).

Population (inclusion and exclusion criteria)	<u>Key inclusion criteria:</u> ● Adult patients (≥18 years) who signed consent form with histologically- or cytologically-confirmed locally advanced or metastatic solid tumor that harbors an NTRK1/2/3, ROS1, or ALK gene rearrangement that is predicted to translate into a fusion protein with a functional TRKA/B/C, ROS1, or ALK kinase domain, respectively, without a concomitant second oncodriver (e.g. epidermal growth factor receptor, KRAS) as determined by Ignyta's CAP/CLIA laboratory or by any nucleic acid-based diagnostic testing method performed at a local CLIA-certified or equivalently-accredited diagnostic laboratory. ● Measurable disease as assessed locally using the RECIST v1.1 (patients with non-measurable disease were eligible for enrollment in the "non-evaluable" basket). ● Patients with CNS involvement, including leptomeningeal carcinomatosis, which is either asymptomatic or previously-treated and controlled, are allowed. Seizure prophylaxis is allowed with non-EIAEDs only. Patients requiring steroids must be at stable or decreasing doses for at least 2 weeks prior to the start of entrectinib treatment. ● Prior anticancer therapy is allowed (excluding approved or investigational TRK, ROS1, or ALK (non-NSCLC patients only) inhibitors in patients who have tumors that harbor those respective gene rearrangements). Prior radiotherapy is allowed if more than 14 days have elapsed since the end of treatment. Patients who received brain irradiation must have completed whole brain radiotherapy at least 14 days prior and/or stereotactic radiosurgery at least 7 days prior to the start of entrectinib treatment. ● ECOG performance status ≤2 and minimum life expectancy of at least 4 weeks ● Adequate liver function (AST and ALT≤3.0×ULN; ≤5.0×ULN if liver metastases are present; total serum bilirubin ≤2.0×ULN; patients with a known history of Gilbert's syndrome and/or isolated elevations of indirect bilirubin are eligible). ● Females of childbearing potential must have a negative serum pregnancy test during Screening and must not be breastfeeding or intending to become pregnant during the study. ● Ability to swallow entrectinib intact without chewing, crushing, or opening the capsules.

	Key exclusion criteria: ● History of other previous cancer that would interfere with the determination of safety or efficacy of entrectinib with respect to the qualifying solid tumor malignancy. ● Incomplete recovery from any surgery. ● Any condition (in the past 3 months) that would interfere with the determination of safety or efficacy of entrectinib: myocardial infarction, unstable angina, coronary/peripheral artery bypass graft, symptomatic congestive heart failure, cerebrovascular accident or transient ischemic attack, stroke, symptomatic bradycardia, or uncontrolled arrhythmias requiring medication. ● History of non-pharmacologically induced prolonged QTc interval (e.g., repeated demonstration of a QTc interval ≥500 milliseconds from ECGs performed at least 24 hours apart). ● History of additional risk factors for torsade de pointes (e.g., family history of long QT syndrome). ● Peripheral neuropathy Grade ≥2. ● Known active infections (bacterial, fungal, or viral, including HIV positive). ● Active gastrointestinal disease (e.g., Crohn's disease, ulcerative colitis, or short gut syndrome) or other malabsorption syndromes that would reasonably impact drug absorption. ● Known interstitial lung disease, interstitial fibrosis, or history of tyrosine kinase inhibitor-induced pneumonitis. Note: radiation-induced lung disorders are not included in this exclusion criterion.

Intervention	Entrectinib 600 mg orally once-daily on a continuous daily dosing regimen in 4-week cycles. Efficacy Evaluable Analysis Set, composed of 54 adult patients with NTRK fusion-positive solid tumour treated with at least one dose of entrectinib across the three studies in adult patients with solid tumours (ALKA, STARTRK-1, and STARTRK-2). All patients included in the NTRK Efficacy Evaluable Analysis Set had measurable disease at baseline and at least 6 months follow-up. Patients included were enrolled up to 30 November 2017. During the procedure, as per CHMP request, data on additional patients and updated analyses have been provided.. The latest dataset include 74 adult patients with >6 months of follow-up.

Baseline characteristics

			MAA primary NTRK efficacy evaluable	D120 NTRK efficacy evaluable
	Enrolment cut-off date		30 Nov 2017	30 April 2018
			N=54	**N=74**
Demographics	Age	median (range), years ≥65 years, n (%)	57.5 (21-83) 20 (37.0)	57.0 (21-83) 26 (35.1)
	Sex, n (%)	Male Female	22 (40.7) 32 (59.3)	35 (47.3) 39 (52.7)
	Race, n (%)	White Asian Black or African American not reported	43 (79.6) 7 (13.0) 0 4 (7.4)	52 (70.3) 13 (17.6) 2 (2.7) 7 (9.5)
	ECOG PS, n (%)			
		0	23 (42.6)	30 (40.5)
		1	25 (46.3)	34 (45.9)
		2	6 (11.1)	10 (13.5)
	History of smoking, n (%)		23 (43.4)	29 (40.3)

Baseline Disease Characteristics	Tumor type (High Level), n (%)		
	Breast	6 (11.1)	6 (8.1)
	Cholangiosarcoma	1 (1.9)	1 (1.4)
	CRC	4 (7.4)	7 (9.5)
	GI other	0	1 (1.4)
	Gynecological	2 (3.7)	2 (2.7)
	Neuroblastoma	0	1 (1.4)
	Neuroendocrine	3 (5.6)	4 (5.4)
	NSCLC	10 (18.5)	13 (17.6)
	Pancreatic	3 (5.6)	3 (4.1)
	Salivary (MASC)	7 (13.0)	13 (17.6)
	Sarcoma	13 (24.1)	16 (21.6)
	Thyroid	5 (9.3)	7 (9.5)
	NTRK gene fusion, n (%)		
	NTRK1	22 (40.7)	30 (40.5)
	NTRK2	1 (1.9)	2 (2.7)
	NTRK3	31 (57.4)	42 (56.8)
	Median time since diagnosis, months (range)	21.4 (2.1-433.1)	21.0 (2.1-433.1)
	Disease stage at initial diagnosis, n (%)	(n=53)[a]	(n=73)[a]
	0	1 (1.9)	2 (2.7)
	I (A/B)	6 (11.3)	7 (9.6)
	II (A/B)	8 (14.8)	12 (16.4)
	III (A/B/C)	12 (22.6)	15 (20.3)
	IV	21 (39.6)	30 (41.1)
	unknown	5 (9.4)	7 (9.6)
	Metastatic disease		
	any site, n (%)	52 (96.3)	72 (97.3)
	bone, n (%)	17 (31.5)	20 (27.0)

	brain, n (%)	12 (22.2)	19 (25.7)
	liver, n (%)	21 (38.9)	28 (37.8)
	lung, n (%)	33 (61.1)	45 (60.8)
	lymph nodes, n (%)	30 (55.6)	39 (52.7)
	skin, n (%)	3 (5.6)	4 (5.4)
	other, n (%)	15 (27.8)	25 (33.8)
Previous Cancer Treatment	No of prior systemic therapies[a], n (%)		
	0	14 (25.9%)[c]	20 (27.0%)
	1	15 (27.8%)	21 (28.4%)
	2	16 (29.6%)	20 (27.0%)
	3	4 (7.4%)	6 (8.1%)
	4	4 (7.4%)	4 (5.4%)
	>4	1 (1.9%)	3 (4.1%)
	Previous therapy, n (%)		
	any systemic therapy[b]	48 (88.9%)	64 (86.5%)
	surgery	43 (79.6%)	61 (82.4%)
	radiotherapy	36 (66.7%)	47 (63.5%)
	Baseline CNS lesions by INV	n=12	n=19
	Prior radiotherapy to brain, n (%)	8[d] (66.7%)	13 (68.4%)

Primary and secondary endpoints	<u>Primary endpoint:</u> ● ORR (confirmed response = persisted on repeated-imaging≥4 weeks after initial documentation of response) <u>Secondary endpoints:</u> ● DOR, TTR, CBR (CR, PR, or SD at 6 months after the first dose of entrectinib), Intracranial tumor response in patients with measurable CNS disease, as determined by BICR using RANO or RANO-BM, as applicable, CNS progression free survival (CNS-PFS) in patients with measurable CNS disease, PFS, OS ● AEs ● Population PK ● Ventricular repolarization ● Quality-of-life and health status <u>Exploratory endpoints:</u> ● Analysis of potential differences in clinicopathologic presentation and response to entrectinib among the various tumor types harboring NTRK1/2/3, ROS1, or ALK gene rearrangements ● Potential mechanisms of resistance to entrectinib ● All radiographic efficacy endpoints were based on BICR using RECIST v1.1 (except for patients with CNS disease where radiographic confirmation of intracranial objective tumor response or disease progression was based on RANO or RANO-BM). ● Tumor assessments were performed at Screening, at the end of Cycle 1 and every 8 weeks, and at the End of Treatment (if more than 4 weeks had passed since the last imaging assessment). Radiographic confirmation of objective tumor response (no earlier than 4 weeks from the first response) or disease progression was based on RECIST v1.1 and assessed both locally and by BICR. Stable disease can be assigned only after a patient meets stable disease criteria for at least 5 weeks (≥35 days) following the first dose of treatment. At Screening, a CT/MRI of the brain was obtained to rule out newly diagnosed, untreated brain metastases or to document stability of previously treated brain

	metastases. If brain metastases were not documented at Screening, then brain scans were performed as clinically indicated.
Method of analysis	The integrated efficacy analyses were based on NTRK efficacy evaluable analysis set. Summary statistics with 95% 2-sided CIs properly calculated were used. ORR, CBR, IC-ORR: proportion and corresponding 2-sided 95% Clopper-Pearson exact CI. Time-to-event endpoints (DOR, PFS, OS, IC-DOR, IC-PFS, Time to CNS progression): median, 25th, and 75th percentiles estimated by using the Kaplan-Meier method. The associated 2-sided 95% CIs were calculated using the method of Brookmeyer and Crowly (1982) and Klein and Moeschberger (1997). Landmark analyses at 6, 9, and 12 months were provided with the corresponding 2-sided 95% CIs calculated using the method of Kalbfleisch and Prentice (1980). Waterfall and swimmer plots were used to depict each patient's best tumor response (BOR) and time on study, respectively, including time to first objective response by BICR (if applicable) and DOR. Formal significance tests were not performed. No statistical adjustment was made to address the sources of multiplicity associated with the integrated analysis. Statistical analyses were carried out overall, by study, by CNS-disease status at baseline.
Subgroup analyses	ORR and DOR by tumour types, Response by NTRK gene and gene fusion partner, ORR by Investigator, CBR by Investigator, DOR by Investigator, PFS by Investigator and Results in primary CNS tumors.

[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.

[b]Includes any chemotherapy, immunotherapy, targeted therapy or hormonal therapy.

[c]The previous lines of cancer therapy were erroneously reported (as 0) for six NTRK adult patients in the initial SCE (2.7.3) and have been corrected in this table.

[d]one patient with CNS disease at baseline had received halocraneal radiation therapy <2 months before entrectinib treatment which was incorrectly reported in the analysis presented in the initial SCE.

Table 28. Main study characteristics of Rosen et al. 2020	
Trial name	Rosen et al. 2020
NCT number	NA
Objective	Key objectives were to further understand the incidence, distribution and wider genomic context of NTRK gene fusions across cancers, and the clinical response of these tumours to various therapies
Publications – title, author, journal, year	TRK Fusions Are Enriched in Cancers with Uncommon Histologies and the Absence of Canonical Driver Mutations, Rosen et al., Clinical Cancer Research, 2020.
Study type and design	Retrospective analysis of individual patient-level data from a prospective genomic screening program at a single centre (Memorial Sloan Kettering Cancer Center[MSKCC], NY, USA)
Follow-up time	Follow-up time in survivors was 3.1 years (range: 0.1–22.5). All pediatric and adult patients with TRK fusion–positive cancers identified at Memorial Sloan Kettering (MSK) between April 7, 2015 and August 15, 2018 were included for analysis.
Population (inclusion and exclusion criteria)	As this observational study is not registered in Clinicaltrials.gov it is not possible to provide the inclusion and exclusion criteria from this source. The publication states that all pediatric and adult patients with TRK fusion–positive cancers identified at Memorial Sloan Kettering (MSK) between April 7, 2015 and August 15, 2018 were included for analysis irrespective of previous therapy, cancer type and disease stage.

Intervention	The study included 76 patients who received several classes of therapy for advanced disease including chemotherapy (n= 35, 69%), immunotherapy (n = 12, 24%), and TRK inhibitors (n = 38, 75%)
Baseline characteristics	

	***N* (%)**
Age, median (range)	52 (0–78)
Gender	
Female	47 (61.8)
Male	29 (38.2)
Cancer type	
Salivary	12 (15.8)
Thyroid	10 (13.2)
Sarcoma NOS	9 (11.8)
Colon	8 (10.5)
Lung	6 (7.9)

Melanoma	5 (6.6)
Glioblastoma multiforme	4 (5.3)
Pancreatic cancer	4 (5.3)
Other	18 (23.7)
Stage at diagnosis (*n* = 58)	
Localized, I–III	34 (58.6)
Metastatic, IV	24 (41.4)
Prior therapy	
Surgery (*n* = 74)	65 (87.8)
Radiation (*n* = 70)	33 (47.1)
Systemic (*n* = 76)	57 (75)
Class of systemic therapy (*n* = 57)	
Chemotherapy	39 (68.4)
Immunotherapy	12 (21.1)

	TRK-Targeted therapy: 39 (68.4)
	Intervals, years, median (range)
	Diagnosis and TRK tissue (*N* = 72): 0.2 (0.0–21.4)
	Diagnosis and NTRK sequencing (*N* = 75): 2.0 (0.0–21.6)
	TRK Tissue and sequencing (*N* = 72): 0.3 (0.0–13.0)
Primary and secondary endpoints	Recurrence-free survival (RFS), progression-free survival (PFS), overall survival (OS) and response rate (ORR).
Method of analysis	Recurrence-free survival (RFS), progression-free survival (PFS), and overall survival (OS) were estimated using Kaplan–Meier methods. OS was assessed from original diagnosis until death from any cause. Patients alive at the time of the data lock (January 23, 2019) were censored at the last date confirmed alive. For RFS, patients treated with curative intent (n = 39) were included. We defined this as patients who were treated with curative intent and non-exploratory surgery for whom date of start of remission was their surgery date, and 1 patient with curative intent chemotherapy and surgery for whom date of remission was date of first imaging study showing no evidence of disease. Patients were excluded from RFS analysis if not treated with curative intent (n = 17), no documentation (n = 8), or if never in remission (n = 12). Of patients included in RFS analysis (n = 39), recurrence was documented on imaging in 27 patients. RFS was calculated from the start of remission until first recurrence or death from any cause. Patients alive without radiologic or pathologic documentation of recurrence were censored at last follow up. PFS was defined from date of first-line therapy for advanced disease (time 0) until radiologic progression (n = 37), changing therapies to start a clinical trial (n = 2), or changing medical therapies for other reasons (n = 4) For PFS, patients

	who developed advanced disease or with de novo metastatic disease were included (n = 51). Patients were excluded if they had curative firstline treatment and remained disease free at time 0 (n = 13), with incurable disease but never treated with systemic therapy for this condition (n = 4), and those with inadequate records (n = 8). PFS was defined from the date of first-line therapy for advanced disease (time 0) until radiologic progression (n = 37), changing therapies to start a clinical trial (n = 2), or changing medical therapies for other reasons (n = 4). Patients alive and progression-free at the time of data cut were censored at last follow-up. Ninety-five percent confidence intervals (95% CI) around survival estimates were calculated with the log-cumulative hazard transformation. For patients who received therapy in the setting of active disease, best overall response was recorded when available as indicated by the treating oncologist.Wecalculated best overall response to any therapy, first-line therapy, and by drug classification (chemotherapy, immunotherapy, and TRK-targeted therapy) with 95% Clopper–Pearson CIs. Patients who received TRK inhibitors as first-line therapy were not included in first-line assessment, and patients who received multiple agents may be counted in both drugs' assessment.
Subgroup analyses	NA

Table 29. Main study characteristics of the CoPPO trial	
Trial name	Copenhagen Prospective Personalized Oncology (CoPPO)

NCT number	02290522
Objective	Assessing clinical benefit of tumor molecular profiling to select treatment in the phase I setting
Publications – title, author, journal, year	Copenhagen Prospective Personalized Oncology (CoPPO) - Clinical Utility of Using Molecular Profiling to Select Patients to Phase I Trials, Tuxen, IV. et al., Clin Cancer Res, 2019
Study type and design	Prospective, single-center, single-arm open-label study
Follow-up time	Not reported
Population (inclusion and exclusion criteria)	Patients with advanced solid malignancies referred to the phase I unit at Rigshospitalet, University of Copenhagen (Copenhagen, Denmark) were offered enrolment. Eligibility criteria were: exhausted treatment options, life expectancy of ≥3 months, normal organ function, measurable disease (RECIST1.1), Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1, age ≥ 18 years, and lesions accessible for biopsy.
Intervention	Targeted treatment based on molecular profiling
Baseline characteristics	Described in Table 8
Primary and secondary endpoints	Primary endpoint: PFS Secondary endpoints ● Percentage of patients allocated to treatment guided by the genomic profile ● Response rate according to RECIST 1.1

Method of analysis	PFS was calculated using Kaplan–Meier method . Patients alive at the date of data cutoff (December 1, 2017) were censored. PFS ratio was defined as PFS2/PFS1, where PFS1 was the time from start of the most recent treatment to progression and PFS2 was the time from the start of molecular profiling–matched treatment to progression according to RECIST1.1, clinical progression or death. Statistical analyses were performed using IBM Statistics SPSS (version 22) and R (version 0.99.903).
Subgroup analyses	None

10.4 Results of the BSC analysis

Table 30. Overview and results of the BSC analysis

Author	Year	Title	Tumor Type	Median OS	Median PFS	ORR (%)	n	Prior lines of therapy
Rao, S., Cunningham, D., de Gramont, A., Scheithauer, W., Smakal, M., Humblet, Y., Kourteva, G., Iveson, T., Andre, T., Dostalova, J., Illes, A., Belly, R., Perez-	2004	Phase III double-blind placebo-controlled study of farnesyl transferase inhibitor R115777 in patients with	CRC	6.08[a]	2.63[a]	0	133	4.5% with 1, 52% with 2, 31% with 3, and 13% with ≥4

Ruixo, J. J., Park, Y. C. and Palmer, P. A.		refractory advanced colorectal cancer						treatment lines
Van Cutsem, E., Peeters, M., Siena, S., Humblet, Y., Hendlisz, A., Neyns, B., Canon, J. L., Van Laethem, J. L., Maurel, J., Richardson, G., Wolf, M. and Amado, R. G.	2007	Open-label phase III trial of panitumumab plus best supportive care compared with best supportive care alone in patients with chemotherapy-refractory metastatic colorectal cancer	CRC	N/A	1.68[b]	0	232	100% with 2 and 38% with 3 treatment lines
Sorbye, H., Pfeiffer, P., Cavalli-Björkman, N., Qvortrup, C., Holsen, M. H., Wentzel-Larsen, T. and Glimelius, B.	2009	Clinical trial enrollment, patient characteristics, and survival differences in prospectively registered metastatic colorectal cancer patients	CRC	2.8	N/A	N/A	244	No previous treatment lines
Grothey, A., Van Cutsem, E., Sobrero, A., Siena, S., Falcone, A., Ychou, M., Humblet, Y., Bouché, O., Mineur, L., Barone, C., Adenis, A., Tabernero, J., Yoshino, T., Lenz, H. J., Goldberg, R. M., Sargent, D. J., Cihon, F., Cupit, L., Wagner, A. and Laurent, D.	2013	Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial	CRC	5	1.7	0.40 %	255	25% with 1-2, 28% with 3, and 47% with ≥4 treatment lines
Caballero-Baños, M., Benitez-Ribas, D., Tabera, J., Varea, S., Vilana, R., Bianchi, L., Ayuso, J. R., Pagés, M., Carrera, G., Cuatrecasas, M., Martin-Richard, M., Cid, J., Lozano, M., Castells, A., García-Albéniz, X., Maurel, J. and Vilella, R.	2016	Phase II randomised trial of autologous tumour lysate dendritic cell plus best supportive care compared with best supportive care in pre-treated advanced colorectal cancer patients	CRC	4.7	2.3	4.20 %	24	42% with 2, 33% with 3. and 25% with >3 treatment lines
Grothey, A., Strosberg, J. R., Renfro, L. A., Hurwitz, H. I., Marshall,	2018	A Randomized, Double-Blind, Placebo-Controlled	CRC	6.14[b]	1.86[b]	2.38 %	42	

