Single Technology Assessment

ID2019_119

Entrectinib for treatment of solid neurotrophic tyrosine receptor kinase (NTRK) fusion positive tumors

12-02-2021

Norwegian Medicines Agency

PREFACE

The National System for Managed Introduction of New Health Technologies within the Specialist Health Service in Norway shall help ensure that assessments of appropriate new technologies are conducted in a systematic manner with respect to effectiveness and safety, as well as impacts on health and society. The main aim of the *The National System for Managed Introduction of New Health Technologies within the Specialist Health Service in Norway* is described in the National Health and Care Plan 2011-2015 and the White Paper 10 (2012-2013), Good quality - safe services. The regional health authorities, the Norwegian Instiute of Public Health, the Norwegian Medicines Agency (NoMA) and the Directorate of Health collaborate on tasks related to the system. Eventually, the *The National System for Managed Introduction of New Health Technologies within the Specialist Health Service in Norway* will assist in the rational use of health care resources.

The Norwegian Medicines Agency has been assigned the responsibility to evaluate Single Technology Assessments of individual pharmaceuticals. A Single Technology Assessment is a systematic summary of evidence based on research on efficacy, safety and impact assessment. For pharmaceuticals, this will usually revolve around budgetary consequences or resource allocation. In addtition, disease severity is assessed. The burden of proof relating to the documentation of efficacy, safety and cost-effectiveness is borne by the MA-holder for the pharmaceutical under review. NoMA can, when necessary, provide guidance to pharmaceutical companies.

NoMA assesses the submitted evidence for all important clinical outcomes, resource use as well as the assumptions made in the analysis presented by the MA-holder and the presented results. NoMA may request additional information from the MA-holder or search for updated information on its own. NoMA does not perform its own health economic analyses but may perform additional calculations of relative effectiveness, the costs, cost effectiveness, disease severity and budget impact using the submitted model.

NoMA assesses each of the three priority setting criteria benefit, resource use and severity. This includes an assessment of the relative effectiveness and incremental costs compared to a relevant comparator. A cost-effectivness-ratio is usually calculated. NoMA does not assess the benefit risk balance already assessed in the market-authorization procedure. Information about this is provided by EMA.

Single Technology Assessment of pharmaceuticals is intended to support sound decision making on potential introductions of new technologies, and prioritization made at the Health Authority level. NoMA has no decision-making authority in this system but their reports appraising the three priority setting criteria are used by the Decision Forum to weigh cost-effectiveness-ratio against severity of the health state/disease under assessement.

NoMA's assessments are published and available to the public (http://www.legemiddelverket.no/).

EXECUTIVE SUMMARY

Rationale

Single technology assessment (STA) of Rozlytrek (entrectinib) for the treatment of patients with solid neurotrophic tyrosine receptor kinase (NTRK-) fusion positive tumours. The benefits and risks of entrectinib have been documented through the approval of a condtional marketing authorisation. In this STA, NoMA has assessed treatment with entrectinib against the priority-setting criteria benefit, resource use and severity according to the Summary of Product Characteristics (SmPC) for entrectinib, and the requested specifications from the Ordering Forum (ID2019_119 Entrectinib for treatment of solid neurotrophic tyrosine receptor kinase (NTRK-) fusion positive tumours). NoMA´s assessment is based mainly, but not exclusively, on the documentation submitted by Roche.

Background

Treatment in a Norwegian setting

NoMA's assessment is based on the assumption that all patients with tumours harbouring NTRK-positive fusions can be identified in the future, most likely through Next generation sequencing (NGS)-screening. Testing for NTRK-fusions is not yet standard procedure in Norwegian clinical practice. The Norwegian Institute of Public Health is evaluating the tests necessary to identify patients with NTRK-positive fusions. As there is no treatment targeting NTRK-fusions in use in Norway, patients with tumours harbouring NTRK-fusions are treated with standard treatment depending on their histology.

According to the approved indication, entrectinib 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). NoMA therefore considers best supportive care to be the relevant comparator in this assessment. For some tumour types best supportive care may include chemotherapy with limited effectiveness.

Patient population

How many patients with NTRK-fusion positive solid tumours that will be treated with entrecinib in Norway given a positive decision regarding use, is so far unknown. The prevalence of NTRK-fusions is estimated to be about 0.3% of solid tumours. This implies that in order to identify one patient with NTRK-fusion, approximately 300 patients would have to be tested. Based on currently available evidence, patients with NTRK-fusions are expected to receive treatment with entrectinib for about 12 months. Assuming that all eligible patients with NTRK-fusion would be identified, approximately 20-50 individuals could potentially receive entrectinib on a yearly basis once next generation sequencing is rutinely used.

Severity and shortfall

NoMA lacked crucial information necesscary to quantify severity, and chose to instead describe expected severity. Details regarding this is elaborated in chapter 1.3.

Based on the average age for the patients receiving entrectinib in the submitted documentation, and the remaining quality-adjusted life years (QALYs) of the general Norwegian population at this age, NoMA expects that patients with NTRK-fusion postive cancers who have exhausted all satisfactory treatment options loose on average about 20 quality-adjusted life years .

In Norway, the degree of severity affects whether the costs are considered reasonable relative to the benefit of the treatment. The description of severity in this single technoloy assessment is based on assumptions and it should be interpreted with caution.

Clinical efficacy

Roche has submitted an analysis of the adult population in the phase I and II trials of entrectinib (STARTRK-1, STARTRK-2, ALKA) hereafter called the integrated analysis. Of the 74 patients in the integrated analysis 71 patients are from the STARTRK-2 trial.

In the trials, 47 of the 74 (63,5%) patients had an objecive response, with a median duration of 12.9 months. The extent to which these data translate into a survival benefit relative to best supportive care is not documented. It seems likely that patients without other treatment options could achieve a clinically meaningful benefit of entrectinib.

However, reliable data on the effectiveness of comparator treatment is lacking due to the fact that all conducted trials are single-armed. NoMA could not accept the submitted naïve indirect comparison. Both EMA, in their regulatory assessment, and NoMA conclude that the submitted documentation does not allow to establish relative effectiveness of entrectinib compared to best supportive care.

Based on this, the generalizability of efficacy results from the clinical trials to patients in Norwegian clinical pratice is questionable.

Safety

The most common adverse reactions experienced by patients receiving entrectinib (≥20%) were fatigue, constipation, dysgeusia, oedema, dizziness, diarrhoea, nausea, dysaesthesia, dyspnoea, anaemia, increased weight, increased blood creatinine, pain, cognitive disorders, vomiting, cough, and pyrexia. The most frequent serious adverse reactions (≥2%) were lung infection, dyspnoea, cognitive impairment, and pleural effusion. Permanent discontinuation due to an adverse reactions occurred in 4.4% of patients.

Cost-effectiveness

The cost-effectiveness of entrectinib could not be assessed in the submitted health economic model. While the model type chosen by Roche might have been appropriate, NoMA cannot approve the input used in the model as sufficient to establish relative effectiveness. Consequently, NoMA could not estimate an ICER to quantify cost-effectivness of introducing entrectinib.

Budget impact

Uncertainty about the number of patients clearly influences the budget impact analyses. Prevalence and testing strategy will impact the number of cases found, and hence the number of patients treated. We therefore present a wide range for budget impact, which could be somewhere between 3 million NOK for

5 patients and 30 million NOK for 50 patients per year including VAT in a stable market. The budget impact analyses for entrectinib can only result in a very rough estimate due to the uncertain number of patients that will be identified in Norwegian clinical practice in the following years.

NoMA´s overall assessment
NoMA concludes that the submitted documentation is not sufficient to establish a reasonably credible estimate for the benefit of entrectinib compared to best supportive care.

Concerning the priority-setting criteria, NoMA could neither evaluate the benefit nor the cost-effectiveness of entrectinib. This is due to lack of evidence on the relative effectiveness of entrectinib in comparison to best supportive care. NoMA chose to describe, rather than quantify severity. NoMA expects that patients with NTRK-positive fusion cancers who have exhausetd their treatment options loose on average about 20 quality-adjusted life years. This number is based on assumptions and it should be interpreted with caution.

The submitted documentation clearly shows the different requirements of the regulatory process and the Health Technology Assessment-process (HTA). The submitted documentation was deemed sufficient to establish a positive benefit/risk by The European Medicines Agency (EMA). However, it is difficult to establish a relative effectiveness against best supportive care, as required for an HTA based on the clinical data available. NoMA identified three major evidence gaps in this HTA that hinder establisment of relative effectiveness and evaluation of the cost-effectiveness of entrectinib:

1. *Unknown prognostic value of NTRK-fusion:* The effectiveness of standard of care in patients harbouring the NTRK-fusion has not been established.
2. *Unknown size of treatment effect:* The efficacy estimates are highly uncertain, given the highly heterogenous and small patient population studied.
3. *Unknown generalizability:* There is great uncertainty regarding the generalizability of the patient population to Norwegian clinical practice.

These issues undermine the validity of the parameters needed as input in a health economic model that could allow evaluation of the cost-effectiveness of entrectinib. NoMA has therefore not assessed the submitted health economic model and has not estimated an ICER to quanitfy cost-effectiveness of introducing entrectinib in Norway.

Roche has provided an outline for how relative effectiveness and cost-effectiveness can be established after the launch of entrectinib using updated trial data, and data from registries. The suggested package and approach could be sufficient to alleviate the challenges of a missing comparator arm, and could form the basis for a reevaluation once available.

NORSK SAMMENDRAG

Metode
Hurtig metodevurdering av legemiddelet Rozlytrek (entrektinib) til behandling av pasienter med solide, NTRK-fusjonspositive svulster. Nytten og risikoen for entrektinib har blitt dokumentert gjennom innvilgelsen av en betinget markedsføringstillatelse. I denne metodevurderingen har Legemiddelverket vurdert prioriteringskriteriene knyttet til nytte, ressursbruk og alvorlighet ved bruk av entrektinib i henhold til bestilling ID2019_119: Entrektinib for pasienter over 12 år som har lokalavansert eller metastatisk kreft med NTRK-fusjonspositive solide svulster og godkjent preparatomtale.
Vurderingen tar utgangspunkt i dokumentasjon innsendt av Roche.

Bakgrunn
Behandling i norsk klinisk praksis
Legemiddelverkets vurdering er basert på at alle pasienter med svulster som har NTRK-fusjoner kan identifiseres. Testing for NTRK-fusjoner er i dag ikke standardprosedyre i norsk klinisk praksis. Folkehelseinstituttet vurderer testene som er nødvendige for å indentifisere pasienter med NTRK-fusjoner. Siden det ikke finnes behandling rettet mot NTRK-fusjoner som er besluttet innført i Norge per i dag, vil pasienter med svulster med NTRK-fusjoner få standardbehandling basert på det histologiske opphavet til svulsten deres.

I følge den godkjente indikasjonen skal entrektinib bare brukes når det ikke finnes annen tilfredsstillende behandlingsalternativer (altså der det ikke finnes behandlinger hvor klinisk nytte er etablert, eller der slike behandlinger allerede er forsøkt). Legemiddelverket mener derfor at beste støttende behandling er relevant komparator i denne saken. For noen tumortyper kan beste støttende behandling også inkludere kjemoterapi med begrenset effekt.

Pasientgrunnlag i Norge
Det er ikke kjent hvor mange pasienter med NTRK-fusjonspositive solide svulster som vil bli behandlet med entrektinib dersom det blir innført i Norge. Forekomsten av NTRK-fusjoner anslås til omtrent 0,3 % av alle solide tumorer. Dette innebærer at omtrent 300 pasienter må testes for å finne én pasient med NTRK-fusjon. Basert på de tilgjengelige dataene, antar vi at pasienter med NTRK-fusjoner vil bli behandlet med entrektinib i omtrent 12 måneder. Dersom alle pasienter med NTRK-fusjoner egnet for behandling med entrektinib blir identifisert, antar Legemiddelverket at mellom 20 og 50 pasienter vil kunne motta entrektinib årlig når «next generation sequencing» (NGS) har blitt tatt i bruk.

Alvorlighet og prognosetap
Legemiddelverket mangler sentral informasjon for å kunne kvantifisere alvorlighet, og velger i stedet å beskrive alvorligheten. Dette blir beskrevet i kapitel 1.3.
Basert på gjennomsnittsalderen på pasientene som fikk entrektinib i de innsendte studiene, og de gjenværende kvalitetsjusterte leveår (QALYs) for den norske normalbefolkningen ved denne alderen,

forventer Legemiddelverket at pasienter med NTRK-fusjonspositiv kreft som ikke har tilfredsstillende behandlingsalternativer taper i gjennomsnitt omtrent 20 QALYs.
Alvorlighetsgraden kan påvirke om kostnadene vurderes å stå i rimelig forhold til nytten av behandlingen. Beskrivelsen av alvorlighet i denne vurderingen er basert på sterke antagelser, og må tolkes med varsomhet.

Effektdokumentasjon i henhold til norsk klinisk praksis
Roche har sendt inn en analyse basert på den voksne populasjonen fra fase I og II-studiene av entrektinib (STARTRK-1, STARTRK-2, ALAK) heretter kalt en integrert analyse. Av de 74 pasientene i den integrerte analysen er 71 fra STARTRK-2-studien.

I denne analysen hadde 47 av 74 pasienter (63,5 %) en objektiv respons, med en median varighet på 12,9 måneder. I hvor stor grad objektiv respons svarer til en overlevelsesgevinst er ikke dokumentert, men det er sannsynlig at dette vil gi en klinisk meningsfull gevinst for pasienter uten andre behandlingsmuligheter.

Troverdige data for effekten av komparatorbehandlingen mangler siden alle de tilgjengelige studiene er enarmede. Legemiddelverket kunne ikke godta den innsendte, naive indirekte sammenligningen for relativ effekt som Roche leverte. Både det europeiske legemiddelbyrået (EMA), i sin regulatoriske vurdering, og Legemiddelverket konkluderer med at den innsendte dokumentasjonen ikke er tilstrekkelig til å etablere relativ effekt av entrektinib sammenlignet med støttende behandling.

Overførbarheten av effektresultatene fra de kliniskes studiene til norsk klinisk praksis er også usikker.

Sikkerhet
De vanligste bivirkningene i den kliniske studien (≥ 20 %) var fatigue, forstoppelse, dysgeusi, ødem, svimmelhet, diaré, kvalme, dysestesi, dyspné, anemi, vektøkning, økt blodkreatinin, smerter, kognitive lidelser, oppkast, hoste og feber. De hyppigste alvorlige bivirkningene (≥ 2 %) var lungeinfeksjon, dyspné, kognitiv svekkelse og pleuraeffusjon. Permanent seponering på grunn av en bivirkning forekom hos 4,4 % av pasientene.

Kostnadseffektivitet
Kostnadseffektiviteten av entrektinib kunne ikke vurderes basert på den innsendte helseøkonomiske modellen. Selv om modelltypen valgt av Roche kan være egnet, kan ikke Legemiddelverket godta de dataene som går inn i modellen. Av den grunn kan ikke Legemiddelverket anslå en IKER for å kvantifisere kostnadseffektiviteten ved å ta i bruk entrektinib.

Budsjettkonsekvenser
Usikkerhet rundt antallet pasienter som vil få entrektinib påvirker klart analysen av budsjettkonsekvenser. Prevalensen og teststrategien vil påvirke antallet tilfeller som identifiseres, og derved antallet pasienter som behandles. Vi viser derfor et stort spenn i budsjettestimatene, som kan være mellom 3 millioner kroner for 5 pasienter, til 30 millioner for 50 pasienter, i et stabilt marked.
På grunn av usikkerheten i antall pasienter som vil bli identifisert i norsk klinisk praksis i årene som kommer, kan Legemiddelverket bare gi et veldig grovt estimat for budsjettkonsekvensene.

Legemiddelverkets vurdering

Legemiddelverket konkluderer med at den innsendte dokumentasjonen ikke er tilstrekkelig for å gi et troverdig estimat for nytten av entrektinib sammenlignet med støttende behandling.

Når det gjelder prioriteringskriteriene, kunne Legemiddelverket hverken evaluere nytten eller kostnadseffektiviteten til entrektinib. Dette skyldes manglende evidens for den relative effekten av entrektinib sammenlignet med støttende behandling. Legemiddelverket har valgt å beskrive alvorligheten, i stedet for å kvantifisere den. Legemiddelverket antar likevel at pasienter med NTRK-fusjonspositiv kreft vil i gjennomsnitt tape omtrent 20 QALYs. Dette estimatet er en antagelse, og må tolkes med forsiktighet.

Den innsendte dokumentasjonen viser tydelig de ulike kravene mellom den regulatoriske prosessen og metodevurderingen. Den innsendte dokumentasjonen ble vurdert av EMA som tilstrekkelig til å etablere et positivt forhold mellom nytte og risiko. Det er derimot utfordrende å etablere den relative effekten for entrektinib sammenlignet med støttende behandling, noe som kreves for en metodevurdering. Legemiddelverket identifiserte tre vesentlige mangler ved dokumentasjonsgrunnlaget i denne metodevurderingen som hindrer etablering av relativ effekt og vurdering av kostnadseffektiviteten til entrektinib:

1. *Ukjent prognostisk verdi av NTRK-fusjoner:* Effekten av dagens standardbehandling i pasienter som har en NTRK-fusjon har ikke blitt dokumentert.
2. *Ukjent størrelsen av behandlingseffekten:* Effektestimatene er svært usikre på grunn av den lille og svært heterogene pasientpopulasjonen som ble studert.
3. *Ukjent overførbarhet til norsk klinisk praksis:* Det er stor usikkerhet knyttet til om data fra pasientene i studiene kan overføres til norsk klinisk praksis.

Disse manglene gjør at de parameterne som går inn i den helseøkonomiske modellen, som kunne ha blitt brukt til å evaluere kostnadseffektivitet av entrektinib, ikke er troverdige. Legemiddelverket har derfor ikke vurdert den innsendte modellen, og har ikke anslått en IKER for å kvantifisere kostnadseffektiviteten ved å ta i bruk entrektinib i Norge.

Roche har levert en skisse for hvordan relativ effekt og kostnadseffektivitet kan bli kvantifisert etter lanseringen av entrektinib ved å bruke oppdaterte studiedata og registerdata. Selv om denne vurderingen må gjøres når dataene blir innlevert, kan den foreslåtte analyseplanen være tilstrekkelig til å kompensere for manglende komparator data og danne grunnlag for en reevaluering når den er tilgjengelig.

ROZLYTREK TIL BEHANDLING AV KREFT MED NTRK-GENFEIL

Hva er Rozlytrek?

Rozlytrek er et legemiddel som hindrer kreftsvulster med genfeil i NTRK-reseptoren i å vokse ukontrollert.

Reseptorfamilien som kalles for neurotrofisk tropomyosin reseptor tyrosinkinase (NTRK) finnes i kreftsvulster flere ulike steder i kroppen, for eksempel i tarm, lunger, og skjoldbruskkjertel.

Hva er en metodevurdering? Du kan lese om Legemiddelverkets arbeid med metodevurderinger *her*

Hva menes med et *godt leveår*? Du kan lese mer om hva som menes med et godt leveår *her*

Rozlytrek er et legemiddel som virker mot flere krefttyper, uavhengig av hvor i kroppen kreftsykdommen har oppstått. Fellesnevneren for svulstene er genfeil i NTRK-reseptoren og derfor kalles Roslytrek for et *histologi-uavhengig* legemiddel. Rozlytrek er en tablett som pasienten skal svelge en gang daglig.

Det er i dag ingen godkjent behandling spesielt rettet mot pasienter med genfeil i NTRK-reseptoren (NTRK-fusjonspositiv kreft). Dagens behandling for disse pasienter varierer fra svulst til svulst, og kan være alt fra ingen behandling til operasjon, kjemoterapi, radioterapi, hormonterapi og/eller immunterapi.

NTRK genfeil er sjeldne, og man antar at så få som 3 av 1000 pasienter som får kreft har denne genfeilen.

Hvor alvorlig er sykdommen?

NTRK-fusjonspositiv kreft er en alvorlig sykdom. Pasientene lever kortere og har nedsatt helserelatert livskvalitet. Prognosen til de pasientgruppene som kan behandles med Rozlytrek er dårlig, men varierer litt mellom pasientgruppene.

Hvem kan få behandling med Rozlytrek?

Pasienter over 12 år med kreftsvulster som er forårsaket av en forandring i nevrotrofisk tyrosinreseptor kinase (NTRK)-genet kan behandles med Rozlytrek. Det er vanskelig å si hvor mange norske pasienter som vil kunne få behandling med Rozlytrek hvis det blir bestemt at behandlingen kan tas i bruk på norske sykehus. Det er fordi kreftsvulsten må testes for genfeil i NTRK-reseptoren før en pasient kan få Rozlytrek, og denne testen er per i dag ikke en rutinetest i norske sykehus.

Folkehelseinsituttet har fått oppgaven med å vurdere gentestene som kan være aktuelle for dette formålet. Før testingen er på plass kan klinikere ikke lete systematisk etter NTRK-fusjoner. Dersom testingen blir innført i norske sykehus kan det være aktuelt å behandle mellom 5 til 50 pasienter årlig i Norge med Rozlytrek.

Hvilken nytte har Rozlytrek?

Studieresultatene viser at Rozlytrek kan krympe krefsvulster med genfeil i NTRK-reseptoren. Rozlytrek virker bra for noen krefttyper, men vi vet fortsatt lite om nytten i andre krefttyper. Rozlytrek gir færre alvorlige bivirkninger enn kjemoterapi. Legemiddelverket mener det er sannsynlig at pasienter uten andre behandlingsalternativer vil ha nytte av behandlingen.

Hvordan er nytten av behandlingen undersøkt?
Flere kliniske studier har sett på nytten av, og risikoen ved, behandling med Rozlytrek ved ulike typer

NTRK-fusjonspositiv kreft. For denne metodevurderingen har disse studiene blitt sammenslått i én analyse som omfatter 74 pasienter med NTRK-fusjonspositiv kreft.

Ingen av studiene har sammenlignet Rozlytrek med andre behandlinger og det er derfor vanskelig å si om Rozlytrek virker bedre, like bra eller dårligere enn dagens standardbehandling. Standardbehandling varierer mellom de ulike krefttypene hvor en finner NTRK-mutasjoner, og Rozlytrek kan ha bedre effekt i noen krefttyper enn i andre.

I den sammenslåtte analysen opplevde 47 av 74 pasienter at kreftsvulstene krympet betydelig (minst 30 %), mens kreftsvulstene vokste hos 6 pasienter. Nesten tre av fire pasienter hadde vedvarende effekt i minst 6 måneder, og halvparten opplevde at effekten fortsatte i mer enn ett år.

Pasientene i de kliniske studiene hadde like god helserelatert livskvalitet før og underveis i behandlingen med Rozlytrek. Dette tyder på at behandlingen tåles godt.

Legemiddelfirmaet Roche har laget en modell for å beregne hvordan behandling med Rozlytrek påvirker livslengde og helserelatert livskvalitet hos pasienter med NTRK-fusjonspositiv kreft. Modellen beregner levetid og sykdomsforløp for personer med NTRK-fusjonspositiv kreft basert på studiedata for behandling med Rozlytrek. Siden studiene ikke har undersøkt levetid eller sykdomsforløp for pasienter NTRK-fusjonspositiv kreft som får dagens standardbehandling, som oftest vil være ren støttebehandling, altså ikke svulstrettet behandling, har Roche brukt ulike eksterne kilder for å modellere sykdomsforløpet til disse pasientene.

Legemiddelverkets vurdering av dokumentasjonen
Studiene viste at Rozlytrek kunne forskyve sykdomsprogresjon i gjennomsnitt med ett år og at 63,5 % av pasientene fikk betydelig svulstskrumping og median levetid på rundt 2 år. Siden studiene følger pasientene bare i en begrenset tidsperiode, vet vi ikke hvor lenge pasienter som får Rozlytrek har effekt av behandlingen. Vi vet heller ikke noe om hvor godt eller dårlig dagens standardbehandling virker for samme pasientgruppe. Legemiddelverket konkluderer derfor med at ikke er mulig å si hvilken effekt pasienter i norsk klinisk praksis vil få av å ta Rozlytrek sammenlignet med dagens standardbehandling.