J. L., Safran, H., Guarino, M. J., Kim, G. P., Hecht, J. R., Weil, S. C., Heyburn, J., Wang, W., Schweizer, C., O'Shannessy, D. J. and Diaz, L. A., Jr.		Phase II Study of the Efficacy and Safety of Monotherapy Ontuxizumab (MORAb-004) Plus Best Supportive Care in Patients with Chemorefractory Metastatic Colorectal Cancer						Not reported (all standard therapies had failed)
Jonker, D. J., Nott, L., Yoshino, T., Gill, S., Shapiro, J., Ohtsu, A., Zalcberg, J., Vickers, M. M., Wei, A. C., Gao, Y., Tebbutt, N. C., Markman, B., Price, T., Esaki, T., Koski, S., Hitron, M., Li, W., Li, Y., Magoski, N. M., Li, C. J., Simes, J., Tu, D. and O'Callaghan, C. J.	2018	Napabucasin versus placebo in refractory advanced colorectal cancer: a randomised phase 3 trial	CRC	4.8	N/A	N/A	144	1 previous chemo-therapy treatment line
Kim, T. W., Elme, A., Park, J. O., Udrea, A. A., Kim, S. Y., Ahn, J. B., Valencia, R. V., Krishnan, S., Manojlovic, N., Guan, X., Lofton-Day, C., Jung, A. S. and Vrdoljak, E.	2018	Final Analysis of Outcomes and RAS/BRAF Status in a Randomized Phase 3 Study of Panitumumab and Best Supportive Care in Chemorefractory Wild Type KRAS Metastatic Colorectal Cancer	CRC	6.9	1.7	2.30 %	128 (Wild Type RAS cohort)	All had received multiple lines of prior chemo-therapy
			CRC	7.4	1.8	2.60 %	114 (Wild Type RAS, Wild Type BRAF cohort)	All had received multiple lines of prior chemo-therapy
Van Cutsem, E., Mayer, R. J., Laurent, S., Winkler, R., Grávalos, C., Benavides, M., Longo-Munoz, F., Portales, F., Ciardiello, F., Siena, S., Yamaguchi, K., Muro, K., Denda, T., Tsuji, Y.,	2018	The subgroups of the phase III RECOURSE trial of trifluridine/tipiracil (TAS-102) versus placebo with best supportive care in patients with	CRC	4.3	1.7	N/A	35 (US cohort)	≥2 treatment lines
				4.9	1.7	N/A	132 (EU cohort)	

Makris, L., Loehrer, P., Lenz, H. J. and Ohtsu, A.		metastatic colorectal cancer						≥2 treatment lines
Chen, E. X., Jonker, D. J., Loree, J. M., Kennecke, H. F., Berry, S. R., Couture, F., Ahmad, C. E., Goffin, J. R., Kavan, P., Harb, M., Colwell, B., Samimi, S., Samson, B., Abbas, T., Aucoin, N., Aubin, F., Koski, S. L., Wei, A. C., Magoski, N. M., Tu, D. and O'Callaghan, C. J.	2020	Effect of Combined Immune Checkpoint Inhibition vs Best Supportive Care Alone in Patients With Advanced Colorectal Cancer: The Canadian Cancer Trials Group CO.26 Study	CRC	4.1	1.9	0	61	All had received multiple lines of prior chemotherapy
median CRC				**4.9**	**1.8**			
Demetri, G. D., Reichardt, P., Kang, Y. K., Blay, J. Y., Rutkowski, P., Gelderblom, H., Hohenberger, P., Leahy, M., von Mehren, M., Joensuu, H., Badalamenti, G., Blackstein, M., Le Cesne, A., Schöffski, P., Maki, R. G., Bauer, S., Nguyen, B. B., Xu, J., Nishida, T., Chung, J., Kappeler, C., Kuss, I., Laurent, D. and Casali, P. G.	2013	Efficacy and safety of regorafenib for advanced gastrointestinal stromal tumours after failure of imatinib and sunitinib (GRID): an international, multicentre, randomised, placebo-controlled, phase 3 trial	GIST	N/A	0.9	1.5%	66	59% with 2 previous treatment lines, 41% with >2 treatment lines
Mir, O., Cropet, C., Toulmonde, M., Cesne, A. L., Molimard, M., Bompas, E., Cassier, P., Ray-Coquard, I., Rios, M., Adenis, A., Italiano, A., Bouché, O., Chauzit, E., Duffaud, F., Bertucci, F., Isambert, N., Gautier, J., Blay, J. Y. and Pérol, D.	2016	Pazopanib plus best supportive care versus best supportive care alone in advanced gastrointestinal stromal tumours resistant to imatinib and sunitinib (PAZOGIST): a randomised, multicentre, open-label phase 2 trial	GIST	12.9	2.3	2.4%	41	At least 2. 51% with 3 or more previous treatment regimens

Median GIST				**12.9**	**1.6**			
Agteresch, H. J., Dagnelie, P. C., van der Gaast, A., Stijnen, T. and Wilson, J. H.	2000	Randomized clinical trial of adenosine 5'-triphosphate in patients with advanced non-small-cell lung cancer	NSCLC	4.7	N/A	N/A	30	42% had received previous treatment lines (chemo-therapy)
Ranson, M., Davidson, N., Nicolson, M., Falk, S., Carmichael, J., Lopez, P., Anderson, H., Gustafson, N., Jeynes, A., Gallant, G., Washington, T. and Thatcher, N.	2000	Randomized trial of paclitaxel plus supportive care versus supportive care for patients with advanced non-small-cell lung cancer	NSCLC	4.8	0.5	N/A	78	6% with radiotherapy (no previous chemotherapy)
Roszkowski, K., Pluzanska, A., Krzakowski, M., Smith, A. P., Saigi, E., Aasebo, U., Parisi, A., Pham Tran, N., Olivares, R. and Berille, J.	2000	A multicenter, randomized, phase III study of docetaxel plus best supportive care versus best supportive care in chemotherapy-naive patients with metastatic or non-resectable localized non-small cell lung cancer (NSCLC)	NSCLC	5.7	2.05[b]	N/A	70	No previous treatment lines (87.1%)
Thatcher, N., Chang, A., Parikh, P., Rodrigues Pereira, J., Ciuleanu, T., von Pawel, J., Thongprasert, S., Tan, E. H., Pemberton, K., Archer, V. and Carroll, K.	2005	Gefitinib plus best supportive care in previously treated patients with refractory advanced non-small-cell lung cancer: results from a randomised, placebo-controlled, multicentre study (Iressa Survival Evaluation in Lung Cancer)	NSCLC	5.1	N/A	1.3%	563	1 previous treatment (75%), ≥2 (25%)
Parikh, P. M., Vaid, A., Advani, S. H., Digumarti, R., Madhavan, J., Nag, S., Bapna, A., Sekhon, J.	2011	Randomized, double-blind, placebo-controlled phase II study of single-agent	NSCLC	3.7	1.38[b]	2%	53	

S., Patil, S., Ismail, P. M., Wang, Y., Varadhachary, A., Zhu, J. and Malik, R.		oral talactoferrin in patients with locally advanced or metastatic non-small-cell lung cancer that progressed after chemotherapy						75% with 1 and 25 with ≥2 previous treatment lines
Belani, C. P., Wu, Y. L., Chen, Y. M., Kim, J. H., Yang, S. H., Zhang, L., Peterson, P. and Orlando, M.	2012	Efficacy and safety of pemetrexed maintenance therapy versus best supportive care in patients from East Asia with advanced, nonsquamous non-small cell lung cancer: an exploratory subgroup analysis of a global, randomized, phase 3 clinical trial	NSCLC	8.5	1.8	N/A	115 (Non-East Asian population)	No previous treatment lines
Lee, S. M., Khan, I., Upadhyay, S., Lewanski, C., Falk, S., Skailes, G., Marshall, E., Woll, P. J., Hatton, M., Lal, R., Jones, R., Toy, E., Chao, D., Middleton, G., Bulley, S., Ngai, Y., Rudd, R., Hackshaw, A. and Boshoff, C.	2012	First-line erlotinib in patients with advanced non-small-cell lung cancer unsuitable for chemotherapy (TOPICAL): a double-blind, placebo-controlled, phase 3 trial	NSCLC	3.6	2.6	2%	320	No previous treatment lines (first line treatment in patient unsuitable for chemotherapy)
Paz-Ares, L., Hirsh, V., Zhang, L., de Marinis, F., Yang, J. C., Wakelee, H. A., Seto, T., Wu, Y. L., Novello, S., Juhász, E., Arén, O., Sun, Y., Schmelter, T., Ong, T. J., Peña, C., Smit, E. F. and Mok, T. S.	2015	Monotherapy Administration of Sorafenib in Patients With Non-Small Cell Lung Cancer (MISSION) Trial: A Phase III, Multicenter, Placebo-Controlled Trial of Sorafenib in	NSCLC	8.3	1.4	N/A	353	>2 treatment lines

		Patients with Relapsed or Refractory Predominantly Nonsquamous Non-Small-Cell Lung Cancer after 2 or 3 Previous Treatment Regimens						55.8% with 2 previous lines 43.3% with 3 previous treatment lines
Mulvenna, P., Nankivell, M., Barton, R., Faivre-Finn, C., Wilson, P., McColl, E., Moore, B., Brisbane, I., Ardron, D., Holt, T., Morgan, S., Lee, C., Waite, K., Bayman, N., Pugh, C., Sydes, B., Stephens, R., Parmar, M. K. and Langley, R. E.	2016	Dexamethasone and supportive care with or without whole brain radiotherapy in treating patients with non-small cell lung cancer with brain metastases unsuitable for resection or stereotactic radiotherapy (QUARTZ): results from a phase 3, non-inferiority, randomised trial	NSCLC	1.95[b]	N/A	N/A	269	Not reported
Satyanarayan, Beniwal, S., Kapoor, A., Mittal, A., Lal Jakhar, S., Sharma, N., Kumar, H. S. and Khichar, S.	2016	Maintenance gemcitabine versus best supportive care following platinum-paclitaxel chemotherapy for patients with advanced nonsmall cell lung cancer	NSCLC	8	7	N/A	49	No previous treatment line
Median NSCLC				**5.1**	**1.8**			
Ciuleanu, T. E., Pavlovsky, A. V., Bodoky, G., Garin, A. M., Langmuir, V. K., Kroll, S. and Tidmarsh, G. T.	2009	A randomised Phase III trial of glufosfamide compared with best supportive care in metastatic pancreatic adenocarcinoma previously treated with gemcitabine	Pancreatic	2.76[a]	1.41[a]	0.65 %	155	1 previous treatment line

Pelzer, U., Schwaner, I., Stieler, J., Adler, M., Seraphin, J., Dörken, B., Riess, H. and Oettle, H.	2011	Best supportive care (BSC) versus oxaliplatin, folinic acid and 5-fluorouracil (OFF) plus BSC in patients for second-line advanced pancreatic cancer: a phase III-study from the German CONKO-study group	Pancreatic	2.3	N/A	0%	23	1 previous treatment line
Tröger, W., Galun, D., Reif, M., Schumann, A., Stanković, N. and Milićević, M.	2013	Viscum album [L.] extract therapy in patients with locally advanced or metastatic pancreatic cancer: a randomised clinical trial on overall survival	Pancreatic	2.7	N/A	N/A	110	1 previous treatment line
Median Pancreatic				**2.7**	**1.41**			
Le Cesne, A., Blay, J. Y., Cupissol, D., Italiano, A., Delcambre, C., Penel, N., Isambert, N., Chevreau, C., Bompas, E., Bertucci, F. and et al.	2016	Results of a prospective randomized phase III T-SAR trial comparing trabectedin vs best supportive care (BSC) in patients with pretreated advanced soft tissue sarcoma (ASTS)	Sarcoma	10.8	1.4	N/A	51	Not reported (at least 1 prior anthracycline treatment line and <3 previous chemo-therapy lines
Socha, J., Kepka, L., Ghosh, S., Roa, W., Kumar, N., Sinaika, V., Matiello, J., Lomidze, D., de Castro, D. G., Hentati, D. and Fidarova, E.	2016	Outcome of treatment of recurrent glioblastoma multiforme in elderly and/or frail patients	Glioblastoma	6.90[b]	3.68[b]	N/A	47	No previous systemic therapy (only radio-therapy)
Hofmann, M. A., Hauschild, A., Mohr, P., Garbe, C., Weichenthal, M., Trefzer, U., Drecoll,	2011	Prospective evaluation of supportive care with or without CVD	Melanoma	4.50[a]	N/A	0%	24	

U., Tilgen, W., Schadendorf, D., Kaatz, M. and Ulrich, J.		chemotherapy as a second-line treatment in advanced melanoma by patient's choice: a multicentre Dermatologic Cooperative Oncology Group trial						1 previous treatment line
Overall median				**4.9**	**1.8**			
[a] Originally reported in days [b] Originally reported in weeks								

10.5 Summary of adverse events - Adults

Tabulated list of adverse reactions in entrectinib

The adverse reactions listed in Table 33 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 31. Summary of Adverse drug reactions per SOC in the adult and pediatric safety population treated with entrectinib in clinical trials (n=504)

System organ class	Adverse reaction	All grades (%)	Frequency	Grade ≥3 (%)
Infections and infestations	Lung infection	13.1	Very common	6.0*
	Urinary tract infection	12.7	Very common	2.6
Blood and lymphatic system disorders	Anaemia	28.2	Very common	9.7
	Neutropenia	11.3	Very common	4.4

Metabolism and nutritional disorders	Weight increased	26.4	Very common	7.3
	Decreased appetite	11.9	Very common	0.2
	Hyperuricemia	9.1	Common	1.8
	Dehydration	7.9	Common	1.0
	Tumour lysis syndrome	0.2	Uncommon	0.2*
Nervous system disorders	Dysgeusia	42.3	Very common	0.4
	Dizziness	39.7	Very common	1.2
	Dysaesthesia	29.0	Very common	0.2
	Cognitive disorders	24.2	Very common	4.4
	Headache	17.5	Very common	1.0
	Peripheral sensory neuropathy	15.7	Very common	1.0
	Ataxia	15.7	Very common	0.8
	Sleep disturbances	13.5	Very common	0.4
	Mood disorders	9.1	Common	0.6
	Syncope	4.6	Common	3.0
Eye disorders	Vision blurred	11.9	Very common	0.4
Cardiac disorders	Congestive heart failure	3.0	Common	2.2
	Electrocardiogram QTc prolonged	2.0	Common	0.6
Vascular disorders	Hypotension	16.5	Very common	2.4

Respiratory, thoracic and mediastinal disorders	Dyspnoea	27.0	Very common	5.8*
	Cough	21.4	Very common	0.6
	Pleural effusion	6.9	Common	2.8
Gastrointestinal disorders	Constipation	42.9	Very common	0.4
	Diarrhoea	33.5	Very common	2.6
	Nausea	32.1	Very common	0.8
	Vomiting	23.2	Very common	1.2
	Abdominal pain	11.1	Very common	0.6
	Dysphagia	10.1	Very common	0.4
Hepatobiliary disorders	AST increased	17.5	Very common	3.6
	ALT increased	16.1	Very common	3.4
Skin and subcutaneous tissue disorders	Rash	11.5	Very common	1.4
	Photosensitivity	2.8	Common	0
Musculoskeletal and connective tissue disorders	Myalgia	19.6	Very common	0.6
	Arthralgia	19.0	Very common	0.6
	Muscular weakness	12.3	Very common	1.2
	fractures	6.2	Common	2.4
Renal and urinary disorders	Blood creatinine increased	25.4	Very common	0.6
	Urinary retention	10.9	Very common	0.6

General disorders and administration site conditions	Fatigue	45.0	Very Common	5.0
	Oedema	37.3	Very Common	1.4
	Pain	24.4	Very Common	1.6
	Pyrexia	20.0	Very Common	0.8
*grades 3 to 5, inclusive of fatal adverse reactions (including 2 reactions of pneumonia, 2 reactions of dysnopea, and 1 reaction of tumour lysis syndrome).				

Description of selected adverse events for entrectinib

This section is based on the updated dataset from the SmPC and EPAR for Rozlytrek [27,28].

- **Cognitive disorders** (i.e. confusional state, cognitive disorder, memory impairment, disturbance in attention, amnesia, mental status changes, hallucination, delirium, disorientation, Hallucination visual, hallucination auditory, mental disorder) were reported in 24.2 % of patients, which is consistent with previously reported. Most patients experienced Grade 1 or 2 and 4.4 % experienced Grade 3 events. The majority of Grade 3 events were manageable and resolved with entrectinib dose interruption and/or dose reduction. Overall, cognitive disorders AEs were reported less frequently in pediatric patients compared to the adult population, with only one Grade 1 event of disturbance in attention in a pediatric patient.

  Cognitive disorders AEs were reported more frequently in patients with baseline CNS metastases compared to patients without baseline CNS metastases with the exception of AE of disturbance in attention. Expressed as percentages in patients with baseline CNS disease (n =176) versus patients without baseline CNS disease (n = 328) by PT were: cognitive disorder (6.3% vs. 6.4%), confusional state (8.5% vs. 6.7%), disturbance in attention (2.8% vs. 4.3%), memory impairment (5.1% vs. 3.7%), amnesia (3.4% vs. 2.4%), mental status changes (3.4% vs. 0%), mental disorder (0.6% vs. 0%), hallucination (2.3% vs. 0.3%), and delirium (1.1% vs. 0.9%).

  As mentioned most patients were able to continue entrectinib and only one case led to discontinuation.

- **Fractures** were reported in 6.2 % of patients. It is more frequently observed in pediatric patients aged <18 (20.7 %) compared to adult patients (5.3 %). In adult patients, some fractures occurred in the setting of a fall or other trauma to the affected area, while in pediatric patients all fractures occurred in patients with minimal or no trauma. Grade 3 fractures were reported in 2.4 % of patients. The median time to onset of the first fracture in patients who experienced fractures was

3.4 months (0.3 to 18.5 months). None of the fracture events led to discontinuation of entrectinib.

- **Ataxia** (i.e. ataxia, balance disorders and gait disturbances) was reported in 15.7 % of patients. The frequency of grade 3 ataxia remained at 0.8 % for the newest CCOD. Ataxia were observed in both patient with and without CNS metastases at baseline for the following preferred terms (expressed as percentages in patients with baseline CNS disease vs. patients without baseline CNS disease): ataxia (5.1% vs. 4.0%), balance disorder (8.0% vs. 4.3%), and gait disturbance (6.3% vs. 7.6%).

- **Syncope** was reported in 4.6 % of patients. All Grade 3 events (3.0 %) had been resolved at the time of CCOD.

- **QTc interval prolongation** was reported in 2.0 % of the patients. Grade 3 events were reported in 0.6 % of patients and in each of the cases entrectinib dose was either interrupted or dose reduced. All AEs were non-serious and with the exception of one, resolved.

- **Peripheral sensory neuropathy** (i.e. neuralgia, neuropathy peripheral, peripheral motor neuropathy) were reported in 15.7 % of patients. Consisting with the previous CCOD most patients experienced Grade 1 or 2 events, that in general were resolved without any dose interruption and/or reduction.

  1.0 % experienced Grade 3 peripheral sensory neuropathy events and all events resolved with entrectinib dose interruption and/or reduction. No Grade 4 AEs of peripheral sensory neuropathy were reported in the overall integrated safety population.

- **Eye disorders** were reported in 26.0 % of patients most frequently (2% of patients) were vision blurred (8.5%), photophobia (4.2%), dry eye (3.2%), diplopia 2.6%), and eye pain (2.2%). The majority of eye disorder events were Grade 1. The only Grade 3 eye disorder events were diplopia reported in 2 patients, which resolved in both cases.

  In the expanded safety population the finding was consistent with the events observed in the primary safety evaluable population.

10.6 Summary of adverse events - Paediatric patients

Table 32. Summary of Adverse Events per SOC in the pediatric safety population			
System organ	Frequency	Adolescents (n=7)	All pediatrics patients (n=32)

class			
Infections and infestations	Very common		Urinary tract infection (18.8), Lung infection (12.5%)
Blood and lymphatic system disorders	Very common	Anaemia (57.1%), Neutropenia (42.9%)	Anaemia (59.4%), Neutropenia (43.8%)
Metabolism and nutritional disorders	Very common	Weight increased (57.1%), Decreased appetite (14.3%)	Weight increased (50%), Decreased appetite (31.3%), Dehydration (25%)
Nervous system disorders	Very common	Dysgeusia (42.9%), Dysaesthesia (28.6), Mood disorders (28.6%), Cognitive disorders (14.3), Headache (14.3%), Syncope (14.3%), Peripheral sensory neuropathy (14.3%), Sleep disturbances (14.3%)	Headache (31.3%), Dysgeusia (21.9%), Mood disorders (28.1%), Ataxia (15.6%), Sleep disturbances (13.3%), Dizziness (12.5%), Peripheral sensory neuropathy (12.5%)
Eye disorders	Very common	Vision blurred (14.3%)	
Vascular disorders	Very common	Hypotension (14.3%)	Hypotension (18.8%)
Respiratory, thoracic and mediastinal disorders	Very common	Dyspnoea (28.6%), Cough (28.6%)	Dyspnoea (18.8%), Cough (50%), Pleural effusion (12.5%)
Gastrointestinal disorders	Very common	Nausea (71.4%), Abdominal pain (28.6%), Constipation (28.6%)	Nausea (46.9%), Abdominal pain (28.1%), Constipation (43.8%), Vomiting (34.4%), Diarrhoea (37.5%)
Hepatobiliary disorders	Very common	AST increased (57.1%), ALT increased (42.9%)	AST increased (50%), ALT increased (50%)
Skin and	Very		Rash (25%)

subcutaneous tissue disorders	common		
Musculoskeletal and connective tissue disorders	Very common	Arthralgia (14.3%), Myalgia (14.3%) Muscular weakness (28.6)	Fractures (21.9%) Muscular weakness (18.8%)
Renal and urinary disorders	Very common	Blood creatinine increased (57.1%)	Blood creatinine increased (43.8%), Urinary retention (21.9%)
General disorders and administration site conditions	Very common	Fatigue (42.9%) Pain (57.1%) Pyrexia (57.1%)	Fatigue (43.8%) Pain (46.9%) Pyrexia (56.3%) Oedema (18.8%)

Description of selected adverse events for pediatric patients

This section is based on the SmPC and EPAR for entrectinib in the pediatric population [27,28]. Please see Section 7.1.6, 7.1.7 and Appendix 10.5 in the safety section for the integrated safety analysis.

- **Fractures** occured in 21.8% (7/32) pediatric patients. In 2 paediatric patients, bilateral femoral neck fractures occurred. In both adult and paediatric patients, most fractures were hip or other lower extremity fractures (e.g., femoral or tibial shaft). No patients discontinued Rozlytrek due to fractures. The fractures occurred with minimal or no trauma. 11 fractures were reported in the 7 pediatric patients. The median time to fracture was 4.3 months (2.46 to 7.39 months). In 42.9 % of pediatric patients that experienced fractures had Rozlytrek interrupted. Three fractures were grade 2 and 4 fractures were Grade 3, of which three were serious. There were no reports of tumour involvement at the site of fractures. All but one event of fractures recovered.
- **Neurologic toxicity** was observed in 87.5% (28/32, Grade ≥3 15.7%) of the pediatric patients: the most common (i.e. ≥10%) AEs by preferred term (PT) were headache (31.3%, Grade ≥3 6.3%), dysgeusia (21.9%, none Grade ≥3), muscular weakness (18.8%, Grade ≥3 3.1%), photophobia (18.8%, none Grade ≥3), anxiety, insomnia, somnolence and urinary incontinence (15.6% each, none Grade ≥3), agitation, dizziness, enuresis, gait disturbance and irritability (12.5% each, Grade ≥3 gait disturbance AEs 6.3%).
- **Ataxia** AE**s** were observed in 5/32 pediatric patients (15.6%, Grade ≥3 6.3%), **peripheral sensory neuropathy** AEs in 4/32 (12.5%, none Grade ≥3), **cognitive disorders** AEs in 3/32 (9.4%, Grade ≥3 3.1%), **dysesthesia** AEs in 3/32 (9.4%, none Grade ≥3), **syncope** AEs in 3/32 (9.4%, Grade ≥3 6.3%), **seizure** AEs in 2/32 (6.3%, none Grade ≥3).
- **Elevated liver laboratory tests and other liver abnormalitie**s were reported in 23 out of 32 patients (71.9%, Grade ≥3 9.4%), the most common (i.e. ≥10%) AEs by PT being ALT increased (50%, Grade ≥3 6.2%), AST increased (50%, Grade ≥3 6.2%) and hypoalbuminemia (18.8%, Grade

≥3 3.1%). The majority of patients for whom elevated liver laboratory tests and other liver abnormalities AEs were reported, had Grade 1 events (46.9%) which resolved.

- **Haematologic** AEs were observe in 68.8% (22/32, Grade ≥3 43.8%) of patients: the most common (i.e. ≥10%) AEs by PT were anaemia (59.4%, Grade ≥3 12.5%), neutrophil count decreased (40.6%, Grade ≥3 25%), white blood cell count decreased (34.4%, Grade ≥3 9.4%), platelet count decreased (21.9%, Grade ≥3 9.4%) and lymphocyte count decreased (18.8%, Grade ≥3 12.5%).
- **Increased creatinine and other renal** AEs were reported in 22/32 patients (68.8%, Grade ≥3 3.1%) the most common (i.e. ≥10%) by PT being blood creatinine increased (43.8%, none Grade ≥3), haematuria (18.8%, none Grade ≥3), urinary tract infection (18.8%, Grade ≥3 3.1%), pollakiuria (15.6%, none Grade ≥3), proteinuria (15.6%, none Grade ≥3), urinary incontinence (15.6%, none Grade ≥3) and enuresis (12.5%, Grade ≥3 12.5%).
- **Changes in weight** AEs were observed in 17/32 patients (53.1%, Grade ≥3 25%), and the most common (i.e. ≥10%) AE by PT was weight increased (50.0%). The majority (13/32 patients [40.6%]) of weight increased events were assessed as related to entrectinib. Grade 1 or Grade 2 weight increased were reported in 9/32 patients (28.2%). Grade 3 weight increased was reported in 7/32 patients (21.9%). Four of 7 patients with Grade 3 weight increased were able to continue entrectinib without dose modifications. One Grade 3 AE of weight decreased (by PT) was reported. A change from baseline in BMI category was measured in 50.0% (16/32) of patients while receiving entrectinib treatment. Treatment-emergent shifts (increases) in body-mass index (BMI) category were observed for 13 patients who were underweight at baseline (to normal, overweight and obese categories), 2 patients who were of normal weight at baseline (to overweight or obese categories) and 1 patient who was overweight at baseline (to obese category).
- **Eye disorders** AEs were reported in 15/32 patients (46.9%, Grade ≥3 3.1%), the most common (i.e. ≥10%) by PT being photophobia(18.8%, none Grade ≥3) and eye pain (12.5%, none Grade ≥3).
- **Qt interval prolongation** AEs in 2/32 (6.3%, none Grade ≥3). All patients met the eligibility criteria of having electrocardiogram corrected QT intervals (QTc; determined using Fridericia's or Bazett's formula) of ≤480 msec. The majority (24/32 [92.3%]) of patients had normal QTc values (≤450 msec) at baseline and of these, all except two patients (with maximum post-baseline QTc intervals of >450 and ≤480 msec and >480 and ≤500 msec, respectively), maintained normal QTc intervals throughout the study. For the majority (23/32 [74.2%]) of patients, the maximum QTc interval increase from baseline was ≤30 msec; six patients had a maximum QTc increase of between 30 and 60 msec and two patients had an increase exceeding 60 msec.
- **Congestive heart failure** AEs in 1/32 (3.1%, Grade ≥3 3.1%) and pneumonitis AEs 1/32 (3.1%, Grade ≥3 3.1%).

10.6 Results per study

Table 33. 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. SmPC, Entrectinib 3. Doebele et al., Lancet Oncol, 2020
NCT number:	NCT: 02097810 NCT: 02568267 EudraCT: 2012-000148-88

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**)*	Entrectinib (Integrated analysis)	74 (24)	23.9 (16.0-NE)								

*Overall Survival rate at 24 months (**Critical outcome**)*	Entrectinib (Integrated analysis)	N/A	N/A										
*Proportion of patients with pCR or radical result of surgery (**Critical outcome)***	N/A	N/A											
EORTC-QLQ-C30 Mean change from baseline (**Critical outcome**)													
*Proportion of patients with objective response (**Important outcome)***	Entrectinib (Integrated analysis)	74 (47)	63.5% (51.5-74.4)										
*Median Progression-Free Survival (PFS) (**Important outcome**)*	Entrectinib (Integrated analysis)	74 (27)	11.2 (8.0-15.7)										
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”	

Table 34. Results of the intrapatient analysis on STARTRK-2 patients

Trial name: **An Open-Label, Multicenter, Global Phase 2 Basket Study of Entrectinib for the Treatment of Patients With Locally Advanced or Metastatic Solid Tumor**

	Published in: 1. Bennett et al., ISPOR (2019)
NCT number:	NCT: 02568267

Efficacy outcomes

Outcome	Study arm	N (patients with event)	Result (CI)	Estimated Difference
*Median Overall Survival (OS) (**Critical outcome**)*	N/A	N/A	N/A	
*Overall Survival rate at 24 months (**Critical outcome**)*	N/A	N/A	N/A	
*Proportion of patients with pCR or radical result of surgery (**Critical outcome)***	N/A	N/A	N/A	
EORTC-QLQ-C30 Mean change from baseline (**Critical outcome**)	N/A	N/A	N/A	

*Proportion of patients with objective response (**Important outcome**)*	N/A	N/A	N/A
Proportion of patients with CR or PR	Entrectinib (Patients with prior therapy)	31 (16)	51.6%
	Most recent prior therapy (Patients with prior therapy)	31 (4)	12.9%
	Entrectinib (Documented progression on prior therapy)	21 (11)	52.4%
	Most recent prior therapy (Documented progression on prior therapy)	21 (2)	9.5%
	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
*Median Progression-Free Survival (PFS) (**Important outcome**)*	N/A	N/A	N/A
Median TTNT	Entrectinib (Patients with prior therapy)	31	**TTNT** 14.8 (10.0-NA) **PFS**

			13.7 (7.7-NA)	
	Most recent prior therapy (Patients with prior therapy)	31	**TTNT** 4.6 (3.5-8.0)	
	Entrectinib (Documented progression on prior therapy)	21	**TTNT** 10.0 (6.4-NA) **PFS** 8.7 (6.2-NA)	
	Most recent prior therapy (Documented progression on prior therapy)	21	**TTNT** 4.0 (2.9-7.0)	
	[redacted]	[redacted]	[redacted]	
	[redacted]	[redacted]	[redacted]	
Safety outcomes				
				Estimated
Outcome	Study arm	N	Result (n)	Difference

*Proportion of patients experiencing grade 3-4 adverse events, % (**Important outcome**)*	N/A	N/A	N/A	
Proportion of patients experiencing grade 3-4 adverse events, %	N/A	N/A	N/A	

Table 35. Results from Rosen et al.											
Trial name:	**TRK Fusions Are Enriched in Cancers with Uncommon Histologies and the Absence of Canonical Driver Mutations** Published in: 1. Rosen et al., Clin Cancer Res (2020)										
NCT number:	01775072										
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**)*	N/A	N/A	N/A								
*Overall Survival rate at 24 months (**Critical outcome**)*	N/A	N/A	N/A								
Proportion of patients with pCR or radical result	N/A	N/A	N/A								

*of surgery (**Critical outcome)* EORTC-QLQ-C30 Mean change from baseline (**Critical outcome**)	N/A	N/A	N/A				
*Proportion of patients with objective response (**Important outcome)***	TRK-fusion positive patients (First-line therapy)	15	46.7% (21.3-73.4)				
	TRK-fusion positive patients (Chemotherapy-containing regimens)	24	62.5% (40.6-81.2)				
	TRK-fusion positive patients (TRK inhibitor therapy)	34	67.6% (49.5-82.6)				
*Median Progression-Free Survival (PFS) (**Important outcome**)*	TRK-fusion positive patients	51	9.1 (4.8-13.1)				
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 experiencing grade 3-4 adverse events, % (**Important outcome**)*	N/A	N/A	N/A								

Table 36. Results from the CoPPO trial

Trial name:	**Copenhagen Prospective Personalized Oncology (CoPPO)** Published in: 1. Tuxen et al., Clin Cancer Res (2020)										
NCT number:	02290522										
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**)*	N/A	N/A	N/A								
*Overall Survival rate at 24 months (**Critical outcome**)*	N/A	N/A	N/A								
*Proportion of patients with pCR or radical result of surgery (**Critical outcome)***	N/A	N/A	N/A								

EORTC-QLQ-C30 Mean change from baseline (**Critical outcome**)	N/A	N/A	N/A										
*Proportion of patients with objective response (**Important outcome)***	Patients receiving matched treatment	101 (15)	15%										
*Median Progression-Free Survival (PFS) (**Important outcome**)*	Patients receiving matched treatment	101	12 weeks (9.9-14.4)										
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 experiencing grade 3-4 adverse events, % (**Important outcome**)*	N/A	N/A	N/A										

Table 37. Results for clinical question 1

Results per outcome										Methods used for quantitative synthesis
				Absolute difference in effect			Relative difference in effect			Naïve comparison
	Studies included in the analysis	Study/intervention	Result	Difference (relative to entrectinib)	CI	*P* value	Hazard/Odds/Risk ratio	CI	*P* value	
Median Overall Survival (OS) (**Critical outcome**)	Integrated analysis (entrectinib, n=74), BSC analysis	Entrectinib (Integrated analysis)	23.9 months (16.0, NE)	N/A	N/A	N/A				
		Best Supportive Care (Median OS)	4.9 months (3.9, 6.9)	19.0 months	N/A	N/A				
Overall Survival rate at 24 months (**Critical outcome**)	N/A	N/A	N/A	N/A	N/A	N/A				
Proportion of patients with pCR or radical result of surgery (**Critical outcome)**	N/A	N/A	N/A	N/A	N/A	N/A				
EORTC-QLQ-C30 Mean change from baseline (**Critical outcome**)	Entrectinib (STARTRK-2), BSC analysis (Grothey et al., Hofmann et al.)	Entrectinib (STARTRK-2)	5.3 (at cycle 13)	N/A	N/A	N/A				
		Best Supportive Care (Grothey et al.)	-12.8 (at end of treatment)	N/A	N/A	N/A				

		Best Supportive Care (Hofmann et al.)	N/A	N/A	N/A	N/A				
Proportion of patients with objective response (**Important outcome)**	Integrated analysis (entrectinib, n=74), Rosen et al (TRK-fusion positive patients, CoPPO trial (matched treatment), BSC analysis	Entrectinib (Integrated analysis)	63.5% (51.5, 74.4)	N/A	N/A	N/A				
		TRK-fusion positive patients on first-line therapy (Rosen et al. 2020)	46.7% (21.3, 73.4)	16.8%	N/A	N/A				
		TRK-fusion positive patients on chemotherapy-containing regimens (Rosen et al. 2020)	62.5% (40.6, 81.2)	1%	N/A	N/A				
		TRK-fusion positive patients on TRK-inhibitor therapy (Rosen et al. 2020)	67.6% (49.5, 82.6)	-4.1%	N/A	N/A				
		Patients receiving matched treatment (CoPPO trial)	15% (9, 24)	48.5%	N/A	N/A				

		Best Supportive Care (median ORR)	1.4% (0%, 2.38%)	62.1%	N/A	N/A				
*Median Progression-Free Survival (PFS) (**Important outcome**)*	Integrated analysis (entrectinib, n=74), Rosen et al (TRK-fusion positive patients, CoPPO trial (matched treatment), BSC analysis	Entrectinib (Integrated analysis)	11.2 months (8.0, 15.7)	N/A	N/A	N/A				
		TRK-fusion positive patients (Rosen et al. 2020)	9.1 months (4.8, 13.1)	2.1 months	N/A	N/A				
		Patients receiving matched treatment (CoPPO trial)	12 weeks (95% CI: 9.9, 14.4) ≈ 2.8 months (4.348 weeks per month)	8.4 months	N/A	N/A				
		Best Supportive Care (median PFS)	1.8 months (1.48; 224)	9.45 months	N/A	N/A				
*Proportion of patients experiencing grade 3-4 adverse events, % (**Important outcome**)*	Integrated analysis (entrectinib, n=504)	Entrectinib (Integrated analysis)	61.1%							

Table 38. Results for clinical question 1 – Intrapatient analysis

Results per outcome										
				Absolute difference in effect			Relative difference in effect			Methods used for quantitative synthesis
	Studies included in the analysis	Study/intervention	Result	Difference (relative to entrectinib)	CI	*P* value	Hazard/Odds/Risk ratio	CI	*P* value	Naïve comparison
Proportion of patients with objective response (**Important outcome)**	Intrapatient analysis (Bennett et al. 2020)	Entrectinib (Documented progression on prior therapy)	52.4%	N/A	N/A	N/A				
		Most recent prior therapy (Documented progression on prior therapy)	9.5%	42.9%	N/A	N/A				
Median TTNT	Intrapatient analysis (Bennett et al. 2020)	Entrectinib (Patients with prior therapy)	14.8 months	N/A	N/A	N/A				
		Most recent prior therapy (Patients with prior therapy)	4.6 months	10.2 months	N/A	N/A				
		Entrectinib (Documented	10.0 months	N/A	N/A	N/A				

		progression on prior therapy)								
		Most recent prior therapy (Documented progression on prior therapy)	4.0 months	6.0 months	N/A	N/A				
Proportion of patients with objective response (**Important outcome**)	[redacted]	[redacted]	[redacted]	N/A	N/A	N/A				
		[redacted]	[redacted]	[redacted]	N/A	N/A				
Median TTNT	[redacted]	[redacted]	[redacted]	N/A	N/A	N/A				
		[redacted]	[redacted]	[redacted]	N/A	N/A				

Table 39. Results for clinical question 2

Results per outcome										
				Absolute difference in effect			Relative difference in effect			Methods used for quantitative synthesis Naïve comparison
	Studies included in the analysis	Study/intervention	Result	Difference (relative to entrectinib)	CI	*P* value	Hazard/Odds/Risk ratio	CI	*P* value	
Median Overall Survival (OS) (**Critical outcome**)	STARTRK-NG	Entrectinib	NR	N/A	N/A	N/A				
Overall Survival rate at 24 months (**Critical outcome**)	STARTRK-NG	Entrectinib	NR	N/A	N/A	N/A				
Proportion of patients with pCR or radical result of surgery (**Critical outcome)**	STARTRK-NG	Entrectinib	N/A	N/A	N/A	N/A				
EORTC-QLQ-C30 Mean change from baseline (**Critical outcome**)	STARTRK-NG	Entrectinib	N/A	N/A	N/A	N/A				
Proportion of patients with objective response (**Important outcome)**	STARTRK-NG	Entrectinib (fusion-positive patients, n=34)	86%	N/A	N/A	N/A				
		Entrectinib (NTRK fusion-	3 CR, 1 PR (and 1 PD)	N/A	N/A	N/A				

		positive patients – CNS tumors, n=5)								
		Entrectinib (NTRK fusion-positive patients – CNS tumors, n=3)	2 CR and 1 PR	N/A	N/A	N/A				
*Median Progression-Free Survival (PFS) (**Important outcome**)*	STARTRK-NG	Entrectinib (fusion-positive patients, n=34)	17.5 months (7.4, NE)	N/A	N/A	N/A				
*Proportion of patients experiencing grade 3-4 adverse events, % (**Important outcome**)*	STARTRK-NG	Entrectinib Paediatric safety population (n=29)	55.2% (16/29) (grade 3-5)	N/A	N/A	N/A				

Cost per patient and budget impact analysis of Rozlytrek (entrectinib) for the treatment of NTRK fusion-positive cancer

On the 18th of June 2020, Roche received the protocol for evaluating the clinical added value of Rozlytrek® (entrectinib for treatment of NTRK-fusion-positive tumours) by the Danish Medicine Council (1). Two clinical questions was presented in the DMC protocol; the first being:"*Hvad er den kliniske merværdi af entrectinib til behandling af voksne med NTRK-fusion-positiv kræft, hvor øvrige behandlingsmuligheder er udtømte, sammenlignet med placebo?*", while the second being: "*Hvad er den kliniske merværdi af entrectinib til behandling af børn med NTRK-fusion-positiv kræft, hvor øvrige behandlingsmuligheder er udtømte, sammenlignet med placebo?"* (1). The economic analysis will only incorporate data from the adult population. This is chosen due to the following reasons:

- As discussed in the clinical application, there is no efficacy data for the population between 12-18 years. The available efficacy data is for younger patients (below 12 years of age).
- No paediatric studies appeared in the systematic literature search (neither for known or unknown NTRK status. For this reason, no efficacy data is available for BSC per tumor type in the paediatric population.
- Due to BSC being a relatively low-cost intervention, the inclusion of additional patients would likely not change the result significantly.