Det er flere grunner til at Legemiddelverket ikke kan sammenligne effekten Rozlytrek med dagens standardbehandling:

1. *Ukjent prognostisk verdi av NTRK-fusjon:*
   Fordi vi ikke tester for NTRK-mutasjon i dag vet vi ikke hvordan sykdomsforløpet til pasientene som har NTRK-fusjonspositiv kreft ser ut sammenlignet med pasienter som har samme krefttype uten genfeil i NTRK-reseptoren.
2. *Ukjent effekt av Rozlytrek:* Tallene som beskriver effekt fra studiene er veldig usikre, siden studien omfatter små pasientgrupper med stor variasjon i prognose og egenskaper.
3. *Ukjent overførbarthet av studiedata til norsk klinisk praksis:* Det er ukjent i hvilken grad resultatene fra studiene kan brukes til å forutsi hvordan det ville ha gått med pasienter i norsk klinisk praksis dersom de får behandling med Rozlytrek.

Hva koster Rozlytrek?

En måneds legemiddelbehandling med Rozlytrek for en pasient koster i dag omtrent 70 000 kroner med maksimalpris, inkludert merverdiavgift. Dette tilsvarer 840 000 kroner i legemiddelkostnader dersom

pasienten behandles i ett år. Kostnadene relatert til gentesting er ikke tatt med siden testkostnadene blir vurdert av Folkehelseinstituttet i en separat rapport.

Hva er forholdet mellom nytte og kostnad?

For å kunne vurdere om behandling med Rozlytrek gir en merverdi må Legemiddelverket vite hvordan det ville ha gått med pasientene med samme sykdom som får en annen behandling enn Rozlytrek. Studiene som ble gjennomført belyser bare nytten av Rozlytrek isolert sett. Legemiddelverket har derfor ikke kunnet vurdere nytten av Rozlytrek sammenlignet med behandlingen disse pasientene får i dag i norsk klinisk praksis.

I en metodevurdering regner vi vanligvis om prisen til det vi kaller kostnaden for et «godt leveår» (på fagspråket kalt «kvalitetsjustert leveår»). Med et godt leveår mener vi ett år helt uten sykdom. Dette er en standardisert måte å regne på som gjør det mulig å sammenlikne nytten av ulike behandlinger som brukes mot ulike sykdommer. På grunn av manglende data på hvordan Rozlytrek virker sammenlignet med dagens standardbehandling kunne ikke Legemiddelverket beregne «kvalitetsjustert leveår» i denne metodevurderingen.

Hvem bestemmer om Rozlytrek skal tas i bruk?
Legemiddelverkets rolle i evalueringen av sykehusmedisiner er å vurdere tre prioriteringskriterier: nytte, ressursbruk, alvorlighet. Hvilken nytte får pasientgruppen i gjennomsnitt av å få denne behandlingen? Hvor mye ressurser (personell, penger) krever det å gi denne behandlingen? Hvor alvorlig er sykdomsforløpet i gjennomsnitt hvis denne behandlingen blir ikke gitt?

Basert på denne rapporten og andre hensyn fatter Beslutningsforum, bestående av direktørene for de regionale helseforetakene, en endelig beslutning om innføring av nye behandlinger i norske sykehus.

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LOGG

Bestilling:	ID2019_119 Entrectinib til behandling av solide tumorer ved NTRK-fusjonspositiv kreft
Forslagstiller:	Statens legemiddelverk
Legemiddelfirma:	Roche
Preparat:	Rozlytrek
Virkestoff:	Entrectinib
Indikasjon relevant for denne metodevurderingen:	Rozlytrek er indisert som monoterapi til behandling av voksne og pediatriske pasienter fra 12 års alder som har solide tumorer som uttrykker nevrotrofisk tyrosinreseptor kinase (NTRK)-genfusjon, • og som har en lokalavansert eller metastatisk sykdom, eller der kirurgisk reseksjon forventes å kunne resultere i alvorlig morbiditet, og • som ikke har mottatt tidligere behandling med NTRK-hemmer • som ikke har noen tilfredsstillende behandlingsalternativer Rozlytrek as monotherapy is indicated for the treatment of adult and pediatric patients 12 years of age and older, with solid tumors 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, and - who have not received a prior NTRK inhibitor - who have no satisfactory treatment options
Øvrige indikasjoner:	Rozlytrek er indisert som monoterapi til behandling av voksne pasienter med ROS1-positiv, avansert ikke-småcellet lungekreft (NSCLC) som ikke tidligere er behandlet med ROS1-hemmere. Rozlytrek as monotherapy is indicated for the treatment of adult patients with ROS1-positive, advanced non-small cell lung cancer (NSCLC) not previously treated with ROS1 inhibitors.
ATC-nr:	L01XE56

Prosess

Tidspunkt for MT for legemiddelet/indikasjonsutvidelsen	31.07.2020
Dokumentasjon bestilt av Legemiddelverket	21.11.2019
Fullstendig dokumentasjon mottatt hos Legemiddelverket	18.05.2020
Klinikere kontaktet for første gang	18.09.2020
LIS kontaktet for første gang av Legemiddelverket	27.05.2020
Legemiddelverket bedt om og motatt ytterligere dokumentasjon	03.06.2020- svar motatt 24.06.2020 21.09.2020- svar motatt 25.09.og 02.10.2020 03.11.2020- svar motatt 04.11.2020

	11.12.2020- svar motatt 14.12.2020 16.12.2020- svar motatt 16.12.2020
Rapport ferdigstilt:	12-02-2021
Saksbehandlingstid:	270 dager hvorav 30 dager i påvente av ytterligere opplysninger fra legemiddelfirma. Dette innebærer en reel saksbehandlingstid hos legemiddelverket på 237 dager.
Saksutredere:	Bjørn Oddvar Strøm Randi Krontveit Yvonne Anne Michel
Kliniske eksperter:	Kliniske eksperter har bidratt med avklaringer av sentrale forutsetninger i analysen (bl.a. pasientgrunnlag, plassering i behandlingslinjene og overførbarhet av studiedata til norsk klinisk praksis). Siden tumoragnostisk behandling av NTRK-fusjons positive tumorer ikke er bruk i klinisk praksis i Norge i dag, har klinikere begrenset erfaring. Helseforetakene har oppnevt to klinikere til denne metodevurderingen: Tormod Kyrre Guren fra OUS Dorota Katarzyna Pazdyk Goplen fra Helse Bergen I tillegg har Legemiddelverket har tatt kontakt med klinikere gjennom Sykehusinnkjøp sin spesialistgruppe innen onkologi, for å få innspill på flere kerfttyper som er omfattet av denne metodevurderingen. I arbeidet med rapporten har følgende klinikerne hatt skriftlig kommunikasjon med saksbehandlere i Legemiddelverket: Heidi Glosli, OUS Odd Terje Brustugun, Vestre Viken HF Tormod Kyrre Guren; OUS Dorota Katarzyna Pazdyk Goplen, Helse Bergen Ved ferdigstillelse av rapporten har følgende klinikerne fått mulighet til å kommentere rapporten: Tormod Kyrre Guren; OUS Dorota Katarzyna Pazdyk Goplen, Helse Bergen Odd Terje Brustugun, Vestre Viken HF Legemiddelverket er ansvarlig for rapportens innhold. Kliniske eksperter har ikke vært involvert i noen konsensusprosess eller hatt noen «peer-review» funksjon ved utarbeidelse av rapporten.

GLOSSARY

AE	Adverse Event
AUP	Apotekenes Utsalgspris, Pharmacy Retail Price
BDNF	Brain-derived neurotrophic factor
BICR	blinded independent central review
BSA	Body surface area
BSC	Best Supportive Care
CBR	Clinical benefit rate
CI	Confidence Interval
CR	Complete response
CRN	Cancer Registry Norway
CUA	Cost-Utility Analyses
DCO	Data Cut-Off
DoR	Duration of response
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EMA	European Medicines Agency
EORTC	European Organisation for Research and Treatment of Cancer
EQ-5D	European Quality of Life-5 Dimensions
GI	gastrointestinal
HRQoL	Health Related Quality of Life
HTA	Health Technology Assessment
ICU	Intensive Care Unit
IHC	Immunohistochemistry
IRC	Independent Review Committee
ITC	Indirect Treatment Comparison
IV	Intravenous
KM	Kaplan-Meier
m	months
MASC	mammary analogue secretory carcinoma
MEM	Mixed-Effects Model
MMRM	Mixed-Effects Model for Repeated Measures
MPR	Medication Possession Ratio
NE	Not estimatable
NET	Neuroendocrine tumors
NICE	The National Institute for Health and Care Excellence
NoMA	Norwegian Medicines Agency
NGF	Nerve growth factor
NGS	Next generation sequencing
NSCLC	Non-small cell lung cancer
NTRK	Neurotrophic tyrosine receptor kinase
OLE	Open Label Extension
OS	Overall Survival
PD	Progressive disease
PFS	Progression-free survival
PICO	Patients, Intervention, Comparator, Outcome.
PR	Partial response
PRP	Pharmacy Retail Price

QALY	Quality Adjusted Life Year
RCT	Randomized controlled trial
RF	Residual Function
SD	Stable disease
SPC	Summary of Product Characteristics
STA	Single Technology Assessment
TRK	Tropomyosin receptor kinase
TTOT	Time-to-off-treatment
VAT	Value added tax

1 BACKGROUND

1.1 SCOPE

Single technology assessment (STA) of Rozlytrek (entrectinib) for the treatment of patients with solid neurotrophic tyrosine receptor kinase (NTRK) fusion positive tumours in adults and adolecents above 12 years of age.

Health service interventions are evaluated against three priority-setting criteria in Norway; the benefit criterion, the resource criterion, and the severity criterion. Roche has submitted a cost utility analysis based on an integrated analysis (see chapter 2 for details) of the adult population in the phase I and II, single-arm trials of entrectinib (STARTRK-1, STARTRK-2, ALKA) in patients with NTRK fusion positive tumours. Of the 74 patients in the integrated analysis, 71 patients are from the STARTRK-2 trial. Since the included studies were single-armed, they did not provide data on comparator treatment. Roche therefore retrieved comparator data from external sources. All three studies are still ongoing and Roche is obliged to collect data on additional 200 patients by EMA's conditional marketing authorisation. NoMA´s assessment is primarily, but not exclusively, based on the documentation presented by Roche.

1.2 SOLID NEUROTROPHIC TYROSINE RECEPTOR KINASE (NTRK) FUSION POSITIVE TUMOURS

The population eligible for treatment with entrectinib is defined based on the presence of a specific genomic alteration (NTRK-fusion), irrespective of tumour type (tumour-agnostic). Patients with any type of locally advanced or metastatic solid tumour, who tested positive for NTRK-fusion, fall into the scope of this assessment. The tropomyosin receptor kinase (TRK) family includes TRK A, B and C, which are encoded by the neurotrophic tyrosine kinase (NTRK) receptor genes 1, 2 and 3, respectively (1). They are expressed in neuronal tissues, where they play a critical role in the development and function of neurons of the central and peripheral nervous systems, as well as a variety of non-neuronal tissues throughout development, including the cardiovascular, endocrine, reproductive, and immune systems (2). Gene fusions involving NTRK1/2/3 (when the 3' region of the NTRK gene is joined with a 5' sequence of a fusion partner gene) result in a constitutive activation or overexpression of TRK-receptors, potentially leading to oncogenesis (3); multiple fusion partners have been identified in NTRK1/2/3-rearranged tumours to date (1).

NTRK-fusions are rare events in common cancers (e.g., frequency of <1% - 3% in NSCLC and 1 - 2% in CRC), and more frequently observed in some rare cancers. One example is mammary analogue secretory carcinoma (MASC), a rare form of salivary gland cancer, where NTRK-fusion expression (ETV6-NTRK3) is a diagnostic marker. NTRK-fusions can be found in 90-100% of MASC, however MASC represents <1% of all cancer malignancies (4-6). Distribution of NTRK-fusions across some cancer types are shown in Table 1.

Table 1: Detection of NTRK gene fusion in various types of cancer: Source: Roche submission.