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

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EXECUTIVE SUMMARY

Baggrund

Den 19. juni 2020 offentliggjordes Medicinrådets protokol for vurdering af entrectinib til behandling af NTRK fusions-positiv kræft. Protokollen omfattede følgende kliniske spørgsmål:

1. *Hvad er den kliniske merværdi af entrectinib til behandling af voksne med NTRK-fusion-positiv kræft, hvor øvrige behandlingsmuligheder er udtømte, sammenlignet med placebo?*
2. *Hvad er den kliniske merværdi af entrectinib til behandling af børn med NTRK-fusion-positiv kræft, hvor øvrige behandlingsmuligheder er udtømte, sammenlignet med placebo?*

Dette tekniske dokument beskriver de økonomiske analyser, hhv. omkostningsanalyser og budgetkonsekvensanalyser, som er udarbejdet som en del af ansøgningen til Medicinrådet og er baseret på den voksne population i den integrerede analyse af entrectinib. 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 baseret på overall survival [OS]) blev udviklet for at estimere de inkrementelle omkostninger per patient for entrectinib sammenlignet med best supportive care (BSC). 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 NTRK-fusion-positive kræft 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 BSC er data identificeret i søgestrengen fra Medicinrådets protokol, hvor median PFS og OS værdier er blevet inkluderet i modellen. Disse værdier anvendes til at estimere omkostning af BSC baseret Entrectinib kohortens fordeling i kræft typer for at genere den mest optimale sammenligning med entrectinib populationen.

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

Resultater

Base casen for analysen viser en inkrementel diskonteret meromkostning på [redacted] og en inkrementel estimeret levetid på [redacted] entrectinib sammenlignet med BSC. Dette resulterede i en omkostning per inkrementelt leveår på DKK [redacted]

Budgetkonsekvenserne estimeres i år 5 (steady state) til at være [redacted] ved anbefaling af entrectinib som behandling for NTRK-fusion-positive kræft patienter.

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1 Introduction

1.1 Background

A solid tumour is an abnormal tissue mass and can be benign or malignant (cancer). Malignant cancers are by definition capable of penetrating other tissues and can spread to other parts of the body.

Knowledge about molecular mutations and biomarkers in cancer have increased in recent years and some of these alterations have been identified as oncogenic drivers. One of such oncogenic drivers is the gene fusion of the encoding genes, neurotrophic receptor tyrosine kinase (NTRK) 1/2/3 for the tropomyosin receptor kinase (TRK) A/B/C cell surface receptors. Gene fusions involving NTRK1, NTRK2 or NTRK3 can cause uncontrolled TRK signalling and thus leading to tumour growth (2). NTRK-fusions (fusions between gene mutations) are rare and have been identified in solid tumours vary across different tumour types in adults and children.

1.2 Intervention treatment

Rozlytrek (entrectinib) is an oral, central nervous system (CNS)-active, selective inhibitor of the TRK A/B/C, c-ros oncogene 1 (ROS1), and anaplastic lymphoma kinase (ALK). Gene rearrangements (fusions) in each of the genes encoding these target kinases can result in fusion proteins that constitutively activate downstream signalling 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.(3)

Entrectinib has been studied in four pivotal trials (phase 1 and 2) of NTRK-fusion positive patients: ALKA-372-001, STARTRK-1, STARTRK-2 and STARTRK-NG. All of these showed a treatment effect significantly beyond historic controls, which led to the application and anticipated regulatory approval(4).

The EMA approved indication for entrectinib is:

"Rozlytrek as monotherapy is indicated for the treatment of adult and paediatric patients 12 years of age and older with solid tumours expressing a neurotrophic tyrosine receptor kinase (NTRK) gene fusion,

- *who have a disease that is locally advanced, metastatic, or where surgical resection is likely to result in severe morbidity,*
- *who have not received a prior NTRK inhibitor, and*
- *who have no satisfactory treatment options."*

It is further described in Section 4.4 of the SmPC, that: "*Rozlytrek should only be used if there are no satisfactory treatment options (i.e., for which clinical benefit has not been established, or where such treatment options have been exhausted)."*(5).

The recommended dosing of entrectinib is adults: 600 mg orally, once daily, and for children with a body surface area (BSA) <1,5 m^2: 300 mg/m^2 orally, once daily.

1.3 Current treatment

Standard treatment is dependent on the cancer type and the stage of the disease. Standard treatment can either be defined as surgical intervention or pharmaceutical intervention. Surgical intervention is usually used as first-line treatment, while pharmaceutical interventions are used in the later treatment lines. For paediatric patients, chemotherapy will often be the first-line treatment.

The pharmaceutical intervention is dependent on various factors, e.g. the cancer type, the progression of the disease, whether the tumour expresses specific molecular genetic changes, to which targeted therapies have been developed. In addition, the patient must be in a condition where they are well enough to be able to receive additional therapy.

For a small proportion of patients with rare cancer types, a standard treatment is not established. Some patients will have exhausted all the standard treatment options during their clinical treatment course, thereby having no standard treatment options with a satisfactory result. The patients in this group can either be treated with experimental treatment or be offered palliative treatment (best supportive care (BSC)).

1.4 Patient population

Based on the DMC protocol, the committee estimates the number of patients with NTRK-fusion positive tumours to be between 10 and 40 patients yearly (1).

2 Purpose

The economic model was developed to estimate the incremental costs per patient as well as the budget impact of entrectinib for treating NTRK-fusion positive tumours. The model will utilize a restricted societal perspective per the DMC's guidelines (6).

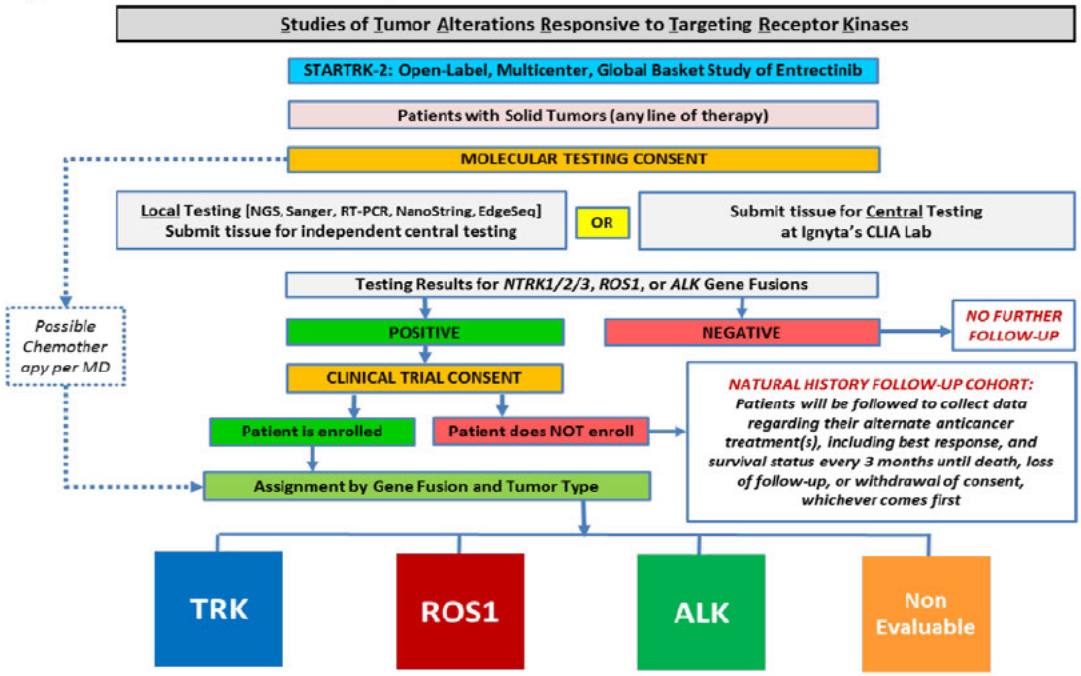
3 Direct clinical evidence

3.1 Description of the pooled entrectinib trials

Two phase 1 clinical studies - ALKA-372-001 (7) and STARTRK-1 (8) - were conducted to determine the recommended Phase 2 dose (RP2D) of entrectinib. Within the Phase 2 trial patients with locally advanced or metastatic solid tumours were enrolled irrespective of tumour type. Within the two Phase 1 trials, NTRK-positive patients were treated.

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

Figure 1: Design of STARTRK-2 Basket study



3.2 Clinical outcomes of the pooled entrectinib trials

- ***NTRK* fusion-positive locally advanced or metastatic solid tumours**
  - Objective response rate of 63.5% (95% CI: [51.5%, 74.4%] Meeting the trial primary objective as the lower limit of 95% CI excludes 30%)
  - DOR (median: 12.9m, 95% CI: [9.3, NE]) and PFS (median: 11.2m, 95% CI: [8.0, 15.7] excluding the lower limit of 6m) showed durability of the effects
  - CNS response is similar to systemic response, with DOR reflecting the durability of effects on pts with CNS disease.

[redacted] reports on the count of NTRK patients from the integrated analysis of 3 clinical trials on entrectinib.

3.3 Pooled Clinical trial results

3.3.1 NTRK+ result overview

Table 2 reports the OS and PFS of entrectinib in the NTRK fusion-positive pooled population. The NTRK OS data is immature at this point in time. The following section describes the data that has been assessed and implemented in the model. Table 2 presents the OS and PFS of entrectinib (PFS is based on a blinded independent central review (BICR)). The KM curves for BICR-PFS and OS is presented in Figure 2 and Figure 3.

Error! Reference source not found. provides an overview of the tumour type distributions among the pooled NTRK cohort.

Table 2. PFS and OS summary for NTRK+ pooled data, (n=74)

Endpoint	PFS (BICR)	OS

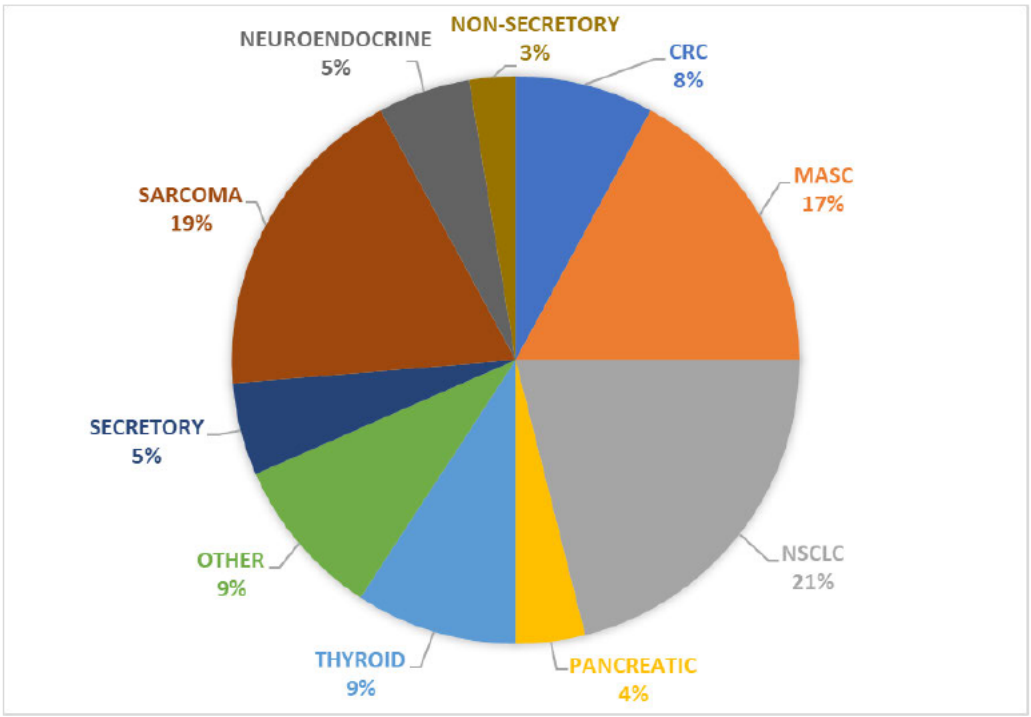
**Probability of not getting the event of interest, in the time horizon assessed*

[redacted]

[redacted]

[redacted]

Figure 4. Tumour distribution on NTRK in pooled cohort (n=74)



Key: CRC: colorectal cancer; MASC: Mammary analogue secretory carcinoma; NSCLC: Non-small cell lung cancer

4 Indirect Clinical Evidence

Based on the literature search string provided in the protocol from the Medicines Council, Roche examined the available literature for studies containing a BSC arm. Although the identified literature was for patients with unknown NTRK fusion status, the study population had to be within scope of the entrectinib indication. The included studies contain data on patients in later lines of therapy with no other identified driver mutation.

The literature search resulted in 28 articles with BSC in late line treatment. Studies were clustered according to their tumour type, and median OS and PFS.

4.1 Colorectal cancer

11 studies presenting relevant outcome data on Colorectal cancer (CRC) was included, as presented in Table 3. Based on the reported data, the following CRC averages and outcome intervals were estimated: 5.19 (2,80-7,40) months median OS and 1,90 (1,68-2,63) months median PFS.

Table 3. Median OS and Median PFS for BSC in colorectal cancer

Publication	Population	Median OS, months	Median PFS, months
Rao et al, 2004	n=133	6,08*	2,63*
Van cutsem et al, 2007	n=232	N/A	1,68
Sorbye et al, 2009	n=244	2,80	N/A
Grothey et al, 2013	n=255	5,00	1,70
Caballero-Baños, M et al, 2016	n=24	4,70	2,30
Grothey, A et al, 2018	n=42	6,14*	1,86*
Jonker, D. J. et al, 2018	n=144	4,80	N/A
Kim, T. W. et al, 2018	n=128 (Wild Type RAS cohort)	6,90	1,70
	n=114 (Wild Type RAS, Wild Type BRAF cohort)	7,40	1,80
Van Cutsem, E. et al, 2018	n=35 (USA cohort)	4,30	1,70
	n=132 (EU cohort)	4,90	1,70
Chen, E. X. et al, 2020	n=61	4,10	1,90

Key: * converted from weeks to months (Number of weeks per month = 4.35); N/A - not available

4.2 Non-small cell lung cancer

10 studies presenting relevant outcome data on Non-Small Cell Lung Cancer (NSCLC) was included, as presented in Table 4. Based on the reported data, NSCLC average and outcome intervals were created. Results were an average of 5.52 (range: 1.95-8.5) months median OS, and an average of 2.49 (range: 0.5-7) months median PFS.

Table 4. Median OS and Median PFS for BSC in Non-Small Cell Lung Cancer

Publication	Population	Median OS, months	Median PFS, months
Agteresch, HJ. et al, 2000	n=30	4,70	N/A
Ranson, M. et al, 2000	n=78	4,80	0,50
Roszkowski, K. et al, 2000	n=70	5,70	2,05
Thatcher, N. et al, 2005	n=563	5,10	N/A
Parikh, P. M. et al, 2011	n=53	3,70	1,38
Belani, C. P. et al, 2012	n=115 (Non-East Asian population)	8,50	1,80
Lee, S. M. et al, 2012	n=320	3,60	2,60
Paz-Ares, L. et al, 2015	n=353	8,30	1,40
Mulvenna, P. et al, 2016	n=269	1,95*	N/A
Satyanarayan, S. et al, 2016	n=49	8,00	7,00

Key: * converted from weeks to months (Number of weeks per month = 4.35); N/A - not available

4.3 Other cancer types

The remaining 8 studies present relevant outcome data on the following cancer types: GastroIntestinal Stromal Tumour (GIST), pancreatic cancer, sarcoma, glioblastoma, and melanoma, as presented in Table 5. Based on the reported data following averages and outcome intervals were created. For GIST, median OS was only reported in one study with 12,9 months. The average median PFS was 1,60 (0,9-2,3) months.

For pancreatic cancer, the average median OS was 2,59 (2,30-2,76) months. Median PFS was only reported for one trial (1,41) months. For sarcoma, glioblastoma and melanoma see Table 5, as only one trial was included for each of these cancer types.

Table 5. Median OS and Median PFS for BSC in other cancer types

Publication	Cancer type	Population	Median OS, months	Median PFS, months
Demetri G et al, 2013	GIST	n=66	N/A	0,90
Mir O et al, 2016	GIST	n=41	12,90	2,30
Ciuleanu, T. E. et al, 2009	Pancreatic	n=155	2,76*	1,41*
Pelzer, U. et al, 2011	Pancreatic	n=23	2,30	N/A
Tröger, W. et al, 2013	Pancreatic	n=110	2,70	N/A
Le Cesne, A. et al, 2016	Sarcoma	n=51	10,8	1.4
Socha, J et al, 2016	Glioblastoma	n=47	6,90*	3,68*
Hofmann, M et al 2011	Melanoma	n=24	4,50*	N/A

Key: * converted from weeks to months (Number of weeks per month = 4.35); N/A - not available

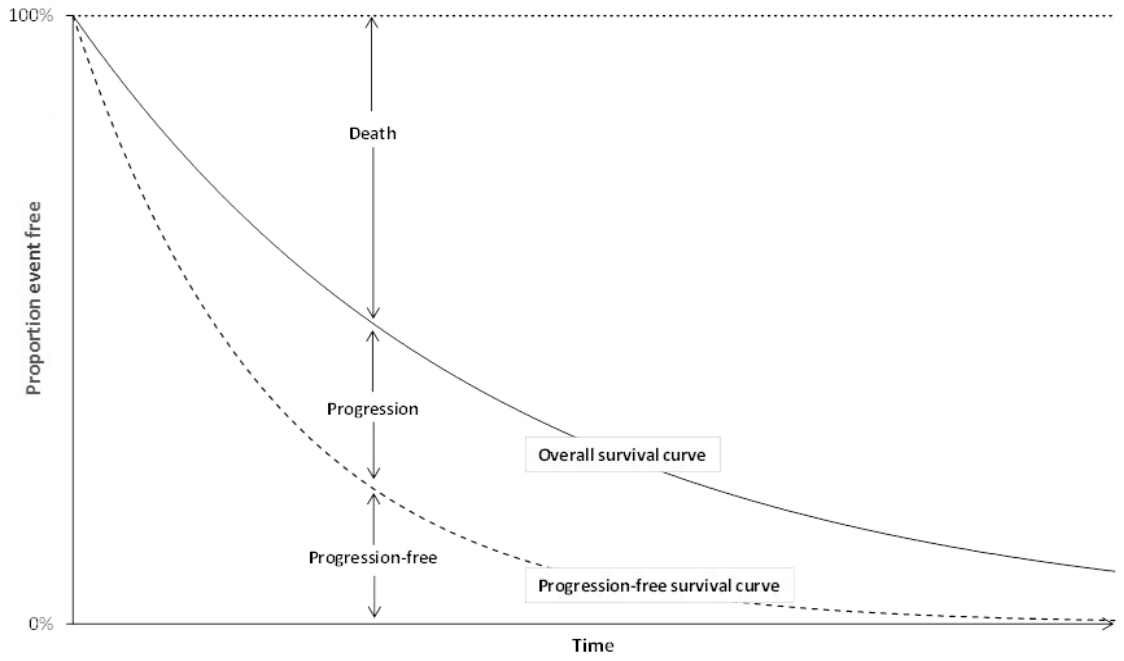
5 Health economic model structure

5.1 Model Description

The health economic model 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 stratification of the proportion of patients alive into on PFS and PPS. The proportion of patients in the PPS health state at any 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.

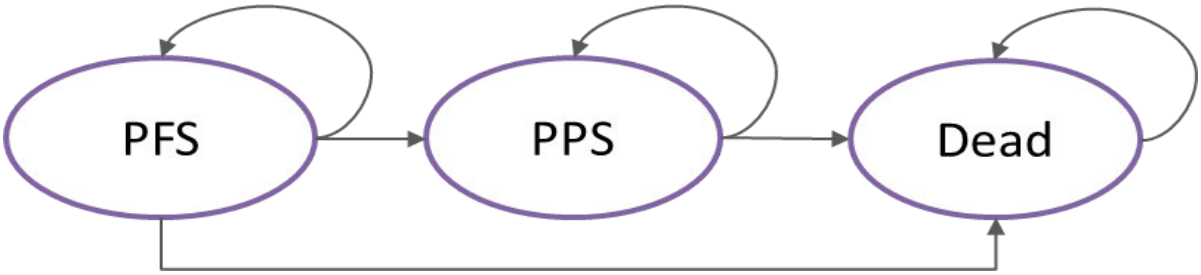
The model inputs were based on the results of the pooled entrectinib trials, as described in section **3**.

Figure 5 Example of a partitioned survival model



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

Figure 6 Diagram of the model for a partitioned survival model



5.1.1 Progression-free state

All patients enter the model in the progression-free state and can transition out of this state to progressed or dead overtime. PFS curves, estimated from the pooled trial data determine the rate at which patients transition out of the PFS state. Within the partitioned survival framework, any patient who is under the PFS curve is considered alive and not yet progressed.

5.1.2 Post-progression state

The post-progression state includes all patients who have experienced disease progression but have not yet died. The proportion of patients in this state is calculated as the difference between the proportion of patients who are alive and the proportion of patients who were in the progression-free health state. Given the partitioned survival framework, transitions into and out from the post-progression health state are not modelled explicitly and are calculated as a residual proportion of patients.

5.1.3 Death state

Death is as an absorbing state meaning that all patients that enter this state and cannot leave it. The transition of patients from the progression-free and post-progression health states into the death state is determined by the overall survival curve derived from the clinical trials. The overall survival curve indicates 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 amount of time that has passed.

5.2 The rationale for model structure

There is a long history of using partitioned survival models for Health Technology Assessments (9). The main reason for this is that this allows the direct use of PFS and OS curves fitted to the clinical trial. This approach makes the model intuitive and easy to communicate whilst also allowing for a good representation of the observed trial data. In addition, partitioned survival models allow for modelling changes in the hazard rates dependent on time in a current state and do not rely on the rather restrictive assumption of time-invariant hazard rates that are made in Markov models (9).

There are limitations to partitioned survival 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 (9). 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 partitioned survival approach used in this economic analysis models the curves independently, and this can result in the curves crossing. We have adjusted the overall survival in the model such that the curves do not cross. This is done by ensuring that survival can never 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 uses a cycle length of 1 week in order to align with the dosing time of the intervention. The model assumes that transitions from one health state to another occur at the beginning of each cycle. However, in reality the patient transition is a continuous process, which may occur at any time during the cycle. By applying a cycle length of one week, the difference between the real possible 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.

5.4 Modelling of Best Supportive Care

The BSC arm also uses the partitioned survival framework. However, synthesis of PFS and OS curves of different tumour types was not feasible as the individual patient data (IPD) required for modelling each tumour type was not available. To get around this, PFS and OS outcomes for BSC have been estimated using medians reported in literature. As the partitioned survival approach requires means (area under the curve), the reported median for OS and PFS was converted to a mean, assuming an exponential distribution (Equation 1).

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

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

The estimated mean PFS and OS of each tumour type from the literature, is then averaged, weighted by the proportion of tumour types present in the pooled entrectinib trials NTRK+ cohort. This approach is an effort to simulate the progression-free and overall survival of the

BSC arm as applied on the entrectinib cohort, in order to allow comparability between entrectinib and BSC. With the PFS and OS estimates, it is possible to estimate the cost within PFS and PPS for the BSC arm. Within the 'Inputs for BSC NTRK+'-sheet, monthly costs have been estimated for treatment, routine care, patient time and administration. Within the 'BSC_NTRK+'-sheet, the means are estimated and the cost-per-patient is estimated with the mean durations of PFS and OS and the monthly costs. The treatment costs and the routine care costs, patients and transportation costs and end of life costs estimated for each patient during PFS and PPS within this sheet. Costs will be discounted following the first year. A mean is estimated across all the entire cohort to generate a comparable result to the entrectinib arm of the model.

6 Model inputs

6.1 Intervention and comparators

Two arms have been included in the model:

- Intervention: Entrectinib
- Comparator: Best supportive care
    - Carboplatin

For the BSC arm, 25% of the patients were assumed to receive a chemotherapy regimen to reflect that some patients will receive palliative chemotherapy as part of their BSC. The proportion of patients receiving chemotherapy is user-definable with the "Cost Inputs"-sheet. For the chemotherapy regimen, a carboplatin-regimen was included, as a low-cost chemotherapy regimen. As we speculate that an expensive chemotherapy regimen would be unlikely in the last line of treatment and could potentially overestimate the cost of the BSC arm. We therefore regard the carboplatin-regimen as a conservative cost estimate of the chemotherapy likely to be used for some patients in the BSC arm.

Although the model does not include costs for non-chemotherapy BSC, it is expected that BSC will result in some costs depending on the form of BSC. Radiation therapy or treatment with medication may result in costs related to e.g. visits, treatment of AEs and more. Due to the heterogeneity in BSC these costs are however difficult to calculate.

The dosing for the intervention, entrectinib, is based on the regimen provided in the DMC protocol for the assessment for entrectinib for NTRK-fusion positive tumours. The dosing of the carboplatin-regimen in the best supportive care arm is based on the SmPC of carboplatin.

6.2 Clinical inputs for Entrectinib

6.2.1 Parametric Fit overview

To enable estimation of cost throughout the entire time horizon, extrapolation of clinical trial data is required, as the follow-up time of the trial is not be long enough to populate the required time horizon in its entirety. Extrapolation beyond the pooled entrectinib trials clinical follow-up period was performed by fitting standard parametric distributions to the observed time to event data from the pooled entrectinib trials on the ITT population. For the naïve comparison parametric distributions were fitted independently to each treatment arm.

6.2.2 PFS: Probability of remaining progression-free and alive

Patients remain in the PFS health state as long as they remain progression-free (as defined by RECIST v.1.1(10)) or have not died.

As the entrectinib trials are single-arm, diagnostic plots of the log cumulative hazard for PFS over the log of time to test the proportional hazards (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) and Bayesian Information Criterion (BIC). Low values for AIC and BIC indicate a better statistical fit of the parametric function to the actual data.
- Visual assessment of each parametric function.

Goodness of fit of the parametric functions
Parametric distributions were assessed for their goodness of fit to the data using the AIC, BIC and visual assessment of each parametric function. Low values for AIC and BIC indicate a better statistical assessment of the fit of the parametric function to the actual data. However, the quality and plausibility of the extrapolation beyond the observed data cannot be assessed statistically as this is not reflected in the calculation of the AIC and BIC.

Table 6 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 statistical fit would be obtained with an exponential function. Upon visual inspection of the curves included in [redacted]

Table 6: AIC and BIC for PFS

Parametric distribution	AIC NTRK	BIC NTRK
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

[redacted]

[redacted]

6.2.3 OS: Probability of remaining in alive

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

Table 7 provides the AIC and BIC goodness of fit results for the functions used to model OS.

[redacted]

[redacted]

[redacted]

Table 7: AIC and BIC for OS

Parametric distribution	AIC NTRK	BIC NTRK
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

[redacted]

[redacted]

6.2.4 Time to treatment discontinuation

The model accounts for treatment duration by utilising time to treatment discontinuation (TTD) curves using the available trial data from the pooled entrectinib trials. TTD is calculated as the difference between the times where the patient is receiving the first dose and when the patient is receiving the last dose.

[redacted]

Goodness of fit of the parametric functions

Since TTD is only modelled for entrectinib patients, there is no need to assume proportional hazards. Table 8 summarizes the AIC and BIC statistics from the parametric models fit on the TTOT observations for entrectinib [redacted]

Table 8: AIC and BIC for TTD

Parametric distribution	AIC NTRK	BIC NTRK
[redacted]		

[redacted]

6.3 Clinical input for best supportive care

Data on the patient's tumour types in the pooled Entrectinib NTRK trial cohort are used to estimate the mean PFS and OS of the BSC arm. The data identified in the literature search string provided by the DMC was used to populate the model for the BSC arm(1), see section 4 for further information. The reported median PFS and OS values from the publications was

synthesised for each tumour group, and for the tumour groups where specific data was not identified, an average median PFS and OS of all the identified data was estimated and inputted in place of specific data. The synthesised PFS and OS values are reported in Table 9.

Table 9. Synthesised median PFS and OS values identified from the best supportive care literature search

Tumour types	PFS (months)	OS (months)
Colorectal cancer	1,90	5,19
MASC*	2,06	5,54
Papillary thyroid*	2,06	5,54
Anaplastic thyroid*	2,06	5,54
Squamous NSCLC	2,39	5,52
Non-squamous NSCLC	2,39	5,52
Pancreatic	1,41	2,59
Sarcoma	1,4	10,80
Neuroendocrine*	2,06	5,54
Secretory breast*	2,06	5,54
Non-secretory breast*	2,06	5,54
Other*	2,06	5,54

Key; * denotes a total average have been inputted due to lack of tumour specific data

[redacted]

6.4 Time horizon

It is recommended that the selected time horizon should be long enough to reflect all the important differences in costs between the technologies being compared (6).

For the base-case analysis, a time horizon of 30 years has been selected. [redacted]

6.5 Perspective

The perspective of the economic model is a restricted societal perspective, which includes cost related to drug acquisition, drug administration, monitoring, adverse events, routine care, patient time, and transportation. Indirect costs are not included following the DMC's guidelines (6).

6.6 Discounting rate

In the base-case, the annual discount rate for future costs were 4% in alignment with DMC's guidelines, where the use of the Danish Ministry of Finance's discount rate is recommended (12).

6.7 Adverse events

In a cost-per-patient model, grade 1 to 2 AE are expected to have minimal impact on the cost. Therefore, only the grade 3 to 5 or serious AEs in pooled entrectinib trials have been included in the cost-per-patient model. The number of occurrences and the number of patients with at least one occurrence are included on the sheet "AE Cost". The frequencies for entrectinib were obtained from the entrectinib trials on the 31st of May 2019 data cut off for the first patients randomized (primary population) who had received at least one dose of the trial drug. As mentioned, the model does not include the AE costs of BSC due to the heterogeneity of BSC. This is a conservative approach as it is expected, that BSC will also be associated with AE costs.

6.8 Cost inputs

6.8.1 Genomic test

The cost of the genomic test has been identified using Interactive DRG. The DRG tariff, 31PR03 "Genetisk risiko vurdering og rådgivning" was identified. As stated, in the clinical application, section 4.2, three regions, the North Denmark Region, the Central Denmark Region and the Capital region of Denmark have screening protocols/programs for incurable cancer patients without standard of care or who have exhausted their treatment options, in order to offer participation in clinical trials or experimental treatment. Screening consists of an NGS test with NTRK already being included in the panel. Additionally, patients that are screened with NGS will also be screened for other biomarkers with approved targeted treatments (EGFR, ALK, ROS1 and others) as well as biomarkers that could allow for enrolment in clinical studies. Clinical studies do generally not result in additional costs related to tests and treatment.

Since these three regions have screening protocols, we assume it would be possible to test for NTRK within the different screening protocols/programs and therefore, implementation would not attribute to further cost in these regions. We, therefore, assume that implementation of entrectinib would only attribute to additional test cost for the remaining two regions. We have therefore applied a modifier to the DRG tariff to account for this. The estimated

cost of genomic test is reported in Table 10. The cost of a genomic test has been applied at the first cycle of the model in the entrectinib arm.

Because of the assumption of no added costs for testing in three out of the five Danish regions, the relevant DRG tariff will only be used in the remaining two regions. The tariff itself will only be applied as 40% to reflect the added costs for the average Danish patient.

As mentioned in the clinical application, the testing landscape in Denmark is rapidly evolving. Technologies such as NGS, liquid biopsies, whole-genome sequencing, whole-exome sequencing, and RNA sequencing are implemented or are likely to be implemented in the coming years with some variance between hospitals and regions. Simultaneously, ESMO guidelines have recommended multigene NGS in NSCLC, cholangiocarcinoma, prostate and ovarian cancers and have stated that university hospitals should perform these tests to enable access to innovative treatments.

These changes are occurring independently of the launch of entrectinib and the testing of NTRK fusions and the implementation of entrectinib and testing of NTRK fusions is only a small component of further implementation of precision medicine. It should also be noted, that the patients currently treated with BSC after treatment exhaustion may also have undergone screening with NGS but without finding any relevant biomarkers. Any costs related to testing are therefore likely applicable to both arms of the economic analysis.

Overall, applying the costs of testing for finding the relevant NTRK fusion-positive patients to the entrectinib arm would significantly overestimate the costs of implementing entrectinib.

Table 10. NTRK Genomic test cost

Activity	Unit cost (DKK)	Reference
Genomic test	DKK 1.378	DRG 2020, 31PR03: Genetisk risikovurdering og rådgivning, Diagnosis: DC349: Kræft i lunge UNS Procedure: BVGA00 Onkogenetisk rådgivning

6.8.2 Drug dosing and acquisition costs

Entrectinib follow a fixed-dose regimen (Table 11). Patients are assumed to be treated until progression in line with the labels. Consequently, the expected drug costs per patient were calculated using the TTOT parametric curves. The expected drug cost per patient of the chemotherapy regimen is estimated using the PFS in the BSC arm, due to the lack of TTOT data for the BSC arm.

The dose per administration was based on average dose intensity as recorded in the STARTRK-2 entrectinib trial. [redacted] was observed in the STARTRK-2 trial. For the chemotherapy regimen, a 100% dose intensity have been assumed.

For entrectinib, a wastage option is included, which assumes that only 1 pack is provided to the patient and the cost is applied at the beginning of that time and if the patient dies before

the next packet duration, this drug quantity is wasted. In the base-case, no wastage is assumed, due to both drugs being fixed-dose, orally administered drugs and therefore wastage is likely to be eliminated in the clinical setting.

For chemotherapy, in the 'with vial sharing' algorithm, the combination of vials used is calculated such that the cost of drug is minimized. However, if the dose required is greater than the largest vial size available, then a large vial will be used in order to minimize the number of total vials used. If a case occurs where the price per mg for a small vial is less than for a large vial, then the algorithm should be adapted to consider this and to minimize costs appropriately.

In the 'without vial sharing' algorithm, it is assumed that health care professionals will select an optimal combination of vials that takes in to account the differences in price per mg according to vial size. Where appropriate, if the dose required is greater than the largest vial size available, then a large vial will always be used in order to minimize the total number of vials used. The model also provides the option of a 'use threshold', this relates to a scenario where healthcare providers require the use of a minimum proportion of a vial to justify its use; this is set to 5% in the base case.

Table 11. Drug cost and dosing used in the model

Treatment	Package size	Composition	Cost per pack (DKK, AIP)	Cost per tab/mg (DKK)	Dosing Regimen
Entrectinib (small pack)	30 pc	100 mg/tablet	8.747,07*	291,57	600 mg administered orally once-daily from day 1 in repeated 4-week cycles
Entrectinib (large pack)	90 pc	200 mg/tablet	51.647,73*	573,86	600 mg administered orally once-daily from day 1 in repeated 4-week cycles
Carboplatin (small vial)	15 ml	10 mg/ml	84,00*	0,56	400 mg/m2 – administered intravenously every 4rd week
Carboplatin (large vial)	45 ml	10 mg/ml	203,00*	0,45	400 mg/m2 – administered intravenously every 4rd week
[redacted]					[redacted]
Chemotherapy weekly costs					*DKK 371*

*Source: Medicinpriser.dk – Accessed 05-10-2020

6.8.3 Drug administration costs

For the assessment of drug administration cost of entrectinib, a one-off cost has been applied to the first administration. As entrectinib is an oral drug, 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 have been assumed for these visits. For the first visit, administration cost has been estimated using Interactive DRG 2020, with the diagnosis code "Kræft i lunge UNS" 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 the entrectinib arm in the first cycle of the model. For the administration of chemotherapy, the DRG tariff

04MA98, "MDC 1-dagsgruppe, pat. mindst 7 år" was identified by Interactive DRG 2020, with the diagnosis code "Kræft i lunge UNS" and the procedure code "Behandling med carboplatin".

The administration costs have been presented in Table 12.

Table 12. Drug administration costs included in the model

Treatment	Cost (DKK)	Source
Entrectinib	1.799	**DRG 2020**, 04MA98: MDC04 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DC349: Kræft i lunge UNS Procedure: BTPD5 Indøvning af administration af egen medicin
Chemotherapy	1.799	**DRG 2020**, 04MA98: MDC04 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DC349: Kræft i lunge UNS Procedure: BWHA109 Behandling med carboplatin

6.8.4 Supportive care cost

Costs were stratified based on patients' disease status (first cycle progression-free, subsequent cycles progression-free and post-progression). The resource use and frequency for the two health states has been estimated in collaboration with a Danish clinical expert within NSCLC (13). This is the same expert testimony that was used for the assessment of entrectinib in ROS1-positive NSCLC. This was deemed appropriate to use, as there is very limited experience with treating NTRK fusion-positive patients in Denmark and most estimates are related to the use of entrectinib. 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 13 reports the cost of the blood samples package. The costs in each health state are reported in Table 14, Table 15 and Table 16.