	NTRK 1	NTRK 2	NTRK 3
NSCLC	<1-3%[a,c]		
Sarcoma	<1%[b,d]		
MASC			91-100%[a,f]
Papillary thyroid	<12%[g]		2-21%[h,i]
CRC	<1-2%[a,b,k]		
Secretory breast			92%[l]
Head and Neck cancer		<1%[b]	<1%[b]
Melanoma	21%[m]		
Neuroendocrine			<1%[n]
Glioblastoma (adult)	1%[o,p]	1%[q]	1%[q]
Low-grade gliomas		<1%[b]	
Cholangiocarcinoma	4%[r]		

Abbreviations: AML, acute myeloid lymphoma; CRC, colorectal cancer; MASC, mammary analogue secretory carcinoma; NSCLC, non-small-cell lung cancer; NTRK, neurotrophic tyrosine receptor kinase.

Based on NGS profiling of 116,398 adult and pediatric tumour samples using the Foundation Medicine Inc. (FMI) NGS platform, an estimated prevalence of 0.32% has been observed (6). Roche assumes that if all eligible patients are tested, and all patients with NTRK-fusions are treated, a maximum of 50 patients will be treated in Norway each year.

1.3 SEVERITY AND SHORTFALL

Patients with NTRK-fusion postive cancers who have exhausted all satisfactory treatment options have poor prognosis when receiving currently available treatment. The patient population potentially eligible for entrectinib is necessarily diverse due to the histology independent indication. Severity and shortfall of patients with solid NTRK-fusion positive tumours is consequently likely to differ by histology. For patients with solid NTRK-fusion positive tumours who do not have other suitable treatment options at current or when surgical resection is likely to result in severe morbidity, prognosis is especially poor.

NoMA could not use the standard quantitative method to calculate the severity for patients with solid NTRK-fusion positive tumours. Both the average age of the patient population and the average QALY-gain with currently available treament options is necessary to quantify severity. As discussed below, NoMA does not consider the comparator arm from the submitted analysis to be reliable in establishing prognosis for patients with tumours harbouring NTRK-fusions. Without a reliable estimate of remaining QALYs for the comparator treatment BSC, absolute shortfall cannot be quantified. The average age of the patient population can be derived from the clinical studies. However, it remains uncertain if the patient population in Norwegian clinical practice will have a comparable average age, no more reliable estimate is available.

In absence of reliable information on remaining QALYs with currently available treatment (BSC), the potential shortfall of patients with NTRK-fusion postive cancers can be described by the following: The average age in the trials was 57 years. A member of the general Norwegian population can on average expect to have 22 QALYs left. Heavily pre-treated cancer patients have poor prognosis, and few remaining

QALYs. NoMA expects that patients with NTRK-fusion postive cancers who have exhausted all satisfactory treatment options loose about 20 QALYs. This estimate is in line with the severity estimation of Roche.

Severity affects whether the costs are considered reasonable relative to the benefit of the treatment. The description of severity in this STA is based on assumptions and it should be interpreted with caution.

1.4 TREATMENT OF SOLID NTRK-FUSION POSITIVE TUMOURS

1.4.1 Treatment with entrectinib (7)

- *Therapeutic indication*
  Entrectinib as monotherapy is indicated for the treatment of adult and pediatric 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

  Entrectinib as monotherapy is also indicated for the treatment of adult patients with ROS1-positive, advanced non-small cell lung cancer (NSCLC) not previously treated with ROS1 inhibitors.

  The latter indication is not assessed in this report, but is discussed in a separate report (8) .

- *Mechanism of action*
  Entrectinib is an inhibitor of the tropomyosin receptor tyrosine kinases TRKA, TRKB and TRKC (encoded by the neurotrophic tyrosine receptor kinase [NTRK] genes NTRK1, NTRK2 and NTRK3, respectively), proto-oncogene tyrosine-protein kinase ROS (ROS1), and anaplastic lymphoma kinase (ALK).

  Fusion proteins that include TRK, ROS1 or ALK kinase domains drive tumourigenic potential through hyperactivation of downstream signalling pathways leading to unconstrained cell proliferation. Entrectinib demonstrated in vitro and in vivo inhibition of cancer cell lines derived from multiple tumour types, including subcutaneous and intracranial tumours, harbouring NTRK, ROS1, and ALK fusion genes.

- *Posology*
  The recommended dose for adults is 600 mg entrectinib once daily. For adults, the dose of entrectinib may be reduced up to 2 times, based on tolerability. Entrectinib treatment should be permanently discontinued if patients are unable to tolerate a dose of 200 mg once daily. For adolecents with a body surface area (BSA) between 1.11 m^2 and 1.50 m^2 a dose of 400 mg daily is reccommended. For adolecents with a BSA over 1.50 m^2, the recommended dose is 600 mg. For

adolcents and children ≥12 years of age, the dose of entrectinib may be reduced up to 2 times, based on tolerability, see separate table in SmPC.

- *Adverse reactions*
  The most common adverse reactions (≥20%) were fatigue, constipation, dysgeusia, oedema, dizziness, diarrhoea, nausea, dysaesthesia, dyspnoea, anaemia, increased weight, increased blood creatinine, pain, cognitive disorders, vomiting, cough, and pyrexia. The most frequent serious adverse reactions (≥2%) were lung infection (5.2%), dyspnoea (4.6%), cognitive impairment (3.8%), and pleural effusion (2.4%). Permanent discontinuation due to an adverse reaction occurred in 4.4% of patients.

1.4.2 Treatment guidelines

At present NTRK-fusions are not mentioned in the treatment guidelines, patients will receive the standard of care recommended for their tumour.

1.4.3 Comparator

According to the SmPC, entrectinib 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). NoMA therefore considers best supportive care to be the relevant comparator in this assessment. Best supportive care for different tumour types, which can include chemotherapy with limited effectiveness in addition to supportive and palliative care, will be further discussed in chapter 3.3 and appendix 1.

2 RELATIVE EFFECTIVENESS

To date four studies have been started for documenting the clinical efficacy of entrectinib:

- ALKA
- STARTRK-1
- STARTRK-2
- STARTRK-NG

All four studies included patients with NTRK-, ALK, or ROS1-fusions, and had similar inclusion and exclusion criteria. STARTRK-1 and ALKA were primarily dose finding studies, whereas STARTRK-2 was a phase II-study using a single starting dose. STARTRK-NG was performed in children and young adults up to 18 years of age.

Roche has submitted an integrated analysis of the adult population in the phase I and II trials of entrectinib (STARTRK-1, STARTRK-2, ALKA). Of the 74 patients in the integrated analysis, 71 patients are from the STARTRK-2 trial (9). The trials in the integrated analysis is summarized Figure 1. The integrated analysis included all patients with NTRK-fusion who had received entrectinib and had been followed for at least 6 months the time of data cut-off. STARTRK-NG was not included in the integrated analysis.

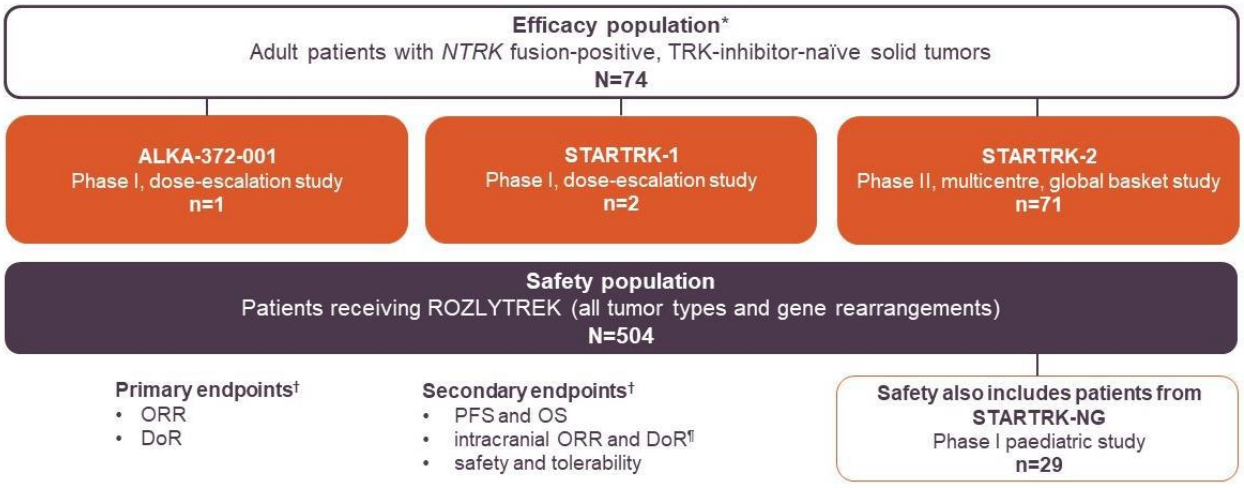


Figure 1: Overall design of the integrated efficacy analysis and included studies (COD October 2018)

2.1 OVERVIEW OF RELEVANT CLINICAL STUDIES

Table 2: Overview of relevant studies (STARTRK-1, STARTRK-2, ALKA)

Study	*Population*	*Intervention*	*Comparison*	*Primary endpoints*	*Secondary endpoints*
STARTRK-2	Patients (≥18 years of age) with advanced or metastatic solid tumours that harbor an NTRK1/2/3, ROS1, or ALK gene fusion, excluding ALK-positive NSCLC	Entrectinib 600 mg daily	None	Objective response rate (ORR) Duration of response (DoR) Best overall response (BOR)	Clinical benefit rate (CBR) Progressionfree survival (PFS) Overall survival (OS) Intracranial tumour response Intracranial PFS
ALKA	Patients (≥18 years of age) with advanced or metastatic solid tumours, including patients with NTRK1/2/3, ROS1, or ALK molecular alterations	Entrectinib, ascending doses	None	ORR DoR BOR	CBR PFS OS Intracranial tumour response Intracranial PFS
STARTRK-1	Patients (≥18 years of age) with solid tumours with NTRK1/2/3, ROS1, or ALK molecular alterations	Entrectinib, ascending doses	None	ORR DoR BOR	CBR PFS OS Intracranial tumour response Intracranial PFS

2.2 ONGOING STUDIES

The three studies described above are all still ongoing with the final integrated analysis for NTRK-fusions planned in March 2021. STARTRK-2 is expected to continue until 2027, and recruit a total of 200 patients, to meet EMA's requirements given by the conditional market authorisation (10).

2.3 DOCUMENTATION TO ESTABLISH RELATIVE EFFECTIVENESS

There is no comparative data forthcoming from the clinical trials. An indirect treatment comparison was not deemed feasible by Roche due to the acknowledged differences between patient and disease characteristics, tumour types and potential comparator therapies meeting the definition of best supportive care. For the purposes of economic evaluation, a naïve histology weighted comparison was therefore developed using published data for a population of patients where NTRK-fusion-positive status was not reported. The comparator data for each of the histologies were based on comparator data used in previous NICE-technology appraisals in which the assessed intervention received reimbursement (Table 3).

Table 3: Comparator arms used in the naïve histology weighted treatment comparisons

NICE TA	Year	Population	Comparator	Line of therapy	Clinical outcomes		
					ORR (%)	Median PFS (m)	Median OS (m)
Breast cancer							
TA515	2018	- Locally advanced or metastatic - 1 prior chemotherapy regimen	Capecitabine	2L	11.5	4.1	14.5
TA423	2016	- Locally advanced or metastatic disease ≥2 prior chemotherapy regimen	Eribulin	3L+	12.2	3.6	13.2
TA423 (aggregated "physician's choice" comparators)	2016	- Locally advanced or metastatic disease ≥2 prior chemotherapy regimen	Vinorelbine	3L+	4.7	2.2	10.5
	2016	- Locally advanced or metastatic disease ≥2 prior chemotherapy regimen	Gemcitabine + paclitaxel		4.7	2.2	10.5
				Average of medians		3.0	12.2
				Average of exponential means		4.4	17.6
Non-small-cell lung cancer							

TA520 (mixed histology)	2018	Locally advanced or metastatic disease ≥ 1 previous chemotherapy regimen	Docetaxel	2L+	13.4	3.4	9.6
TA428 (mixed histology)	2017				9.0	4	8.5
TA483 (squamous histology)	2017				9.0	2.8	6
TA484 (non-squamous histology)	2017				12.0	4.2	9.4
TA403 (mixed histology)	2016				13.6	3	9.1
TA347 (non-squamous histology)	2015				3.6	2.8	10.3
TA124 (non-squamous histology)	2007				8.8	2.9	7.9
Docetaxel average of medians						3.3	8.7

TA347 (non-squamous histology)	2015	Locally advanced or metastatic disease ≥ 1 previous chemotherapy regimen	Nintedanib + docetaxel	2L+	4.7	4.2	12.6
					Average of medians	3.8	10.7
					Average of exponential means	5.4	15.4
Colorectal cancer							
TA307	2014	Advanced or metastatic disease Progression following oxaliplatin-based therapy	FOLFIRI	2L	11.1	4.7	12.1
TA242	2012	Advanced or metastatic disease Following first line chemotherapy	Irinotecan	2L	34.8	6.2	15.6
TA405	2016	Advanced or metastatic disease Following previous treatment with available therapies	Trifluridine-tipiracil	3L	0.9	2	9
			Trifluridine-tipiracil		1.6	2	7.2
			Best supportive care		0.0	1	6.6

			Best supportive care		0.0	1.7	5.2
Average of medians						2.6	9.1
Average of exponential means						3.8	13.1
Neuroendocrine tumours (refractory/unsuitable for lutetium therapy)							
TA449 and TA539	2017 and 2018	Unresectable or metastatic neuroendocrine tumours	Everolimus (pancreatic NET)	1L	4.8	11	44.0
			Best supportive care (pancreatic NET)		2	4.6	37.7*
			Everolimus (GI/Lung NET)		2	11	37.2
			Best supportive care (GI/Lung NET)		1	3.9	39.6*
Average of medians						8.0	39.6

					Average of exponential means	11.6	57.1
Pancreatic tumours							
TA476	2017	Metastatic disease	Gemcitabine + nab-paclitaxel	1L	23	5.5	8.7
			Gemcitabine monotherapy		7	3.7	6.6
NICE Guideline NG85	2018	Metastatic disease	FOLFIRINOX	1L	31.6	6.4	11.1
					Average of medians	5.2	8.8
					Average of exponential means	7.5	12.7
Papillary and anaplastic thyroid cancer (unsuitable/progressed following radioactive iodine)							
TA535	2018	Locally advanced or metastatic disease Unresponsive to radioactive iodine	Best supportive care	2L+	1.5	3.7	19.1 (after cross-over adjustment)
			Best supportive care	2L+	0.5	5.4	42.8*

					Average of medians	4.6	31.0
					Average of exponential means	6.6	44.7
Soft tissue sarcoma							
TA465	2017	Advanced disease Unsuitable for curative surgery or unresponsive to radiotherapy	Doxorubicin	1L+	7.5	4.1	14.7
TA185	2010	Locally advanced or metastatic disease Relapsed/refractory following one anthracycline and ifosfamide	Trabectedin	2L+	5.1	3.3	13.9
					Average of medians	3.9	14.3
					Average of exponential means	5.6	20.6

2.4 NoMA's assessment of the submitted clinical documentation

All the clinical trials are single arm, with objective response rate and duration of response as primary end points. This is in accordance with the EMA-guidelines for single arm clinical trials in oncology (11). However, EMA did not consider the submitted documentation sufficient to establish the treatment effect relative to other treatments. As relative effectiveness could not be assessed, EMA limited the indication to patients who have exhausted all treatments shown to be of benefit for a given histological form of cancer (7).

Relative effectiveness of entrectinib vs. comparator for use in health economic modelling has to be established through an indirect treatment comparison. In Roche's documentation the relative effectiveness vs. comparator treatments is not based on the integrated analysis (STARTRK-1, STARTRK-2, ALKA) vs. a feasible population selected based on NTRK-fusion. Rather, Roche derived comparator data from previous NICE-technology appraisals in which the assessed intervention received reimbursement. How many patients harbouring the NTRK-fusion in the comparator data is not known, but is likely to be low.

The indirect treatment comparison is naïve, although weighted for histologies to match the distribution of different histologies in the integrated analysis of entrectinib. According to the approved indication, NoMA considers best supportive care as the relevant comparator. There are several issues that make results of the comparison difficult to interpret and hamper establishment of relative effectiveness. This will be further discussed in chapter 3.

For these reasons, NoMA considers the submitted documentation insufficient to establish relative effectiveness for entrectinib versus best supportive care for use in health economic modelling.

3 PICO[1]

3.1 PATIENT POPULATION

Clinical practice in Norway

Entrectinib is indicated for patients 12 years of age and older with solid tumours carrying a NTRK-fusion, regardless of tumour histology, who have exhausted other available therapies. Testing for NTRK-fusions is not yet routinely performed in Norway, the testing capacity is limited and data on patient characteristics from Norwegian clinical practice are not available yet.

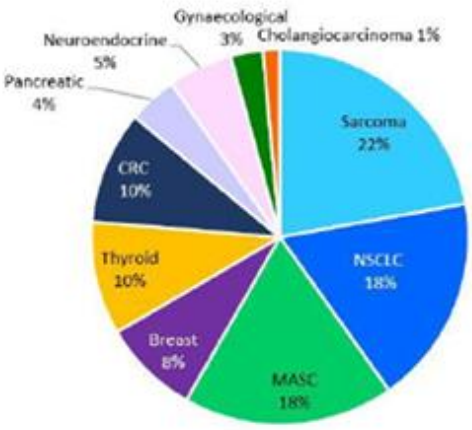
NTRK-fusions are included in most commercially available sequencing panels used in Norway, and it seems likely that most patients with metastatic cancer will be tested in the future. The Norwegian Institute of Public Health is evaluating the tests necessary to identify patients with NTRK-positive fusions. At present, not all relevant patients will be tested, but the capacity is likely to increase in the next few year. This means that fewer patients will be indentified in the next few years than would be the case if the everyone was tested from the onset.

Submitted clinical documentation (in relation to clinical practice)

The patient characteristics from the integrated analysis submitted by Roche is summarized in Table 4.

[1] Patients, Intervention, Comparator, Outcome.

Table 4: Patient characteristics from the integrated analysis. Source: Roche submission.

				Adult NTRK efficacy evaluable analysis set (N=74)
Demographics and Baseline Characteristics	Age		median (range), years	57.0 (21-83)
			≥65 years, n (%)	26 (35.1%)
	Sex		male/female, n (%)	35 (47.3)/ 39 (52.7)
	Race		White/Asian/not reported, n (%)	52 (70.3)/ 13 (17.6)/ 7 (9.5)
	ECOG PS 0/1/2		n (%)	30 (40.5)/ 34 (45.9)/ 10 (13.5)
	History of smoking		n (%)	29 (40.3)
Baseline Disease Characteristics	Tumor type (High Level)			
	Gene fusion detected		NTRK1/2/3, n (%)	30 (40.6)/ 2 (2.8)/ 42 (56.9)
	Time since diagnosis		median (range), months	21.0 (2.1, 433.1)
	Disease stage at initial diagnosis, n (%)		0, I or II (A/B)	21 (28.7)[a]
			III (A/B/C) or IV	45 (61.7)[a]
			unknown	7 (9.6)[a]
	Metastatic disease		any site, n (%)	72 (97.3)
			brain metastases, n (%)	19 (25.7)[b]
Previous Cancer Treatment	No. of lines of therapy since metastatic disease diagnosis[c]		0	20 (27.0)
			1	21 (28.4)
			2	20 (27.0)
			3	6 (8.1)
			≥4	7 (9.5)
	Previous therapy, n (%)		any systemic therapy[d]	64 (86.5)
			surgery	61 (82.4)
			radiotherapy	47 (63.5)[e]

[a]Percentages calculated based on denominator of 73 patients as one patient in the ALKA study for whom the initial diagnosis field on the case report form was blank and was excluded.

[b]Includes two patients with measurable disease.

[c]Patients may have received other therapies in the adjuvant or neo-adjuvant setting that are not included as a line of therapy from the time of metastatic disease diagnosis.

[d]Includes chemotherapy, immunotherapy, targeted therapy or hormonal therapy.

[e]Includes 13 patients who received prior radiotherapy of the brain.

Abbreviations: CRC, colorectal cancer; ECOG PS, eastern cooperative oncology group performance staus; MASC, mammary analogue secretory carcinoma; NSCLC, non-small-cell lung cancer; NTRK, neurotrophic tyrosine receptor kinase

NoMA requested data on mean age and number of previous treatment lines for each histology separately, (Table 5). The last column in Table 5 shows Roche's assumed positioning of entrectinib in Norwegian clinical practice.

Table 5: Overview of patient characteristics and positioning. Source: Roche submission.

			Previous lines of treatment				
	n	Average age	0	1	2	3+	Company positioning
Breast cancer	6	57,5	50 %	0 %	0 %	50 %	2L/3L
Colorectal cancer	7	66,6	14 %	29 %	29 %	29 %	3L
Neuroendocrine tumours	4	57,5	0 %	75 %	0 %	25 %	1L
Non-small cell lung cancer	13	63,2	23 %	31 %	23 %	23 %	2L/3L
Pancreatic cancer	3	42,3	33 %	33 %	33 %	0 %	2L
MASC	13	56,5	46 %	15 %	23 %	15 %	1L
Sarcoma	16	59,0	19 %	44 %	25 %	13 %	1L/2L
Thyroid cancer	7	57,7	29 %	14 %	57 %	0 %	2L+
Others	5	54,2	20 %	60 %	0 %	20 %	NA
Total	**74**	**58,7**	**27 %**	**31 %**	**23 %**	**19 %**	

NoMAs assessment

The patient characteristics in Norwegian clinical practice is difficult to elucidate, given that patients currently are not routinely tested for NTRK-fusions. Comparing the patient population that is potentially eligible for entrectinib to the average patients with similar histologies might also be misleading, as patients with certain mutations may differ from the overall patient population in prognostic factors like age and smoking status. In the integrated analysis of entrectinib for ROS1-positiv NSCLC submitted by Roche, the patient population included in the clinical trials was clearly younger than what have been seen for unselected NSCLC patients in Norwegian clinical practice (8). Given that Roche has not provided any other sources for patients characteristics for patients carrying the NTRK-fusion, the best data available is the data from the clinical trials for entrectinib and larotrectinib, another NTRK-inihibitor (12). However, these data might be preseleceted for better prognosis compared to the anticipated patient population in clinical practice.

The approved indication, and the order from the Ordering forum, includes patients above 12 years of age. As shown in Table 4, the youngest patient included in the analysis was 21 years old. However, there is no reason to expect a different efficacy in adolecents. The efficacy of the NTRK-inhibitor larotrectinib was similar in adolecents and adults (13).

The distribution of different histologies in clinical practice is also difficult to estimate, and will depend on which tumour histology types that will be tested. Roche states that the patients included in intergrated analysis probably are a preselected population of patients with higher likelihood of being NTRK-fusion-positive. This might bias the assessment, but the direction is difficult to elucidate. However, better data are not available at present, and the best estimate of the patient population in Norwegian clinical practice is still the entrectinib trial program. Future data from clinical practice can be informative.

Regarding previous treatment, the STARTRK-2 trial had more liberal inclusion criteria compared to the label granted by EMA. Some of the patients in the submitted analysis had received fewer previous treatments than required by the approved indication (Table 5). As previous treatment is likely to affect both prognosis and response to therapy, as well as the treatment options being replaced, the inclusion of less heavily pretreated patients is problematic and can bias the results in favour of entrectinib. Based on the information submitted, about 25% - 30% of the patients should have received other treatments before being candidates for the comparators proposed by Roche if they did not receive entrectinib.

Breast cancer is used to illustrate challenges related to representiveness of the patients included in Roche's analysis: The STARTRK-2 trial included 6 patients with breast cancer, of which 4 had secretory breast cancer. This cancer type is known to be rather benign, to have a better prognosis than triple negative breast cancer and occurs in young women (14). Patients with secretory breast cancer is clearly a different patient population than commonly encountered in breast cancer. Similar cases with better or worse prognosis may exist for other tumours as well, although not described in the medical literature yet.

To summarize, the patient characteristics in Norwegian clinical practice is not known. Consequently, it is also unknown to what extent the STARTRK-2 trial represents the patients likely to be encountered in Norwegian clinical practice, both with regard to functional stage, age, and in particular tumour origin. A significant number of the patients included in the analysis had received fewer previous treatments than forseen by the approved indication. This can make the results from the STARTRK-2 better than what will be seen in clinical practice. NoMA assumes that treatment with entrectinib in Norwgian clinical practice will align with the approved indication and include patients from 12 years of age and older

NoMA has reached out to clinicians working in Norwegian clinical practice. However, their feedback was limited to which treatments would likely be replaced by entrectinib in Norwegian clinical practice. As NTRK-fusions are not routine tested in clinical practice yet, clinicians so far have limited experience with NTRK-inhibitors.