Table 13 Cost of blood sample package

Activity	Unit cost (DKK)	Reference
Alanine aminotransferase	DKK 24	Rigshospitalets Labportal
Heamoglobin + thrombocytes	DKK 31	Rigshospitalets Labportal
Lactate dehydrogenase	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 14 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 15 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
Blood sample package	100%	0,33 x	DKK 352	Blood sample package
Totals	**Monthly cost:**	**DKK 1.386**	**Per cycle cost:**	**DKK 320**

Table 16 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
Nurse	100%	0,33 x	DKK 554	Danish Medicine Council's "Estimating unit costs", Clinical expert validation
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
Blood sample package	100%	0,33 x	DKK 352	Blood sample package
Totals	**Monthly cost:**	**DKK 1.386**	**Per cycle cost:**	**DKK 320**

6.8.5 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. The costs of the AEs for entrectinib are estimated to be DKK 8.883. The costs have been added in the first cycle for the entrectinib arm in the model.

The AE rates from the entrectinib trial and the DRG tariffs with diagnosis codes are presented in Table 17.

Table 17 Adverse event costs

AEs	% AE Entrectinib	Unit cost (DKK)	Reference
ALANINE AMINOTRANSFERASE INCREASED	[redacted]	DKK 1.748	DRG 2020, 23MA98: MDC23 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DR740: Transaminase- og laktatdehydrogenaseforhøjelse
ANAEMIA	[redacted]	DKK 22.212	DRG 2020, 16MA98: MDC11 1-dagsgruppe, pat. Mindst 7 år + 16MA05: Hæmolystiske anæmier og anæmier forårsaget af enzymatiske forstyrrelser m.m., Diagnosis: DD592: Hæmolytisk ikke-autoimmun anæmi forårsaget af lægemiddel
ANAPHYLACTIC REACTION	[redacted]	DKK 4.564	DRG 2020, 21MA01: Allergiske og allergi lignende reaktioner, Diagnosis: DT886: Anafylaktisk shock ved korrekt administration af lægemiddel
ASPARTATE AMINOTRANSFERASE INCREASED	[redacted]	DKK 1.748	DRG 2020, 23MA98: MDC23 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DR740: Transaminase- og laktatdehydrogenaseforhøjelse
BLOOD CREATININE INCREASED	[redacted]	DKK 4.082	DRG 2020, 23MA03: Symptomer og fund, u. kompl. bidiag., Diagnosis: DR798: Anden abnorm blodprøve
CARDIAC ARREST	[redacted]	DKK 15.926	DRG 2020, 05MA07: Hjertearytmi og synkope, Diagnosis: DI469: Hjertestop UNS
CARDIAC FAILURE	[redacted]	DKK 17.750	DRG 2020, 05MA98 + 05MA04: Hjertesvigt og shock, Diagnosis: DI509: Hjertesvigt UNS
COGNITIVE DISORDER	[redacted]	DKK 30.628	DRG 2020, 01MA06: Degenerative sygdomme i nervesystemet, Diagnosis: DG318: Anden degenerativ sygdom i nervesystemet
DIARRHOEA	[redacted]	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

DYSPNOEA	[redacted]	DKK 1.799	DRG 2020, 04MA98: MDC04 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DR060: Dyspnø
FATIGUE	[redacted]	DKK 2.711	DRG 2020, 18MA98: MDC18 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DR509: Feber UNS
HYPERMAGNESAEMIA	[redacted]	DKK 1.540	DRG 2020, 10MA98: MDC10 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DE384A: Anden endokrin sygdom som følge af sygdom klassificeret andetsteds
HYPERURICAEMIA	[redacted]	DKK 4.082	DRG 2020, 23MA03: Symptomer og fund, u. kompl. bidiag., Diagnosis: DE790: Asymptomatisk hyperurikæmi
HYPOKALAEMIA	[redacted]	DKK 13.048	DRG 2020, 10MA06: Andre ernærings- og stofskiftesygdomme, Diagnosis: DE876: Hypokaliæmi
HYPONATRAEMIA	[redacted]	DKK 13.048	DRG 2020, 10MA06: Andre ernærings- og stofskiftesygdomme, Diagnosis: DE871A: Hyponatriæmi
HYPOPHOSPHATAEMIA	[redacted]	DKK 1.540	DRG 2020, 10MA98: MDC10 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DE833A: Hypofosfatæmi
HYPOTENSION	[redacted]	DKK 1.847	DRG 2020, 05MA08: Andre hjertesygdomme, Diagnosis: DI952: Hypotension forårsaget af lægemiddel
LOCALISED OEDEMA	[redacted]	DKK 4.082	DRG 2020, 23MA03: Symptomer og fund, u. kompl. bidiag., Diagnosis: DR609: Ødem UNS
LYMPHOPENIA	[redacted]	DKK 3.149	DRG 2020, 16MA98: MDC16 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DD728: Anden forstyrrelse i hvide blodlegemer
MUSCULAR WEAKNESS	[redacted]	DKK 1.676	DRG 2020, 08MA15: Reumatologiske sygdomme i bløddele, Diagnosis: DM628: Anden muskelsygdom
NEUTROPENIA	[redacted]	DKK 20.376	DRG 2020, 16MA98 + 16MA03: Granulo- og trombocytopeni, Diagnosis: DD709A: Neutropeni og agranulocytose forårsaget af lægemiddel
OEDEMA	[redacted]	DKK 4.082	DRG 2020, 23MA03: Symptomer og fund, u. kompl. bidiag., Diagnosis: DR609: Ødem UNS
OEDEMA PERIPHERAL	[redacted]	DKK 4.082	DRG 2020, 23MA03: Symptomer og fund, u. kompl. bidiag., Diagnosis: DR609: Ødem UNS
ORTHOSTATIC HYPOTENSION	[redacted]	DKK 8.544	DRG 2020, 05MA98 + 05MA07: Hjertearytmi og synkope, Diagnosis: DI951: Ortostatisk hypotension
OSTEOARTHRITIS	[redacted]	DKK 1.796	DRG 2020, 08MA17: Øvrige sygdomme i knogler og led, Diagnosis: DM199: Artrose UNS
SYNCOPE	[redacted]	DKK 8.544	DRG 2020, 05MA07: Hjertearytmi og synkope, Diagnosis: DR559: Besvimelse eller kollaps
THALAMIC INFARCTION	[redacted]	DKK 36.280	DRG 2020, 01MA05: Specifikke karsygdomme i hjernen ekskl. forbigående utilstrækkelig blodforsyning til hjerne, Diagnosis: DI639: Hjerneinfarkt UNS
	Total cost:	**DKK 8.883**	

6.8.6 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. 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 18 Progression-free state, patient cost of entrectinib

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
Blood samples	100%	0,33 x	½ hour	Assumption of 30 mins
	Weighted weekly time usage:		**0,31 hours**	
	Weekly patient cost:		**DKK 55**	

Table 19 Post-progression state, patient cost of entrectinib

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
Blood samples	100%	0,33 x	½ hour	Assumption of 30 mins
	Weighted weekly time usage:		**0,31 hours**	
	Weekly patient cost:		**DKK 55**	

6.8.7 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 is calculated based on the number of visits assumed for administration and routine care. Transportation costs are illustrated in Table 20.

Table 20 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

6.8.8 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(14).

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 the DMC in previous assessments. The cost has been converted from GPD to DKK using the Danish National bank's exchange rates per 3rd September 2020 (15), inflated from January 2013 to September 2020 costs using Statistics Denmark 2020 (PRIS114) (16), and adjusted for price level indices between UK and DK in 2013 using the EUROSTAT's price level indices list(17). The end-of-life cost applied in the model is illustrated in Table 21.

Table 21 End of life care costs

Reported cost (DKK)	Cost inflated to 2020	Reference
54.681	**69.855**	Round et al., 2015(14). Mean cost of health care over all cancer types (table 5)

6.9 Base case settings

Element	Base-case	*Rationale*
Discount rate (per annum)	4%	*DMC Guidelines*(6)
Time horizon	30 years	*Life-time time horizon to enable capture of all relevant cost*(6)
Comparator	BSC	*DMC protocol*(1)
Proportion of patient on chemotherapy	25%	*Assumption*
Wastage - Entrectinib	No wastage	*No wastage assumed due to oral administration of entrectninb*
Dosing option - Entrectinib	Mean observed dose	*Study dosis*
Drug dosing assumption – IV Chemotherapy	Labelled dose in mode cohort (w.o. vial sharing)	*No study dosis on chemotherapy, therefore dosing follows SmPC*
Progression-free survival (PFS)		
[redacted]	[redacted]	[redacted]
Overall Survival (OS)		
[redacted]	[redacted]	[redacted]
Time to off treatment (TTOT)		
[redacted]	[redacted]	[redacted]

7 Results

7.1 Base-case

In the base-case, the cost per patient analysis results in a cost of [redacted] The model estimated the mean life years in the entrectinib arm to [redacted] and in the BSC arm to be [redacted]

7.1.1 Incremental analysis

The cost analysis results in an average incremental cost per patient of [redacted] for entrectinib compared to BSC. The results of the base-case cost analysis are presented below in Table 22. The mode estimated the incremental life years to be [redacted], which resulted in an incremental cost per life year of DKK [redacted].

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

Table 22 Incremental cost per patient

	Entrectinib (DKK)	Best supportive care (DKK)	Incremental costs (DKK)
Drug costs	[redacted]	[redacted]	[redacted]
Administration costs	[redacted]	[redacted]	[redacted]
AE costs	[redacted]	[redacted]	[redacted]
Supportive care	[redacted]	[redacted]	[redacted]
Patient costs	[redacted]	[redacted]	[redacted]
Transportation costs	[redacted]	[redacted]	[redacted]
End of life costs	[redacted]	[redacted]	[redacted]
Genomic test	[redacted]	[redacted]	[redacted]
Total costs	[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 23.

In the scenario where a log-normal distribution is applied for the TTD extrapolation for the Entrectinib arm, the incremental cost of entrectinib increases to [redacted]

Table 23, Results of scenario analyses

Number	Parameter	Value	Incremental costs
Base-case			[redacted]
1	Distribution Entrectinib NTRK+ OS	Weibull	
2	Distribution Entrectinib NTRK+ OS	Log-normal	
3	Distribution Entrectinib NTRK+ OS	Gamma	
4	Distribution Entrectinib NTRK+ OS	Log-logistic	
5	Distribution Entrectinib NTRK+ OS	Gompertz	
6	Distribution Entrectinib NTRK+ PFS	Weibull	
7	Distribution Entrectinib NTRK+ PFS	Log-normal	
8	Distribution Entrectinib NTRK+ PFS	Gamma	
9	Distribution Entrectinib NTRK+ PFS	Log-logistic	
10	Distribution Entrectinib NTRK+ PFS	Gompertz	
11	Distribution Entrectinib NTRK+ TTD	Weibull	
12	Distribution Entrectinib NTRK+ TTD	Log-normal	
13	Distribution Entrectinib NTRK+ TTD	Gamma	
14	Distribution Entrectinib NTRK+ TTD	Log-logistic	
15	Distribution Entrectinib NTRK+ TTD	Gompertz	
16	Dosing scenarios	Labelled dose in model cohort (w. vial sharing)	
17	Dosing scenarios	Labelled dose in trial (wo. vial sharing)	
18	Dosing scenarios	Labelled dose in trial (w. vial sharing)	
19	Oral wastage	With Wastage	
20	Time horizon	5	
21	Time horizon	17,5	
22	Time horizon	30	
23	Proportion of patient in BSC receiving chemotherapy	0%	
25	Proportion of patient in BSC receiving chemotherapy	50%	

7.3 Intrapatient scenario analysis

Based on the intrapatient analysis on the NTRK+ cohort (11), chemotherapy regimens was reported in some patients as the most recent prior treatment. [redacted]

Based on the costs related to the chemotherapies in the intrapatient analysis as well as the TTNT of [redacted] a scenario analysis was conducted comparing the cost accrued in the prior treatment line, to the cost in the PFS state for the entrectinib arm. The scenario analysis estimated a total cost of DKK [redacted] for the previous treatment line, while the PFS state for the entrectinib arm accrued a total of DKK [redacted] This results in an incremental cost of DKK [redacted], when comparing the cost of the prior treatment line to the PFS state of the entrectinib arm.

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, as mandated in the DMC guidelines (6).

The cost per patient model was nested within the budget impact model, and therefore any changes in the settings of the cost per patient model affects 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 Patient population

The Danish Medicine Council (Fagudvalget) estimates the patient population for entrectinib to be approx. 10 to 40 patients in Denmark every year. 20 patients were applied in the base-case.

8.1.2 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 24.

Table 24. Market shares for treatment of NTRK-fusion positive patients

	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%
Best supportive care	95%	100%	100%	100%	100%	0%	0%	0%	0%	0%
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 NTRK-fusion positive patients, and therefore will gain the market share of BSC in this therapy regiment.

8.1.3 Costs

The costs included 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 (6). 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 BSC.

8.1.4 Scenario analyses

Alternative scenarios were tested to assess the result of different assumptions to market uptake and patient count. The scenarios tested for the budget impact model are described in Table 25.

Table 25. Scenarios for budget impact model

Scenario	Assumptions made for scenario analyses
Base case	**100 % of patients receive entrectinib in year 5 and 20 patients**
Lower market uptake	40 % of patients receive entrectinib in year 5 and 20 patients
Upper market uptake	80 % of patients receive entrectinib in year 5 and 20 patients
Lower patient count	100 % of patients receive entrectinib in year 5 and 10 patients
Upper patient count	100 % of patients receive entrectinib in year 5 and 40 patients

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 5 as shown in Table 26.

The budget impact analysis is indicating, a recommendation of entrectinib is resulting in added costs at AIP-level. The yearly added costs are rising throughout the time horizon to [redacted] in year 5.

Table 26. Budget impact for base case scenario

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

8.2.2 Scenario analysis results

The results of the scenario analyses are presented in Table 27, Table 28, Table 29 and Table 30.

Table 27. Budget impact analysis results, lower market uptake scenario

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

Table 28. Budget impact analysis results, upper market uptake scenario

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

Table 29. Budget impact analysis results, 10 patient-scenario

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

Table 30. Budget impact analysis results, 40 patient-scenario

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

9 Discussion

In the BSC arm, only 25% of the patient are assumed to receive a low-cost chemotherapy regimen, and the cost within the BSC arm is primarily driven by the end-of-life costs. Within the entrectinib arm, the cost is primarily driven by the drug cost.

The incremental cost result is sensitive to changes to the chosen distribution for the extrapolation of the TTD, where the choice of distribution with long right-sided tail, e.g. log-normal and log-logistic distributions, would result in a higher incremental cost.

Entrectinib leads to added costs compared to best supportive care but resulted in [redacted] additional life years compared to BSC, which is a palliative treatment. When taking the survival benefit into consideration the incremental cost per life year was DKK[redacted]

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Medicinrådet

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Medicinrådets protokol for vurdering af entrectinib til behandling af NTRK-fusion-positiv kræft

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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Medicinrådet, Dampfærgevej 27-29, 3. th., 2100 København Ø
www.medicinraadet.dk
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Indhold

1 Begreber og forkortelser

BSC	*Best supportive care*
CI	Konfidensinterval
CNS	Centralnervesystemet
CR	Komplet respons
ECOG	*Eastern Cooperative Oncology Group performance status*
EMA	Det Europæiske Lægemiddelagentur (*European Medicines Agency)*
EORTC-QLQ-30	*European Organisation for Research and Treatment of Cancer Quality-of-life Questionnaire-Core 30*
EPAR	*European Public Assessment Report*
FISH	*Flourescence in situ hydridization*
GRADE	System til at vurdere evidens (*Grading of Recommendations, Assessment, Development and Evaluation*)
HR	*Hazard ratio*
IHC	Immunhistokemi
ITT	*Intention to treat*
MKRF	Mindste klinisk relevante forskel
NGS	*Next-generation sequencing*
NSCLC	Ikke-småcellet lungecancer
NTRK	Neurotrofisk tyrosinreceptorkinase
OR	*Odds ratio*
ORR	Objektiv responsrate
OS	Overlevelse
pCR	Patologisk komplet respons
PedsQL	*The Pediatric Quality of Life Inventory*
PICO	Population, intervention, komparator og effektmål (*Population, Intervention, Comparator and Outcome)*
PFS	Progressionsfri overlevelse
PP	*Per-protocol*
PR	Partielt response
R0	Komplet resektion

RANO	Response Assessment in Neuro-Oncology
RCT	Randomiseret kontrolleret studie *(Randomised Controlled Trial)*
RECIST	Response Evaluation Criteria in Solid Tumors
ROS1	ROS proto-oncogene 1 receptor tyrosine kinase
RR	Relativ risiko
SMD	*Standardized Mean Difference*
Trk	Tyrosinreceptorkinase

2 Introduktion

Protokollen er udarbejdet, fordi Medicinrådet har modtaget en foreløbig ansøgning fra Roche, som ønsker, at Medicinrådet vurderer entrectinib som mulig standardbehandling af patienter med lokalt avancerede eller metastaserende solide tumorer, som uanset tumortype har fået påvist en genfusion af neurotrofisk tyrosinreceptorkinase (NTRK), og som ikke har andre tilfredsstillende behandlingsmuligheder. Vi modtog den foreløbige ansøgning den 30. marts 2020.

Protokollen danner grundlag for den endelige ansøgning for vurdering af entrectinib sammenlignet med dansk standardbehandling. Alle effektmål, der er opgivet i denne protokol, skal besvares med en sammenlignende analyse mellem entrectinib og *best supportive care* (BSC) eller placebo af både absolutte og relative værdier for de udspecificerede populationer i de angivne måleenheder (se Tabel 1). Litteratursøgning og databehandling udføres som beskrevet i protokollen.

Entrectinib forventes at få indikation til både behandling af solide tumorer med NTRK-fusion (vævsagnostisk indikation) samt til behandling af uhelbredelig ROS1-positiv ikke-småcellet lungekræft. Nærværende protokol beskæftiger sig udelukkende med den del af indikationen, som vedrører NTRK-fusion. Medicinrådets Fagudvalg vedr. lungekræft har sideløbende udarbejdet en protokol for den del af indikationen, som vedrører ROS1.

Medicinrådet vurderer aktuelt det lignende lægemiddel larotrectinib, som også har en vævsagnostisk indikation til behandling af solide tumorer med NTRK-fusion.

2.1 Kræft med NTRK-fusioner

En solid tumor er en unormal vævsmasse (svulst). Solide tumorer kan være benigne (ikke kræft) eller maligne (kræft), hvor sidstnævnte per definition evner at gennemtrænge væv eller sprede sig til andre dele af kroppen. Kræft inddeles i forskellige typer, afhængig af hvilken celletype kræften udgår fra. Solidt voksende kræfttyper kan overordnet underinddeles i sarkomer (bløddels- og knoglekræft), karcinomer (epitel deriverede kræftformer) og melanomer (modermærkekræft). Leukæmier (blodkræft) danner generelt ikke solide tumorer. For hver af disse overordnede typer af kræft findes yderligere talrige undertyper, baseret på hvilket organ eller væv de udgår fra, og hvilke histopatologiske og eventuelle molekylærbiologiske forandringer der kendetegner kræften [1,2]. De forskellige kræftformer rammer forskelligt i befolknings- og aldersgrupper og kræver forskellige former for diagnostik og behandling.

Forekomsten af kræft er stigende, og ca. 1/3 af alle danskere vil få kræft i løbet af deres liv. Antallet af nye tilfælde pr. år er ca. 40.000 med en lille overvægt af mænd. Den ældre del af befolkningen står for den største andel af nye kræfttilfælde, således står mænd og kvinder over 60 år for mere end 2/3 af alle nye kræfttilfælde. Lidt over 280.000 nulevende danskere har på et tidspunkt fået konstateret kræft, og 6 ud af 10 kræftpatienter overlever deres sygdom i mindst 5 år [3].