3.2 INTERVENTION

Clinical practice in Norway

Concerning the dosage, it is assumed that entrectinib will be used according to the approved SmPC, with a dose of 600 mg daily taken orally. According to the SmPC, patients may reduce the dose twice due to adverse reactions before discontinuing due to adverse events. According to clinical experts and based on experience with other kinase inhibitors, some patients may continue treatment beyond radiological progression if they, in the opinion of the treating physician, are still likely to benefit from the treatment.

Submitted clinical documentation (in relation to clinical practice in Norway)

Of 74 patients included in the integrated analysis, 71 received the approved starting dose in the STARTRK-2 trial. The discontinuation criteria were similar to what was is described in the SmPC. The last three patients received different doses higher than 600 mg daily. Two received 400 mg/m^2, and the last patient received an escelating dose in the dosefinding trial. In the integrated analysis, the median time on treatment were 8.6 months.

NoMA's assessment

NoMA assesses the dosing used in the STARTRK-2 trial to be likely to reflect the use in Norwegian clinical practice and acceptable for the HTA-assessment. Duration of therapy may differ according to the patients prognosis as described in chapter 3.1.

3.3 COMPARATOR

Clinical practice in Norway

According to the approved SmPC entrectinib should only be used if there are no other satisfactory treatment options. All treatments shown to be effective for a given type of cancer, if available, should have been administered to the patient in advance. Thus, best supportive care will be the relevant comparator in clinical practice.

According to the clinical experts entrectinib might be used in place of late line palliative chemotherapy, in particular where the effectiveness of this treatment is not convincing.

Submitted clinical documentation (in relation to clinical practice in Norway)

In the submitted naïve histology weighted comparison, an averaged chemotherapy comparator was created. This averaged comparator arm consists of clinical comparator data that have been reported in previous NICE-technology appraisals in which the assessed intervention received reimbursement. Roche weighted these average outcomes by the proportions of tumour types represented in the integrated analysis population of the entrectinib trials. The comparators that Roche proposed for each histology are shown in Table 6Table 6: Comparators by histology, Source: Roche submission.

	Weight	Comparator Treatment	Line	NICE technology appraisals	Assessed by NoMA
Breast Cancer	8 %	Capecitabine	2L	TA515	No
		Eribulin	3L+	TA423	Yes (15)
		Vinorelbine or Gemcitabine +paclitaxel	3L+	TA423	Yes (15)
NSCLC	19 %	Docetaxel	2L+	TA520, TA428, TA483, TA484, TA403, TA347, TA124	Yes (16-19)
		Nintedanib + docetaxel	2L+	TA347	No
Colorectal cancer	8 %	FOLFIRI	2L	TA307	Yes (20)
		Irinotecan	2L	TA242	No
		Trifluridine-tipiracil	3L+	TA405	Yes (21)
		Best supportive care	3L+	TA405	Yes (21)

Neuroendocrine tumours	5 %	Everolimus	1L	TA449 and TA539	No
		Best supportive care	1L	TA449 and TA539	No
Pancreatic cancer	4 %	Gemcitabin with or witout paclitaxel	1L	TA476	No
		FOLFIRINOX	1L	NICE guideline NG85	No
Thyroid cancer	9 %	Best supportive care	2L+	TA555	Yes (22)
Soft tissue sarcoma	19 %	Doxorubicin	1L+	TA465	Yes (23)
		Trabectedin	2L+	TA185	No
MASC	18 %	BSC	1L	Based on (24)	
Other	8 %			Based on average of other histologies	

NoMA's assessment

NoMA considers the lack of comparator data from the entrectinib trials as a major weakness of the submitted documentation. The use of comparator data from previous NICE-technology appraisals in which the assessed intervention received reimbursement can be a pragmatic choice to estimate the efficacy of the different comparator treatments. Still, NOMA has severe reservations about the methodology used to generate the comparator data. NoMA does not approve the submitted comparator data based on the following:

Data source for the comparator arm

The averaged comparator arm is based comparator data used in previous NICE-technology appraisals in which the assessed intervention received reimbursement in the UK. The fact that comparator data of new treatments are used, means that the comparator treatments have been replaced by the respective new treatments or moved to a later treatment line. NoMA does not agree with Roche's assumption that this averaged comparator arm provides a representative picture of how patients with an NTRK-fusion without access to targeted therapy would fare. Roche's assumption implies that prior therapy does not affect the prognosis of future therapies. NoMA does not consider this assumption to be substantiated.

Unknown prognositic value of the NTRK-fusion

The main challenge with the submitted documentation on comparator data is that all NICE-technology appraisals are from populations that were not tested for NTRK-fusions. Given the rarity of NTRK-fusions, it seems likely that hardly any of the patients informing the analysis were carrying NTRK-fusions. For the comparator to be acceptable, this would imply that NTRK-fusions have to be prognostically neutral, meaning that patients with and without NTRK-fusions had comparable prognosis. NoMA has asked Roche to provide documentation of the prognostic value of NTRK-fusions, ideally through a systematic litterature review. Roche has not provided a systematic literature review, but has referred to articles

supporting the assumption that NTRK-fusions have a negative prognostic value in metastatic colorectal cancer (25) and papilary thyroid cancer (26, 27). Roche also referred to one study in congenital mesoblastic nephroma, where the presence of an NTRK-fusion seems to confer a more favourable prognosis (28). All articles are from small case studies with small clinical efficacy estimates which are difficult to interpret. However, the articles support that in many tumour forms, like in breast cancer and salivary cancer, NTRK-fusion positive tumours might form a distinct subset with a distinct prognosis and presentation. NoMA considers the unknown prognostic value of NTRK-fusions as a major barrier to meaningfully interpret the comparison between patients with NTRK-fusions receiving one treatment, in this case entrectinib, and patients without NTRK-fusions receiving comparator treatments.

Relevance of comparators compared to clinical practice and approved indication.

In general, as mentioned above, patients receving entrectinib should have exhausted all satsifactory treatment options. The definition of satisfactory treatment option is not clear, and the excact placement in the treatment algoritm will depend on phycisian and patient preference, and might change as more data and clinical experience becomes available. On a group level, it is assumed that patients should have received the treatments that demonstrated a reasonable survival benefit for patients with a given histology, and patients will be treated with best supportive care. Best supportive care does imply that patients could receive active palliative treatment primarily to increase life quality. However, the effectiveness of this treatment is poorly documented, or gives a very limited benefit. The precise positioning also depends on clinical experience.

Roche assumed that the patients should have received fewer treatment lines before receiving entrectinib than the available guidelines and clinician feedback indicates. As a consequence of this mismatch, NoMA questions wether the patient population from the integrated analysis is representative for the patients likely to receive entrectinib in Norwegian clinical practice. A discussion on the different parts of the comparator arm is shown in appendix 1.

It can be assumed that treatment given in later treatment lines are less effective. Roche uses less pretreated patients in the comparator arm than what is expected for Norwegian clinical practice. Since treatment in earlier lines can be expected to be more effective, Roche’s approach can potentially bias the relative efficactiveness in favour of entrectinib.as the patients in the comparator arm are expected to have shorter effect, regardless of treatment received than some of the paitents in the intervention arm.

3.4 OUTCOME MEASURES

3.4.1 Effectiveness

Submitted clinical documentation (in relation to clinical practice in Norway)

The efficacy data in the integrated analysis is from the latest data cut-off in October 2018. The primary end points of the integrated analysis were objective response rate (ORR) and duration of response (DOR). ORR was 63.5% (95% CI: 51.,5% - 74.4%). The median duration of response assessed by the independent

central review, was 12.9 months (95% CI: 9.3 - NE). It was estimated that 70% of the patients had response of more than 6 months duration.

The objective response rate (ORR) and duration of response (DOR) by tumour type is summerized in

.

Table 7: Summary of PRR and DOR by tumour type. Source: Roche submission.

Tumor Type	Patients (N=74)	ORR		DOR
		n (%)	95% CI	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	Miss, 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	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	Miss	NA	NA

* Censored

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; Miss: missing.

Median progression free survival (PFS) based on the integrated analysis was 11.2 months (95% CI: 8.0 – 15.7), and Kaplan-Meier curve is shown below.

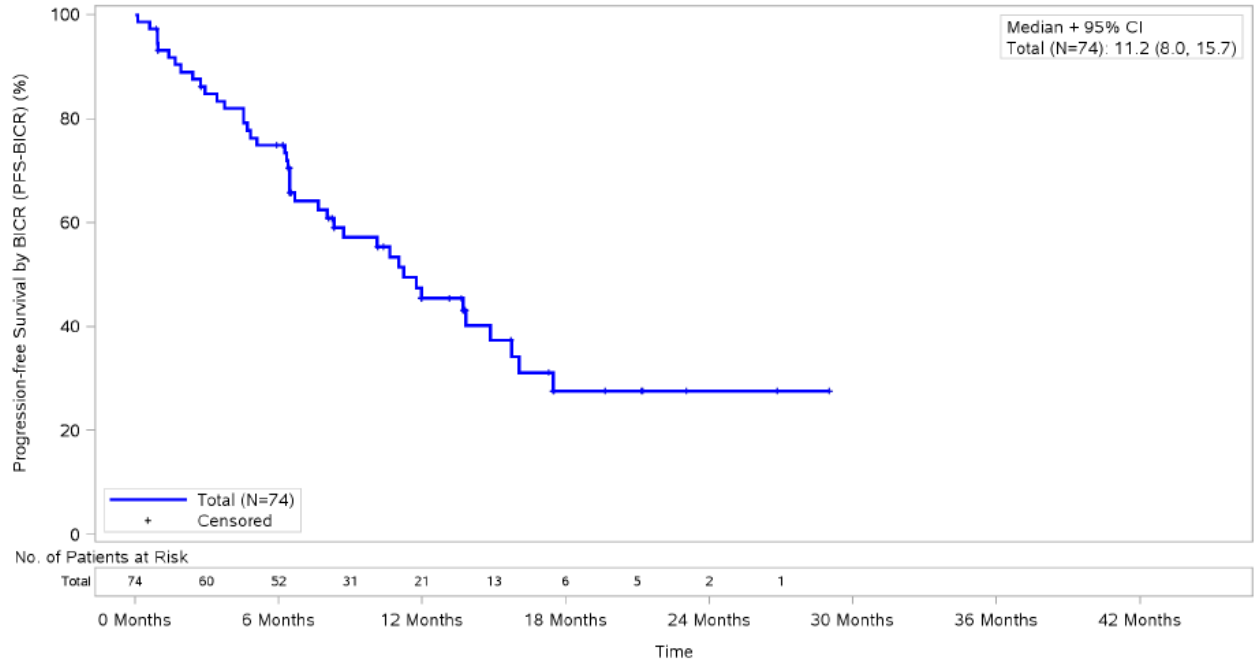


Figure 2: Kaplan-Meier plot of progressionfree survival. Source: Roche submission.