Kræft er sjældent hos børn (under 18 år), men det er den næsthyppigste dødsårsag efter 1-årsalderen. Mindre end 1 % af alle kræfttilfælde forekommer hos børn, og ca. 170 børn får årligt konstateret kræft. Den 5-årige overlevelsesrate for børn med kræft er på ca. 80 %. Fordelingen af kræfttyperne hos børn er helt anderledes end hos voksne [3]. Voksne får således typisk karcinomer, mens børn hyppigst får blodkræft [4].

Neurotrofisk tyrosinkinase (NTRK) er navnet på en gruppe af tre gener, NTRK1, NTRK2 og NTRK3, der koder for tyrosinreceptorkinaser (Trk) A, B og C. Trk er afgørende for normale nervecellers udvikling og overlevelse. Genfusioner, der involverer NTRK1, NTRK2 eller NTRK3, koder for Trk-fusionsproteiner, som kan medføre ukontrolleret Trk-signalering og dermed tumorvækst [5,6]. NTRK-fusioner er sjældne og påvises med yderst varierende hyppighed på tværs af tumortyper hos både børn og voksne. Herudover er det

uvist, om der er geografiske og epidemiologiske forskelle i forekomst af NTRK-fusioner. I enkelte sjældne kræfttyper såsom infantil fibrosarkom og sekretorisk karcinom i både spytkirtel og bryst påvises NTRK-fusioner med en frekvens på næsten 100 %. I andre mere hyppige kræfttyper i luftveje, fordøjelseskanal, bryst, modermærker og hjerne påvises NTRK-fusioner med en frekvens på mindre end 5 % [7,8]. For flere af de allerhyppigste kræftformer, herunder lungekræft, tyk- og endetarmskræft, modermærkekræft og brystkræft, vurderes frekvensen af NTRK-fusioner dog til at være mellem 0,1-1 % [9].

2.2 Entrectinib

Information om lægemidlet

Trk-fusionsproteiner virker som 'onkogene drivere' til fremme af celledeling og overlevelse af tumorceller. Entrectinib er en Trk-hæmmer, som hindrer neurotrophin-Trk-interaktion og dermed Trk-aktivering. Dette inducerer celledød og hæmning af tumorer, som overudtrykker Trk [8,10]. Entrectinib hæmmer desuden ROS proto-oncogene 1 receptor tyrosine kinase (ROS1), der også ved fusion med andre gener kan resultere i aktiverede proteiner. ROS1-fusionerede gener er en 'onkogen driver' ved blandt andet ikke-småcellet lungekræft (NSCLC) [11].

Patienter kan behandles med entrectinib, hvis de har en NTRK-fusion i en tumorprøve. Der testes i dag ikke rutinemæssigt for NTRK-fusion i tumorprøver, og der er ingen klinisk validerede tests eller 'companion diagnostics' tilgængelige til at udføre testen. Man kan både anvende *next-generation sequencing* (NGS), immunhistokemi (IHC) og *fluorescence in situ hydridization* (FISH) for at påvise fusioner (se afsnittet 'andre overvejelser').

Der er ansøgt om markedsføringstilladelse hos Det Europæiske Lægemiddelagentur (*European Medicines Agency* (EMA)). *Committee for Medicinal Products for Human Use* (CHMP) har afgivet *positive opinion* d. 28. maj 2020. Den forventede indikation for lægemidlet er:

"[Entrectinib] as monotherapy is indicated for the treatment of adult and paediatric patients 12 years of age and older with solid tumours expressing a neurotrophic tyrosine receptor kinase (NTRK) gene fusion,
- who have a disease that is locally advanced, metastatic or where surgical resection is likely to result in severe morbidity, and
- who have not received a prior NTRK inhibitor
- who have no satisfactory treatment options"

Den forventede ATC-klasse er LO1XE.

Der er samtidig søgt om markedsføringstilladelse for entrectinib som monoterapi indiceret til behandling af voksne patienter med uhelbredelig ROS1-positiv NSCLC.

De anbefalede doser af entrectinib er for voksne 600 mg oralt en gang dagligt, og for børn med et kropsareal <1,5 m^2 300 mg/m^2 oralt en gang dagligt. Behandlingen fortsættes indtil sygdomsprogression eller uacceptabel toksicitet.

Estimat for antal patienter i Danmark

Antallet af patienter, der årligt er kandidater til behandling med entrectinib i Danmark, er usikkert. Dels findes der ikke tilstrækkelige data for hyppigheden af NTRK-fusion hos danske kræftpatienter, og derudover er entrectinib først indiceret, når øvrige muligheder for behandling er udtømte. Derfor skal et estimat af patientantal tage højde for frafald imellem behandlingslinjer på tværs af mange forskellige kræftformer.

En af forudsætningerne for behandling med entrectinib er, at alle øvrige behandlingsmuligheder er udtømte. I denne sammenhæng henviser fagudvalget til gældende nationale retningslinjer og Medicinrådets behandlingsvejledninger inden for de forskellige relevante kræftområder.

Fagudvalget skønner, at der årligt er ca. 10.000 danske patienter, som har uhelbredelig kræft [4], og at ca. 1/3 af disse vil udtømme øvrige behandlingsmuligheder men stadig være i tilstrækkelig performance status til at modtage yderligere behandling. Dette er baseret på et skøn af det typiske antal behandlingslinjer og frafald herimellem. Det er således i ovenstående population, at man skal identificere de patienter, som kan være kandidater til behandling med entrectinib.

Fagudvalget tager i sit skøn højde for, at der vil være ganske få patienter med meget sjældne kræftformer, hvor NTRK-fusionen er hyppig (f.eks. infantil fibrosarkom) samt mange patienter med hyppigere kræfttyper (f.eks. tyk- og endetarmskræft, lungekræft og modermærkekræft), hvoraf kun ganske få (ca. 0,3 %) vil have en NTRK-fusion. Derudover skønner fagudvalget, at der blandt de 1.400 årlige tilfælde af hjernetumorer i Danmark [4] vil være ca. 10 patienter, som kan have gavn af behandlingen. Fagudvalget skønner således samlet, at mellem 10 og 40 patienter årligt kan blive kandidater til behandlingen i Danmark. Ansøger angiver det samme estimat for antal patienter med reference til Medicinrådets protokol vedr. vurdering af larotrectinib.

Fagudvalget understreger, at der ikke foreligger tilstrækkelige data til at foretage en valid vurdering af antallet af patienter, hvorfor ovenstående skøn er forbundet med væsentlig usikkerhed. Estimatet afhænger tilmed i vid udstrækning af, hvordan screening efter NTRK-fusion implementeres, samt hvordan indikationen fortolkes, særligt udsagnet vedr. at øvrige behandlingsmuligheder skal være udtømte.

Fase 1-enheden på Rigshospitalet deltager i klinisk afprøvning af NTRK-inhibitoren larotrectinib. Fagudvalget oplyser kendskab til tre danske patienter med NTRK-fusion-positiv kræft, som siden forsøgsstart i 2016 har modtaget behandling med larotrectinib.

Fagudvalget bemærker, at ovenstående estimat for antallet af patienter alene omhandler den del af entrectinibs indikation, som vedrører NTRK-fusion.

2.3 Nuværende behandling

Hovedparten af patienter med kræft modtager standardbehandling, som primært afhænger af kræfttype samt stadie. For en række kræfttyper er operation med henblik på helbredelse oftest førstevalg. Når kirurgisk behandling ikke er mulig eller ikke er tilstrækkelig, tilbydes patienterne enten strålebehandling og/eller medicinsk behandling (kemoterapi, targeteret behandling eller immunterapi). For flere pædiatriske kræftformer er kemoterapi dog ofte førstevalg. Den valgte medicinske behandling afhænger af mange faktorer, herunder hvilken kræfttype, hvor udbredt sygdommen er, samt om kræfttypen eventuelt udtrykker særlige molekylærgenetiske forandringer, hvortil der er udviklet specifikke (targeterede) lægemidler. Herudover skal patienterne være i tilstrækkelig almen tilstand til at kunne tåle yderligere behandling. I studier måles almen tilstand ofte med ECOG-performance status [12].

For en lille andel af patienterne med meget sjældne kræftformer findes der ingen etableret standardbehandling. Derudover er der patienter med hyppigere kræftformer, som i løbet af deres behandlingsforløb udtømmer alle standardbehandlingsmuligheder. Disse patienter kan indgå i forsøg med eksperimentel behandling eller få tilbudt lindrende behandling (*best supportive care* (BSC)).

I modsætning til den traditionelle fremgangsmåde for kræftbehandling, kendetegnet ved i vid udstrækning at være histologi (vævstype)-afhængig, er entrectinib ikke indiceret til én bestemt kræfttype, men til alle tilfælde af solide tumorer med NTRK-fusion (ofte benævnt som 'vævs-/tumor-agnostisk'). Af denne årsag,

og fordi entrectinib er indiceret, når øvrige muligheder for behandling er udtømte, findes der ikke standardbehandling for de patienter, som kandiderer til behandling med entrectinib. Derfor kan der heller ikke fastslås et enkelt eller nogle få medicinske behandlingsalternativer til entrectinib.[1]

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.

De nedenstående to kliniske spørgsmål vedrører hhv. patienter over og under 18 år. Dette skyldes, at børn og voksne behandles i forskellige regier, samt er der er væsentlige forskelle på, hvilke kræfttyper med NTRK-fusion der ses hos hhv. børn og voksne.

3.1 Klinisk spørgsmål 1

Hvad er den kliniske merværdi af entrectinib til behandling af voksne med NTRK-fusion-positiv kræft, hvor øvrige behandlingsmuligheder er udtømte, sammenlignet med placebo?

Population
Patienter ≥ 18 år med lokalfremskreden eller metastatisk kræft med NTRK-fusion, hvor alle øvrige tilfredsstillende behandlingsmuligheder er udtømte.

Intervention
Entrectinib.

Komparator
Placebo eller best supportive care.

Effektmål
Se tabel 1. Resultaterne præsenteres både for den samlede patientgruppe og for hver af de inkluderede kræftdiagnoser.

3.2 Klinisk spørgsmål 2

Hvad er den kliniske merværdi af entrectinib til behandling af børn med NTRK-fusion-positiv kræft, hvor øvrige behandlingsmuligheder er udtømte, sammenlignet med placebo?

Population
Patienter mellem 12 og 18 år med lokalfremskreden eller metastatisk kræft med NTRK-fusion, hvor alle øvrige tilfredsstillende behandlingsmuligheder er udtømte.

Intervention
Entrectinib.

Komparator
Placebo eller best supportive care.

[1] Det lignende præparat larotrectinib, som også er en NTRK-hæmmer, vurderes dog aktuelt af Medicinrådet.

Effektmål
Se tabel 1. Resultaterne præsenteres både for den samlede patientgruppe og for hver af de inkluderede kræftdiagnoser.

3.3 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.

Tabel 1. Effektmål

Effektmål*	Vigtighed	Effektmålsgruppe	Måleenhed	Mindste klinisk relevante forskel
Overlevelse (OS)**	*Kritisk*	*Dødelighed/ overlevelse*	Median, mdr.	3 mdr.
			OS-rate ved 24 mdr.	10 %-point
			Andel patienter med patologisk komplet respons eller radikalt operationsresultat	5 %-point
Livskvalitet	*Kritisk*	*Livskvalitet, alvorlige symptomer og bivirkninger*	Gennemsnitlig ændring i EORTC-QLQ-C30 (voksne) eller PedsQL (børn)	10 point (QLQ-C30) 4,5 point (PedsQL)
Objektiv responsrate (ORR)**	*Vigtig*	*Livskvalitet, alvorlige symptomer og bivirkninger*	Andel patienter med objektivt respons	Narrativ gennemgang
Progressionsfri overlevelse (PFS)**	*Vigtig*	*Livskvalitet, alvorlige symptomer og bivirkninger*	Median PFS *eller* andel progressionsfri patienter ved 12 mdr.	3 mdr. *eller* 10 %-point
Uønskede hændelser	*Vigtig*	*Livskvalitet, alvorlige symptomer og bivirkninger*	Andel patienter, der får én eller flere grad 3-4 AE's	5 %-point
			Kvalitativ gennemgang af uønskede hændelser	Narrativ vurdering

*For alle effektmål ønsker vi data med længst mulig opfølgningstid, med mindre andet er angivet.
**Der ønskes for disse effektmål opgørelser for hver af de samlede patientgrupper (hhv. klinisk spørgsmål 1 og 2) samt fordelt på hver af de kræftdiagnoser, der er inkluderet i entrectinibstudierne.

3.3.1 Kritiske effektmål

Overlevelse

Helbredelse eller forbedret samlet overlevelse (OS) med bedst mulig livskvalitet og mindst mulig toksicitet er det optimale mål for kræftbehandling. For OS anvendes to mål til at vurdere den absolutte effekt: median OS og OS-rate. De to mål supplerer hinanden. Median OS giver svar på, hvornår halvdelen af den samlede patientgruppe er død eller forventes at dø. OS-raten giver et estimat for, hvor mange som er i live ved et bestemt tidspunkt. Prognosen for patienter med NTRK-fusion er yderst variabel, da der er tale om vidt forskellige kræfttyper. Overordnet må man dog betragte gruppen som uhelbredeligt syge med en relativt kort gennemsnitlig restlevetid. Fagudvalget vurderer, at begge måleenheder for OS er informative. Fagudvalget ønsker derfor at se på median OS, som kan belyse, hvorvidt halvdelen af patienterne får en overlevelsesgevinst ved behandling med entrectinib. Den mindste klinisk relevante forskel (MKRF) fastsættes til 3 måneder. For at belyse, hvorvidt behandlingen resulterer i øget langtidsoverlevelse, ønsker

fagudvalget at se på OS-raten ved 24 måneder, som forventes at være lav (< 20 %) for denne gruppe patienter. Her fastsættes den mindste klinisk relevante forskel til 10 %-point.

Fagudvalget ønsker, som supplement til ovenstående mål, en opgørelse over patienter, som enten får patologisk komplet respons (pCR) eller patienter, hvis tumorsvind betyder, at de kan få fjernet deres tumor komplet med frie resektionsrande ved operation (komplet resektion (R0)). Patologisk komplet respons indebærer i tillæg til komplet radiologisk respons også komplet tumorsvind vurderet på operationspræparatet. Fagudvalget vurderer, at denne andel af patienter vil repræsentere patienter, som er helbredt for deres sygdom og dermed har en nær normal forventet restlevetid. Den mindste klinisk relevante forskel fastsættes til 5 %-point.

Livskvalitet

Livskvalitet er et afgørende helbredsrelateret mål for den enkelte patient. Hos kræftpatienter kan livskvalitet måles med en række forskellige instrumenter, som omfatter både sygdomsspecifikke og generiske værktøjer. I dette tilfælde vil vurdering af livskvalitet hos voksne blive baseret på European Organisation for Research and Treatment of Cancer Quality-of-life Questionnaire-Core 30 (EORTC QLQ-C30) [13,14]. QLQ-C30 er et hyppigt anvendt generisk måleredskab, som består af fem funktionsskalaer, tre symptomskalaer og en 'global' livskvalitetsskala. Der anvendes en scoringsskala fra 0-100. Den mindste klinisk relevante forskel baserer sig på en lille ændring, defineret som 10 point på tværs af domæner [15]. For måling af livskvalitet hos børn og unge findes der ligeledes en række validerede værktøjer. I dette tilfælde vil vurdering af livskvalitet hos børn blive baseret på The Pediatric Quality of Life Inventory (PedsQL) [16], som kan anvendes til børn og unge i alderen 2-18 år. Testen kan enten besvares af børnene selv eller deres forældre. PedsQL består af fire funktionsskalaer med i alt 23 domæner, hvorfra der kan udregnes dels en psykosocial livskvalitetsscore og en fysisk livskvalitetsscore samt en samlet score. Data transformeres til en scoringsskala fra 0-100. Fagudvalget har fastsat den mindste klinisk relevante forskel til 4,5 point jf. litteraturen [17].

3.3.2 Vigtige effektmål

Objektiv responsrate

Objektiv responsrate (ORR) anvendes til belysning af behandlingsrespons og afspejler interventionens umiddelbare antineoplastiske potentiale. Ved vurdering af ORR kategoriserer man ændringer af tumors størrelse efter påbegyndt behandling, jævnfør standardiserede guidelines (Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 eller Response Assessment in Neuro-Oncology (RANO) for primære CNS-tumorer [18,19]). Fagudvalget vurderer, at et væsentligt tumorsvind ofte vil bevirke en reduktion i patientens sygdomsbyrde, og at patienter, som ikke modtager aktiv behandling for praktiske formål, vil have en objektiv responsrate på 0 %.

ORR underinddeles i følgende kategorier:

- Komplet respons (CR): Radiologisk kræftfri. Alle tumorlæsioner er væk, og ingen nye er fremkommet.
- Partielt respons (PR): Mindst 30 %-reduktion af tumorlæsioner sammenlignet med baseline.

Objektiv respons (OR) opnås for en patient, hvis vedkommende er klassificeret som CR eller PR, og objektiv responsrate defineres som CR + PR delt med det samlede antal patienter, inklusive evt. patienter, som ikke er evaluerbare.

Fagudvalget vil vurdere den samlede andel af patienter, som opnår OR, samt andelene af patienter, som opnår CR eller PR. I studierne af entrectinib er der inkluderet patienter på tværs af mange kræftdiagnoser, og for flere af disse subgrupper indgår der kun ganske få patienter, hvilket medfører betydelig usikkerhed omkring resultaterne. Fagudvalget finder derfor, at det er mest hensigtsmæssigt at foretage en narrativ vurdering af resultaterne for ORR både for de samlede patientpopulationer; hhv. voksne (klinisk spørgsmål 1) og børn (klinisk spørgsmål 2) samt inden for hver enkelt kræftdiagnose, hvor der findes data for entrectinib.

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 sygdomsprogression i henhold til Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 [20] eller dødsfald.

Fagudvalget vurderer, at det er vigtigt for patienterne ikke at have sygdomsprogression i længst mulig tid. Patienter med sygdomsprogression kan have meget generende symptomer, og den aktuelle patientgruppe har ingen efterfølgende behandlingsalternativer. Fagudvalget betragter PFS som et vigtigt effektmål og et udtryk for fravær eller reduktion af symptomer samt for varighed af respons. Såfremt PFS ved behandling med entrectinib overstiger OS i historiske data for lignende patienter, taler dette for, at præparatet har en væsentlig effekt på overlevelse.

Der er væsentlige forskelle i prognose på tværs af forskellige kræfttyper med NTRK-fusion. Entrectinib er indiceret til lokalavanceret eller metastatisk kræft, når øvrige behandlingsmuligheder er udtømte. Derfor vurderer fagudvalget, at patientgruppen generelt vil have en relativt kort tid til sygdomsprogression. På den baggrund fastsættes den mindste klinisk relevante forskel som 3 måneder (vedr. median PFS) eller 10 %-point (vedr. PFS-rate ved 12 måneder). Fagudvalget vil i sin vurdering prioritere effektmålet opgjort som forskel i median PFS over andel patienter, der er progressionsfri efter 12 måneder.

Uønskede hændelser

Forekomst af uønskede hændelser grad 3-4 [21] er et udtryk for alvorlig toksicitet af lægemidlet, og disse kan have væsentlig indvirkning på patienternes velbefindende. Da entrectinib skal anvendes til behandling af uhelbredeligt syge patienter, som forventes at dø af deres sygdom, vurderes det, at uønskede hændelser er et vigtigt effektmål. Fagudvalget ønsker data på nedenstående måleenheder.

<u>Uønskede hændelser grad 3-4</u>
Fagudvalget finder, at forskellen i andelen af patienter, som i løbet af opfølgningstiden oplever en eller flere bivirkninger af grad 3 eller 4, er relevant for vurderingen. Bivirkninger af grad 3-4 er defineret i henhold til National Cancer Institute CTCAE version 4.03 [21].

Fagudvalget vurderer, at en forskel på 5 %-point i andelen af patienter, der får bivirkninger af grad 3-4, er klinisk relevant.

<u>Kvalitativ gennemgang af uønskede hændelser</u>
Ansøger skal indsende en opgørelse for frekvensen af alle uønskede hændelser. Fagudvalget ønsker at foretage en gennemgang af alle uønskede hændelser, der opstår ved behandling med entrectinib versus komparator med henblik på at vurdere hændelsernes type, håndterbarhed og reversibilitet.

3.3.3 Mindre vigtige effektmål

CNS-progression

Metastaserende kræft spreder sig hos nogle patienter til hjerne eller det øvrige centralnervesystem, hvilket medfører betydelig morbiditet. Det estimeres, at mellem 6 og 14 % af alle patienter, der diagnosticeres med kræft, udvikler metastaser i hjernen, og at patienter med metastaser i hjernen har en forventet levetid på 2 måneder uden behandling og 4-12 måneder ved behandling med stråling og kemoterapi [22,23].

I de kliniske studier af entrectinib havde 11 ud af i alt 54 inkluderede patienter metastaser i hjernen på inklusionstidspunktet.

Effektmålet omfatter både tid til CNS-progression hos patienter med CNS-metastaser på inklusionstidspunktet samt tid til CNS-progression hos patienter, der får tilkomst af CNS-metastaser under behandlingen.

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 komparator (BSC eller placebo).

Sekretariatet har ikke fundet artikler, som kan anvendes til direkte sammenligning af entrectinib og placebo eller BSC.

Virksomheden skal derfor søge efter studier, der kan anvendes til en indirekte sammenligning af entrectinib og placebo eller BSC. Det betyder, at der både skal søges efter primærstudier af entrectinibs effekt og efter primærstudier af effekten af placebo eller BSC. Til det formål har sekretariatet udarbejdet søgestrenge, som skal anvendes i MEDLINE (via PubMed) og CENTRAL (via Cochrane Library). Søgestrengene kan findes som bilag. Derudover skal EMAs European public assessment reports (EPAR) konsulteres for det aktuelle lægemiddel.

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 (se dog 'Prioriteret søgestrategi', nedenfor). 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).

Søgestrategi og studiedesigns: der skal foretages en trinvis søgning efter data vedr. effekten af komparator, som kan tillade en naiv sammenstilling. Der skal først søges efter et eller flere RCTs med en studiepopulation, som i tilstrækkeligt omfang afspejler de patienter, som indgår i udviklingsprogrammet for entrectinib. Herunder studier, hvor én eller flere af kræftdiagnoserne, som indgår, også er repræsenteret i studierne af entrectinib. Hvis der ikke findes relevant data fra RCTs søges dernæst efter observationelle studier.

Prioritet søgestrategi

1. RCT-data for patienter med NTRK-fusion (se søgestrenge i Bilag 1)
2. Observationelt data for patienter med NTRK-fusion (se søgestrenge i Bilag 1)
3. RCT-data for patienter uden kendt NTRK-status (se søgestrenge i Bilag 2)

For ovenstående gælder det, at populationen i videst muligt omfang skal svare til studiepopulationen, der indgik i entrectinibs udviklingsprogram. Findes der ikke relevante RCT-data ved søgning med søgestreng i Bilag 1, gennemgås derpå de observationelle søgeresultater og dernæst anvendes søgestrenge i Bilag 2. Data fra en evt. placebogruppe prioriteres over data for BSC.

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 skønner, at datagrundlaget for vurderingen kan være begrænset grundet den vævsagnostiske indikation og designet af de studier, der er tilgængelige for vurdering af entrectinib. Fagudvalget ønsker en opgørelse, som sammenligner PFS og ORR-data for den behandling, patienterne modtog i behandlingslinjen umiddelbart inden behandling med entrectinib versus tilsvarende data for behandling med entrectinib (også kaldet *'Growth modulation index'*).

Fagudvalget vurderer, at der er væsentlige udfordringer i relation til hensigtsmæssig screening for NTRK-fusion. I dag screenes de fleste pædiatriske patienter med solide tumorer med NGS, mens NGS ikke er standard i diagnosticeringen af voksne patienter. Derfor bedes ansøger redegøre for, hvor mange patienter, som det estimeres, skal screenes for at identificere ca. 10-40 patienter (ansøgers eget skøn for antallet af patienter, der årligt vil kunne behandles med entrectinib i Danmark) samt et bud på, hvilke kræftdiagnoser som bør screenes. Fagudvalget beder også virksomheden oplyse hvilke(n) konkret(e) metode(r) til screening af NTRK-fusion, der vurderes at være bedst, og hvorvidt der evt. skal præ-screenes f.eks. med IHC forud for mere avancerede metoder med højere sensitivitet såsom NGS. Endeligt bør ansøger komme med et bud på, hvornår i udrednings- og/eller behandlingsforløb screening for NTRK-fusion bør foregå.

Ansøger bedes indsende evt. litteratur, som belyser den prognostiske betydning af NTRK-fusion.

8 Relation til behandlingsvejledning

Der findes ikke en relevant behandlingsvejledning. Fagudvalget vil i et bilag til vurderingsrapporten foretage en naiv sammenstilling af effekten af entrectinib overfor det lignende præparat larotrectinib, der har en tilsvarende indikation, og som aktuelt vurderes af Medicinrådet.

9 Referencer

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10 Sammensætning af fagudvalg og kontaktinformation til Medicinrådet

Medicinrådets fagudvalg vedrørende tværgående kræftlægemidler

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11 Versionslog

Version	Dato	Ændring
1.0	18. juni 2020	Godkendt af Medicinrådet.

12 Bilag 1

Søgestrenge for identifikation af RCTs og observationelle studier i PubMed. NTRK-fusion.

https://www.ncbi.nlm.nih.gov/pubmed/advanced

#	Søgetermer	Kommentar
1	entrectinib[nm] OR entrectinib[tiab] OR Rozlytrek*[tiab] OR NMS-E628[tiab] OR RXDX-101[tiab]	Søgetermer for intervention
2	(NTRK[tiab] OR NTRK1[tiab] OR NTRK2[tiab] OR NTRK3[tiab]) AND (fusion[tiab] OR fusions[tiab])	Søgetermer for patienter med NTRK-fusion
3	neurotrophi*[tiab] AND (TRK[tiab] OR TRKA[tiab] OR TRKB[tiab] OR TRKC[tiab]) AND (fusion[tiab] OR fusions[tiab])	
4	neurotrophi*[tiab] AND tropomyosin receptor kinase*[tiab] AND (fusion[tiab] OR fusions[tiab])	
5	TRK[tiab] AND (fusion[tiab] OR fusions[tiab]) AND positive[tiab]	
6	TRK[tiab] AND (fusion[tiab] OR fusions[tiab]) AND proteins[tiab]	
7	TRK[tiab] AND (fusion[tiab] OR fusions[tiab]) AND (cancer[tiab] OR cancers[tiab])	
8	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7	
9	Animals[mh] NOT Humans [mh]	Eksklusion af ikke relevante publikationstyper og dyrestudier
10	animal*[ti] OR murine[ti] OR mouse[ti] OR mice[ti] OR rat[ti] OR rats[ti] OR rodent[ti]	
11	Case Reports[pt] OR Comment[pt] OR Editorial[pt] OR Letter[pt] OR Guideline[pt] OR Review[pt] OR Systematic Review[pt] OR case report[ti] OR review[ti]	
12	#9 OR #10 OR #11	
13	#8 NOT #12	
14	randomized[tiab] OR randomised[tiab] OR randomly[tiab] OR placebo[tiab] OR sham*[tiab] OR dummy*[tiab]	Søgefilter til identifikation af RCT/kontrollerede studier
15	controlled trial[tiab] OR controlled study[tiab]	
16	control group*[tiab] OR control arm[tiab]	
17	phase 1*[tiab] OR phase 2*[tiab] OR phase 3*[tiab] OR phase I*[tiab]	
18	enrolled[tiab]	
19	multicenter[tiab] OR multi-center[tiab] OR multicentre[tiab] OR multi-centre[tiab]	
20	comparative[tiab] AND (trial[tiab] OR study[tiab])	
21	trial[ti] OR study[ti]	
22	open-label[tiab]	
23	single blind*[tiab] OR double-blind*[tiab] OR triple-blind*[tiab]	
24	Clinical Trial[pt] OR Clinical Trials as Topic[mesh:noexp]	
25	Comparative Study[pt] OR Multicenter Study[pt]	
26	#14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25	
27	#13 AND #26	**Endelig søgning RCT** (screenes først)
28	Observational Study[pt] OR Epidemiologic Studies[mh:noexp] OR Case Control Studies[mh] OR Cohort Studies[mh] or Cross-Sectional Studies[mh]	Søgefilter til identifikation af observationelle studier
29	observational[tiab] OR case control[tiab] OR cohort[tiab] OR cohorts[tiab] OR follow-up[tiab] OR longitudinal[tiab] OR prospective[tiab] OR retrospective[tiab] OR cross sectional[tiab] OR database[tiab] OR registry[tiab] OR nationwide[tiab]	
30	Registries[mh]	
31	#28 OR #29 OR #30	
32	#13 AND #31	

33	#32 NOT #27	**Endelig søgning på observationelle studier** (de tidl. screenede RCT-resultater er ekskluderede)

Søgestrenge for identifikation af RCTs og observationelle studier i CENTRAL (Cochrane Library). NTRK-fusion.

https://www.cochranelibrary.com/advanced-search/search-manager

#	**Søgetermer**	**Kommentar**
1	entrectinib:kw	Søgetermer for intervention
2	(entrectinib or Rozlytrek* or "NMS E628" or "RXDX 101"):ti,ab	
3	((NTRK OR NTRK1 OR NTRK2 OR NTRK3) NEAR/5 (fusion OR fusions)):ti,ab	Søgetermer for patienter med NTRK-fusion
4	neurotrophi*:ti,ab AND (TRK OR TRKA OR TRKB OR TRKC):ti,ab AND (fusion OR fusions):ti,ab	
5	neurotrophi*:ti,ab AND (tropomyosin NEXT receptor NEXT kinase*):ti,ab AND (fusion OR fusions):ti,ab	
6	TRK:ti,ab AND (fusion OR fusions):ti,ab AND positive:ti,ab	
7	TRK:ti,ab AND (fusion OR fusions):ti,ab AND proteins:ti,ab	
8	TRK:ti,ab AND (fusion OR fusions):ti,ab AND (cancer OR cancers):ti,ab	
9	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8	
10	("conference abstract" OR review):pt	Eksklusion af ikke relevante publikationstyper
11	NCT*:au	
12	("clinicaltrials.gov" OR trialsearch):so	
13	#10 OR #11 OR #12	
14	**#9 NOT #13**	**Endelig søgning**

Søgestrenge for identifikation af RCTs i PubMed. Ukendt NTRK-status.

https://www.ncbi.nlm.nih.gov/pubmed/advanced

#	**Søgetermer**	**Kommentar**
1	solid[ti] AND (tumor[ti] OR tumors[ti] OR tumour[ti] OR tumours[ti])	Søgetermer for tumortyper
2	(soft tissue[ti] OR soft-part[ti] OR connective tissue[ti]) AND (sarcoma[ti] OR sarcomas[ti] OR cancer[ti] OR cancers[ti])	
3	angiosarcoma[ti] OR hemangiosarcoma[ti] OR chondrosarcoma[ti] OR fibromyxosarcoma[ti] OR fibrosarcoma[ti] OR infantile fibrosarcoma[ti] OR myxofibrosarcoma[ti] OR leiomyosarcoma[ti] OR liposarcoma[ti] OR malignant mesenchymoma[ti] OR malignant mesenchymal tumor[ti] OR neurofibrosarcoma[ti] OR rhabdomyosarcoma[ti] OR synovial sarcoma[ti] OR spindle cell sarcoma[ti]	
4	bone cancer[ti] OR bone sarcoma[ti] OR Ewing sarcoma[ti] OR osteosarcoma[ti]	
5	MASC[ti] OR mammary analogue secretory carcinoma[ti]	

6	(salivary[ti] OR parotid[ti] OR submandibular[ti] OR sublingual[ti]) AND (gland[ti] OR glands[ti]) AND (masc[ti] OR cancer[ti] OR carcinoma[ti] OR adenocarcinoma[ti])	
7	(bowel[ti] OR colon[ti] OR colonic[ti] OR colorectal[ti] OR rectal[ti] OR rectum[ti] OR sigmoid[ti] OR intestinal[ti]) AND (cancer[ti] OR carcinoma[ti] OR adenocarcinoma[ti])	
8	(thyroid[ti] OR parathyroid[ti]) AND (cancer[ti] OR carcinoma[ti] OR adenocarcinoma[ti])	
9	gastrointestinal stromal[ti] AND (tumor[ti] OR tumour[ti] OR tumors[ti] OR tumours[ti])	
10	GIST[ti]	
11	lung[ti] AND (adenocarcinoma[ti] OR carcinoma[ti])	
12	NSCLC[ti] OR non-small cell lung cancer[ti] OR nonsmall cell lung cancer[ti]	
13	melanoma[ti]	
14	cholangiocarcinoma[ti]	
15	(bile duct*[ti] OR biliary duct*[ti]) AND (carcinoma[ti] OR cancer[ti])	
16	(appendiceal[ti] OR appendix[ti]) AND (cancer[ti] OR carcinoma[ti])	
17	breast[ti] AND secretory[ti] AND (carcinoma[ti] OR carcinomas[ti])	
18	congenital mesoblastic nephroma[ti]	
19	(pancreatic[ti] OR pancreas[ti]) AND (cancer[ti] OR carcinoma[ti] OR adenocarcinoma[ti])	
20	primary[ti] AND (CNS[ti] OR central nervous system[ti] OR brain[ti]) AND (cancer[ti] OR tumour[ti] OR tumor[ti] OR lymphoma[ti])	
21	glioblastoma[ti] OR glioma[ti] OR astrocytoma[ti] OR oligodendroglioma[ti] OR primary cerebral lymphoma[ti]	
22	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21	
23	metastatic[ti] OR metastasis[ti] OR metastases[ti] OR advanced[ti] OR recurrent[ti] OR refractory[ti]	Søgetermer for avanceret/metastatisk sygdom
24	treatment resistant[tiab] OR treatment resistance[tiab] OR chemotherapy resistant[tiab]	Søgetermer for patientstadie
25	incurable[tiab] OR "no cure"[tiab] OR untreatable[tiab]	
26	late stage[tiab]	
27	Terminally Ill[mh] OR Terminal Care[mh] OR (terminal[tiab] NOT terminal half-life[tiab]) OR terminally[tiab]	
28	best supportive care[tiab] OR active supportive care[tiab] OR optimal supportive care[tiab] OR supportive care alone[tiab] OR supportive care only[tiab]	
29	symptomatic treatment[tiab] OR symptomatic therapy[tiab] OR experimental treatment[tiab] OR late-line[tiab]	
30	Palliative Care[mh] OR palliation[tiab] OR palliative[tiab] OR palliatively[tiab]	
31	eol care[tiab] OR end of life[tiab]	
32	#24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31	
33	#22 AND #23 AND #32	
34	(Randomized Controlled Trial[pt] OR Controlled Clinical Trial[pt] OR randomized[tiab] OR randomised[tiab] OR placebo[tiab] OR	RCT-filter

	randomly[tiab] OR random allocation[tiab] OR trial[ti]) NOT (Animals[mh] NOT Humans [mh])	
35	English[la]	Sproglig afgrænsning
36	#33 AND #34 AND #35	
37	Case Reports[pt] OR Comment[pt] OR Editorial[pt] OR Guideline[pt] OR Letter[pt] OR Meta-Analysis[pt] OR News[pt] OR Observational Study[pt] OR Review[pt] OR Systematic Review[pt] OR case report[ti] OR meta-analysis[tiab] OR review[ti] OR Retrospective Studies[mh] OR retrospective[ti] OR systematic review[tiab]	Eksklusion af irrelevante publikationstyper
38	**#36 NOT #37**	**Endelig søgning**

Søgestrenge for identifikation af RCTs i CENTRAL (referencer fra Embase]. Ukendt NTRK-status.

https://www.cochranelibrary.com/advanced-search/search-manager

#	**Søgetermer**	**Kommentar**
1	solid:ti AND (tumor OR tumors OR tumour OR tumours):ti	Søgetermer for tumortyper
2	(soft tissue OR soft-part OR connective tissue):ti AND (sarcoma OR sarcomas OR cancer OR cancers):ti	
3	(angiosarcoma OR hemangiosarcoma OR chondrosarcoma OR fibromyxosarcoma OR fibrosarcoma OR infantile fibrosarcoma OR myxofibrosarcoma OR leiomyosarcoma OR liposarcoma OR "malignant mesenchymoma" OR "malignant mesenchymal tumor" OR neurofibrosarcoma OR rhabdomyosarcoma OR synovial next sarcoma OR spindle next cell next sarcoma):ti	
4	(bone next cancer OR bone next sarcoma OR "Ewing sarcoma" OR osteosarcoma):ti	
5	(MASC OR "mammary analogue secretory carcinoma"):ti	
6	(salivary OR parotid OR submandibular OR sublingual):ti AND (gland OR glands):ti AND (masc OR cancer OR carcinoma OR adenocarcinoma):ti	
7	(bowel OR colon OR colonic OR colorectal OR rectal OR rectum OR sigmoid OR intestinal):ti AND (cancer OR carcinoma OR adenocarcinoma):ti	
8	(thyroid OR parathyroid):ti AND (cancer OR carcinoma OR adenocarcinoma):ti	
9	"gastrointestinal stromal":ti AND (tumor OR tumour OR tumors OR tumours):ti	
10	GIST:ti	
11	lung:ti AND (adenocarcinoma OR carcinoma):ti	
12	(NSCLC OR "non-small cell lung cancer" OR "nonsmall cell lung cancer"):ti	
13	melanoma:ti	
14	cholangiocarcinoma:ti	
15	(bile next duct* OR biliary next duct*):ti AND (carcinoma OR cancer):ti	
16	(appendiceal OR appendix):ti AND (cancer OR carcinoma):ti	
17	breast:ti AND secretory:ti AND (carcinoma OR carcinomas):ti	
18	congenital next mesoblastic next nephroma:ti	
19	(pancreatic OR pancreas):ti AND (cancer OR carcinoma OR adenocarcinoma):ti	

20	primary:ti AND (CNS OR "central nervous system" OR brain):ti AND (cancer OR tumour OR tumor OR lymphoma):ti	
21	(glioblastoma OR glioma OR astrocytoma OR oligodendroglioma OR "primary cerebral lymphoma"):ti	
22	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21	
23	(metastatic OR metastasis OR metastases OR advanced OR recurrent OR refractory):ti	Søgetermer for avanceret/metastatisk sygdom
24	((treatment OR chemotherapy) next (resistant OR resistance)):ti,ab	Søgetermer for patientstadie
25	(incurable OR "no cure" OR untreatable):ti,ab	
26	late-stage:ti,ab	
27	("Terminally Ill" OR "Terminal Care" OR "terminal disease"):kw OR (terminal OR terminally):ti,ab	
28	("best supportive care" OR "active supportive care" OR "optimal supportive care" OR "supportive care alone" OR "supportive care only"):ti,ab	
29	((symptomatic OR experimental) next (treatment OR therapy)):ti,ab OR "late-line":ti,ab	
30	(palliation OR palliative OR palliatively):ti,ab,kw	
31	("eol care" OR "end of life"):ti,ab	
32	#24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31	
33	#22 AND #23 AND #32	
34	("conference abstract" OR review OR meta-analysis):pt	Eksklusion af irrelevante publikationstyper
35	NCT*:au	
36	("clinicaltrials.gov" or trialsearch):so	
37	(abstract OR review):ti	
38	#34 OR #35 OR #36 OR #37	
39	#33 NOT #38	
40	Embase:an NOT Pubmed:an	Afgrænsning til poster fra Embase
41	#39 AND #40	**Endelig søgning**