At the time of the submitted data cut-off, 24 of the 74 included patients had died. The Kaplan-Meier estimate for the median overall survial (OS) was 23.9 months (95% CI: 16.0 – NE), and the Kaplan-Meier curve is shown below:

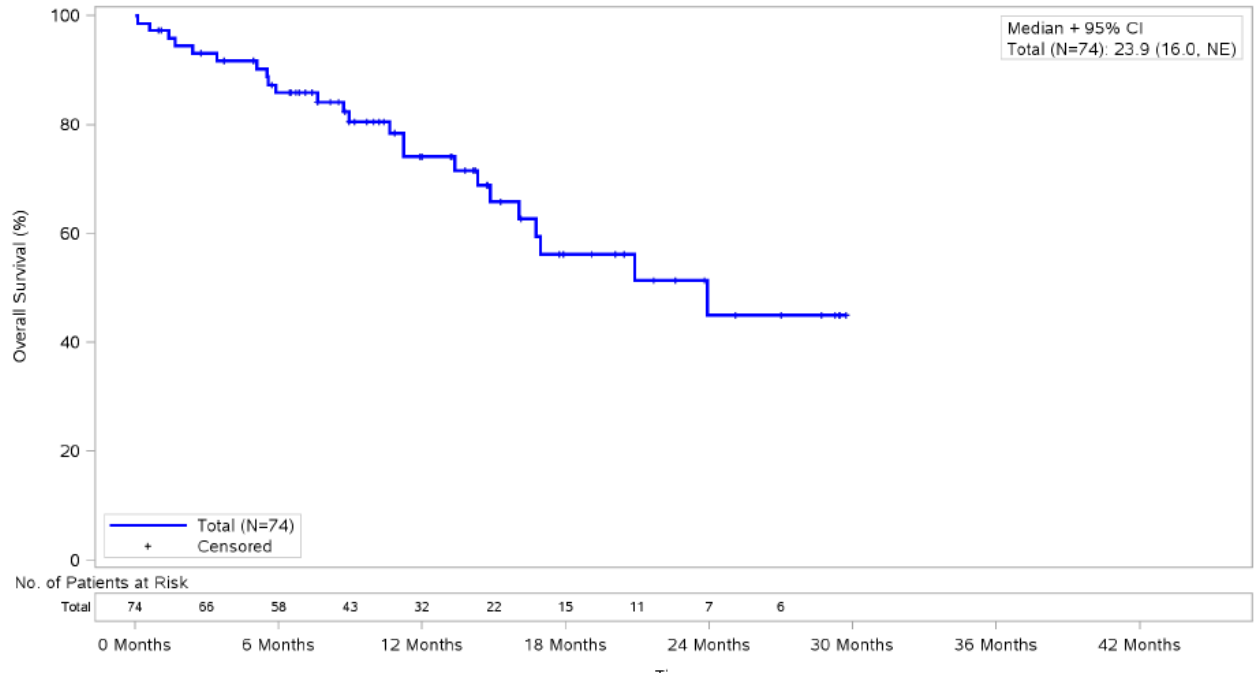


Figure 3: Kaplan-Meier plot for overall survival, Source: Roche submission.

NoMA's assessment

Entrectinib has shown promising efficacy with regards to duration of response and reducing tumour size across different tumours carrying NTRK-fusions. Clinical efficacy has been demonstrated across tumour types. There is weak indication in the data, as well as in the data for larotrectinib (another NTRK-inhibitor), that the efficacy is somewhat better in tumour types where NTRK-fusions are common, like MASC and secretory breast cancer(13). The present data indicate clinical efficacy across tumour types and assessment across tumour types, as opposed to single histologies, are considered appropriate, given the rarity of the tumour and the small sample size provided.

The provided data give no information on the effectiveness of entrectinib compared to best supportive care, in particular in regard to improvement in survival and health-related quality of life. NoMA acknowledges that entrectinib is a promising option for patients with no other treatment options, regardless of tumour origin, and that it is likely to provide a cinically meaningful benefit for these patients.

However, NoMA does not consider the submitted efficacy data to be sufficient to establish relative effectiveness.

3.4.2 Safety

Submitted clinical documentation

The most common adverse reactions (≥20%) in the clinical trials were fatigue, constipation, dysgeusia, oedema, dizziness, diarrhoea, nausea, dysaesthesia, dyspnoea, anaemia, increased weight, increased blood creatinine, pain, cognitive disorders, vomiting, cough, and pyrexia. The most frequent serious adverse reactions (≥2%) were lung infection (5.2%), dyspnoea (4.6%), cognitive impairment (3.8%), and pleural effusion (2.4%). Permanent discontinuation due to an adverse reactions occurred in 4.4% of patients (7).

The severe adverse events reported in the clinical trial, are summarized in Table 8.

Table 8: Grade 3-4 adverse events in the total safety database, both for NTRK-patients (n=113), and in the total population (n=504). Source: Roche submisson.

	NTRK SE	Total SE*
Total number of pts with >=1 event	74 (65.5%)	303 (60.1%)
AE n (%)		
Anemia	16 (14.2%)	49 (9.7%)
Weight Increased	10 (8.8%)	37 (7.3%)
Dyspnea	5 (4.4%)	27 (5.4%)
Fatigue	11 (9.7%)	24 (4.8%)
Pneumonia	6 (5.3%)	19 (3.8%)
AST Increased	4 (3.5%)	18 (3.6%)
ALT Increased	4 (3.5%)	17 (3.4%)
Syncope	6 (5.3%)	15 (3.0%)
Pulmonary Embolism	4 (3.5%)	14 (2.8%)
Pleural Effusion	3 (2.7%)	14 (2.8%)
Neutrophil Count Decreased	0	14 (2.8%)
Urinary Tract Infection	4 (3.5%)	13 (2.6%)
Hypoxia	5 (4.4%)	12 (2.4%)
Hypophosphatemia	3 (2.7%)	11 (2.2%)
Neutropenia	2 (1.8%)	8 (1.6%)

*In-cludes pediatric and NSCLC ROS1 patients. For ROS1 specific data, refer to relevant Rozlytrek AED for NSCLC ROS1 patients.

NoMA's assessment

In general, entrectinib appears to be reasonably well-tolerated and NoMA considers its safety profile in line with what is observed for other tyrosine kinase inhibitors. The safety database, while still limited, is more extensive than the efficacy database, as patients on other dosing regimens and with other mutations are included, as well as data from children ≥12 years of age.

3.4.3 Health-related quality of life

Submitted HRQoL data for the intervention arm

Non-preference based cancer-specific HRQoL instrument: EORTC Core Quality of Life Questionnaire (QLQ-30, QLQ-LC13 & QLQ-CR29).

HRQoL for the treatment with entrectinib in the intervention arm is documented by data from STARTRK-2. STARTRK-2 included the condition-specifc EORTC Core Quality of Life Questionnaire (QLQ-30), as well as the lung cancer and the colorectal cancer-specific modules (QLQ-LC13 & QLQ-CR29). The analysis of these patient-reported outcome measures is based on the data cut in May 2018 and does not include all patients that were part of the integrated analysis which is based on the latest data cut-off in October 2018.

In the condition-specific QLQ-C30 which assesses cancer patients' general health state, study participants reported moderate-to-high function scores at baseline. On a scale between 0 and 100, 100 being equivalent to full functioning, the patients had an average score of 69.79 for their general health state, 74.71 for physical functioning, 67.10 for role functioning and 84.72 for cognitive functioning.

While receiving treatment with entrectinib patients reported levels comparable with baseline values for general health state, physical functioning and role functioning, with a decreasing trend for cognitive functioning. In the QLQ-C30 some patients reported experiencing treatment-related symptoms such as insomnia (15.7%), lack of appetite (7.8%), diarrhoea (9.8%), nausea (3.9%), and vomiting (3.9%) "quite a bit" or "very much" at some time points while receiving treatment. The majority of patients reported that they did "not at all" experience treatment-related symptoms in the past week.

Generic preference-based HRQoL instrument: EQ-5D-3L

A generic preference-based HRQoL instrument, like the EQ-5D-3L, is needed to generate health state values that can be used to estimat quality-adjusted lifeyears (QALYs). EQ-5D-3L was applied in STARTRK-2 at baseline, the first day of each treatment cycle, and at the end of treatment. The UK tariff has been used to estimate utilities. See appendix 2 for number of observations and estimated utilities by tumour type based on STARTRK-2.

Submitted HRQoL data for the comparator arm

STARTRK-2 is a single arm, open label study which does not provide data on HRQoL for the comparator arm. Roche presented three approaches to generate information on HRQoL for the comparator arm.

First, a literature search was conducted to identify utility values for patients with NTRK-fusion positive solid tumours. This search did not result in any relevant articles.

Second, HRQoL data for the comparator arm have been derived from previous NICE-technology appraisals in which the assessed intervention received reimbursement. Roche used a similar approach to derive effectiveness data for the comparator(see 3.3).

Roche applied the following criteria to identify utility values for each tumour type:

- Data collected from patients with relevant tumour type
- Metastatic/advanced stage disease
- Included utility values for the health states progression-free (PF) and post-progression (PD)
- Level of consistency with NICE reference case

Appendix 2 provides the results of applying these criteria to the HRQoL data for the comparator in NICE apparaisals in which the assessed intervention received reimbursement. Weighted by the proportion of patients with each tumour type in STARTRK-2, an average PF-utility value of 0.73 and an average PD-utility value of 0.59 was estimated by Roche.

Third, a targeted search was performed taking into account tumour type and progression assumptions, irrespective of genomic profile and line or type of treatment. The utility values resulting from the search can be found in appendix 2.

Health utility values used in Roche's base case

Table 9 provides an overview of the utility values that Roche used in its base case.

Table 9: Overview of utility values used in Roche's base case. Source: Roche submisson.

State	Utility value: mean (standard error)	95% confidence interval	Justification
Progression-free survival			
Rozlytrek	0.8083	(0.75, 0.87)	Utility derived from clinical trial
Established management weighted average	0.73	Applied at individual tumor level	Weighted average of tumor-specific utilities
Progressed disease			
Rozlytrek	0.59	Applied at individual tumor level	Assumption of equivalent PPS utility to comparator
Established management	0.59	Applied at individual tumor level	Weighted average of tumor-specific utilities

The PF utility value for entrectinib is taken from STARTRK-2 while the utilty value for PD is set equal the PD value for the comparator arm. PD values from STARKTRK-2 could not been used as they were unrealiable due to small sample size.
Roche used the utility values based on NICE appraisals in which the assessed intervention received reimbursement, to populate the comparator arm in the health economic model. This led to the PF utility value in the comparator arm being lower (0.73) than in the intervention arm (0.808). Roche explains this by entrectinib's relatively tolerable safety profile when compared with traditional cytotoxic chemotherapies used in the comparator arm.

NoMA's assessment

NoMA acknowledges that it is challenging to provide high-quality HRQoL data for the different histologies included in this STA.

NoMA evaluates positively that Roche has assessed HRQoL in STARKTRK-2 using a generic preference-based instrument like the EQ-5D-3L. This type of instruments provide health utilities that can be directly used in a health economic model. The choice of instrument and the tariff used to estimate utilities is in line with NoMA's guidelines.

HRQoL data from non-preference based cancer-specific EORTC Core Quality of Life Questionnaire support that patients that receive entrectinib on average report better HRQoL as compared to patients receiving chemotherapy. Further, patients' HRQoL scores measured at baseline and while receiving treatment are comparable. HRQoL data support that entrecinib is on average well-tolerated.

NoMA concludes that the preference-based HRQoL data provided by Roche have two major weaknesses:

1) The majority of the HRQoL data presented for the intervention arm are based on very few number of observations for each histology, especially for measurements at baseline and for progressed disease (PD) (see appendix 2). The small sample size at PD adds uncertainty to conclusions about the health utility patients gain on average when receiving treatment with entrectinib. HRQoL data are subjective, patient-reported data that vary naturally both between and within patients depending on how patients perceive their HRQoL in different points in time. More than half of the utility values collected in the histology-subgroups are based on less than 10 observations. The uncertainty in these utility values does not resolve when aggregated to averaged numbers. NoMA concludes that these data are not sufficient to draw reliable and valid conclusions on how patients that received entrectinib perceived their HRQoL.

2) No HRQoL data for the comparator arm were collected in STARTRK-2 as this trial is single-armed.

Both, the utility values for patients in the intervention and the comparator arm are considered to be highly uncertain. However, NoMa considers the size of a health utility loss or gain for patients in the comparator arm as even more uncertain than in the intervention arm. While the utility values for the intervention arm are weakly substantiated, but at least derived from STARKTRK-2, the utilty values for the comparators are derived from various external sources. This approach introduces considerable uncertainty concerning the utility values for the comparator arm. As discussed in 3.3, NoMA questions Roches assumption that the generated comparator arm provides a representative picture of how patients with an NTRK-fusion without access to targeted therapy would fare.

NoMA does not approve the submitted documentation on HRQoL.

3.5 NoMA's overall assessment of the submitted documentation on relative effectiveness and cost-effectiveness of entrectinib and discussion on how to proceed

Novel concept

Entrectinib represents a novel concept for approval and evaluation of pharmaceutical products, where the product is approved for solid tumours regardless of their origin as long as the tumour carries a given genetic alteration, in this case NTRK-fusions (so called histology independent or tumour agnostic indications)[2]. Ideally, one should evaluate every mutation/histology combination to establish relative

[2] At present, the only other products approved in this way is larotrectinib in EU and the US for the same indication as entrectinib, and pembrolizumab in the US for MSI-H/dMMR in solid tumours.

efficacy for each histology. Commonly, medicinal products targeting several different mutations in specified tumours are being approved each year.

NTRK-fusions are rare. Two of the most common patient groups in the submitted analysis were non-small cell lung cancer, a very common cancer where NTRK-fusions are rare, and mammary-analogue salvary cancer, where NTRK-fusions are diagnostic for the disease, but the cancer is very rare.

Roche has submitted an analysis based on 74 patients with different tumours carrying the NTRK-fusion. In the submitted analysis 47 of 74 patients (63,5%) experienced tumour shrinkage of at least 30% in tumour diameter. Half of these patients benefited from their treatment for more than a year, and 70% of patients had responses lasting longer than 6 months. Entrectinib appears to be reasonably well tolerated, compared to many other cancer treatments, and is clearly less toxic than chemotherapy, in the cases where that is part of the best supportive care. Based on this, entrectinib was approved by EMA for patients with NTRK-fusion who do not have satisfactory treatment options. It is a valuable treatment option for patients who otherwise would have few other treatment alternatives. However, EMA was uncertain of the effect size of entrectinib and hence approved entrectinib for patients who have exhausted other satisfactory treatment options. Neither EMA nor NoMA consider Roche's documentation on entrectinib sufficient to establish its effectiveness relative to other treatments. (7).

<u>Evidence gaps</u>

For establishing relative effictiveness and evaluating the cost-effectiveness of entrectinib in an HTA, NoMA consideres three evidence gaps as essential remaining challenges:

1. *Unknown prognostic value of NTRK-fusion:* The effectiveness of standard of care in patients harbouring the NTRK-fusion has not been established.
2. *Unknown size of treatment effect:* The efficacy estimates are highly uncertain, given the highly heterogenous and rather small patient population.
3. *Unknown generalizability:* There is great uncertainty regarding the generalizability of the patient population to Norwegian clinical practice.

These issues undermine the validity of the parameters needed as input in a health economic model that is central in every STA.

Unknown prognostic value of NTRK-fusion

> Roche's approach of demonstrating relative effictiveness relies on the strong assumption that histology is not important for the prognosis of the patients receiving standard of care. This assumption has not been thoroughly substiantiated by Roche *e.g.* by a systematic literature review. Upon request, Roche has provided some literature references on the prognostic value of NTRK-fusions. The literature provides a mixed picture, indicating that for some histologies, the prognosis is worse, but that some also show more favourable prognosis. Some articles mention that tumours with NTRK-fusions show distinct histology, which indicates that pooling them with all other tumours of the same origin might not be appropiate (25-28). NoMA considers the information provided by Roche as not sufficient to conclude on the prognostic value of NTRK-fusions, and hence the effectiveness of the current standard of care.

When the prognostic value of NTRK-fusions is unknown, establishment of relative effictiveness in a credible way is not possible. EMA issued a conditional approval, and required Roche to submit updated efficacy data, which will include more patients, from the entrectinib development program to confirm the efficacy across different tumour types.

In order to learn more about the prognostic value of NTRK-fusions, it is essential to identify patients carrying the NTRK-fusion in the relevant patient population. This will be demanding. The prevalence of NTRK-fusions is estimated to be about 0.3% of solid tumoturs (29). This would imply that in order to identify one patient with NTRK-fusion, about 300 patients would have to be tested. The recommended test method at present, gene panel sequencing, trigger a refund of 7127,96 NOK, and this only covers the smaller gene panels (30). The costs of identifying one patient could therefore be prohibitive, at least for common histologies as lung cancer where NTRK-fusions are rare. The validity of the tests currently available and in use is being assessed by the Norwegian Institue of Public Health.

For ethical reasons, a randomized clinical trial can be difficult to perform, but *one* RCT would be enough to establish relative effectiveness and anchor a decision. No reliable natural history study is available for NTRK-fusion positive cancers despite that several treatments targeting NTRK-fusions are being developed. A natural historical study might make an indirect comparison feasible, and could be feasible for estimation of relative effectiveness for use in a health economic analysis. The possiblity of generating data on efficacy of the current standard of care in NTRK-fusions from registries and biobanks in different countries should be pursued. Upon request from NoMA, Roche has provided a description of how data on the effectiveness of the current standard of care in patients with NTRK-fusion can be gathered from the FLATIRON and WAYFIND-R registries. Roche assumes that a matched comparison between these registries and the STARTRK-2-trial will be available in 2023. Roche and NICE have agreed on a plan for data collection and an updated interim analysis will be performed in 2023, and the final analysis in 2026 (31). While the acceptability of the matched comparison would have to be assessed when it is submitted, this could potentially allieviate the challenges of a missing comparator arm.

Unknown size of treatment effect

Roche has not corrected for any other variables that might influence treatment in their indirect comparison, including prior treatment, age, performance status or other known prognostic and effect modifying factors. This is particularily challenging, as the patient population is diverse not only in tumour types, but also in previous treatment experience, age, and performance status. The risk of bias in the comparison provided to demonstrate relative efficacy increases. Naïve comparisons are rarely accepted for establishment of relative effictiveness because of inherent risk of bias, and they are not in line with the NoMA guidelines (32).

EMA is requesting data from more patients on entrectinib from the clincal trial, and these data will be helpful in reducing the uncertainty in the clinical efficacy estimates for entrectinib. Of course, data from other countries could also be helpful, and it is noted that in UK, entrectinib is funded through the Cancer Drug Fund, where data generation is required which will be used in a

reassessment (33). Roche is considering gererating data on treatment effect and patient characteristics from the Cancer Registry in Norway, which could generate some efficacy data, as well as patient characteristics in Norwegian clinical pracitce which also could be used in a re-assessment.

Unknown generalizability

The submitted analysis is small, with only 74 patients with 10 different tumour histologies. The integrated analysis included patients with different previous treatments, from none to heavily pre-treated patients.

The presented data are sampled from a very diverse population with a limited sample size. Interpretation of time to event end points like PFS and OS is challenging, given that these are highly dependent on the underlying tumour growth and the general health condition of the patients. This makes the efficacy results and the health-related quality of life data from the trial uncertain. According to the indication approved by EMA, a substantial proportion of the study patients (approximately 30%) would not be within the approved indication.
The exact line of treatment of entrectinib in the clinical pathway is not possible to establish at present. It may also change over time. The efficacy of entrectinib demonstrated in the integrated analysis can therefore not be directly transferred to the patient population in Norwegian clinical practice.

Information on which patients would receive entrectinib in Norway and internationally is scarce. This means that the generalizability from the trial population is difficult to assess.

More information about the patient population in Norwegian clinical practice might be gained from analysing patients receiving entrectinib from the Cancer Registry Norway (CRN). Roche has submitted a proposed plan for collecting such data Data from CRN might be helpful in evaluating the effectiveness of entrectinib in clinical practice, and is included in the proposed analysis plan.

<u>Conclusion</u>

NoMA concludes that it is not possible to establish relative effectiveness and to evaluate the cost-effectiveness of entrectinib based on available clinical data and the documentation submitted by Roche.

NoMA cannot approve the input parameters used in the health economic model. The model submitted by Roche is a partitioned survival model that could be appropriate to evaluate the cost-effectiveness of entrectinib, had the input data been of sufficient quality for the model to yield a credible result. NoMA has not assessed the submitted health economic model and has not calculated an ICER. NoMA presents drug acquisition costs and roughly estimated budgetary impact based on an anticipated number of patients in Norwegian clinical practice in chapter 4.

Roche has provided an outline of a plan for how relative effectiveness and cost-effectiveness can be established after the launch of entrectinib. The proposal is based on an agreement with NICE, with the addition of some data from the Norwegian Cancer registry. Roche plans to use data from the extended clinical trial, Norwegian, and international registries to improve the data on generalizablity and clincal

efficacy. Data on the efficacy of standard of care in patients with NTRK-fusion positive solid tumours will be provided from two international registries (FLATIRON and WAYFIND). Even though assessement will have to be done after submission, the suggested package and approach could be sufficient for an evaluation of relative effectiveness and cost-effectiveness and could be suitable for a reevaluation.

4 BUDGET IMPACT ANALYSES

The budget impact for year 1-5 after introduction is based on the assumption that the intervention will be recommended for use in clinical practice by the four regional health authorities and possibly implemented in the guidelines of the Directorate of Health. Two scenarios are considered:

A) The technology is recommended for use in clinical practice by the regional health authorities for the eligible patient population as described in this STA
B) The technology is not recommended for use in clinical practice.

The budget impact is the difference between the budget impact in the two scenarios.

The budget impact analyses for Rozlytrek (entrectinib) can only result in a very rough estimate due to lacking information on central parameters. NoMA considers the unknown number of patients with NTRK-fusions that will be identified in Norwegian clinical practice in the first 5 years after introduction as main issue which makes it necessary to simplify the budget impact analyses for Rozlytrek (entrectinib).

4.1 ESTIMATION OF THE NUMBER OF PATIENTS POTENTIALLY ELIGIBLE FOR TREATMENT

NoMA considers the number of patients expected to be treated with Rozlytrek (entrectinib) as highly uncertain. While NoMA assumed throughout this report that all patients with NTRK-fusion can be identified, the budget impact analyses are based on the expected number of patients that actually can be identified in current clinical practice in Norway. The number of treated patients depends on the ability to identify patients with NTRK-fusions. It is unknown how fast next generation sequencing will be implemented and routinely used in Norwegian hospitals. Due to this uncertainty budget impact analyses for Rozlytrek (entrectinib) need to be considered to be a rough estimate associated with considerable uncertainty.

To reflect this uncertainty, NoMA, in line with Roche's submission, present the budget impact as a range. Table 10 presents lower and upper range for patients that could receive Rozlytrek (entrectinib) if the treatment is recommended, while Table 11 shows a scenario in which Rozlytrek (entrectinib) is not recommended. The presented patient numbers are based on the documentation submitted by Roche who presented 50 patients as an upper range under the condition that all eligible patients are tested, and all patients with NTRK-fusions are treated.

Table 10: Number of patients expected to be treated with Rozlytrek (entrectinib) in the next 5 years – scenario where treatment is recommended. Source: Roche submission.

	Year 1	Year 2	Year 3	Year 4	Year 5
Total NTRK positive cancer patients expected to be treated with Rozlytrek (lower range)	5	5	5	5	5
Total NTRK positive cancer patients expected to be treated with Rozlytrek (upper range)	10	20	30	40	50
Total NTRK positive cancer patients expected to be treated with BSC (lower and upper range)	0	0	0	0	0

Table 11: Number of patients expected to be treated with Rozlytrek (entrectinib) in the next 5 years – scenario where treatment is not recommended. Source: Roche submission.

	Year 1	Year 2	Year 3	Year 4	Year 5
Total NTRK positive cancer patients expected to be treated with Rozlytrek	0	0	0	0	0
Total NTRK positive cancer patients expected to be treated with BSC (lower and upper range)	5-10	5-20	5-30	5-40	5-50

It is expected that all eligible patients receive Rozlytrek (entrectinib) in case of reimbursement which is equivalent to a 100% market share.

4.2 COST ESTIMATES

The main cost estimate in NoMA's simplified budget impact analyses is drug acquisition costs for Rozlytrek (entrectinib).

Costs related to testing for NTRK-fusion are of relevance. However, they have not been included in this budget impact analyses due to the fact that The Norwegian Institute of Public Health is in charge of providing information on testing.

NoMA simplified the drug costs for different chemotherapies used in the comparator arm as part of best supportive care. It is not feasible to include the costs of all chemotherapies use as best supportive care for the different tumour histologies. It is not obvious which chemotherapy and its associated costs should be used as a cost proxy for best supportive care in the simplified budget impact analyses. NoMA chose to adapt Roche's approach to costs in the comparator arm: NoMA and Roche use pemetrexed in combination with carboplatin or cisplatin as a proxy for all the different chemotherapy regimens given in the comparator arm. NoMA considers this pragmatic approach to be viable, as the costs of chemotherapy are generally low, especially with price discounts, in comparison to the costs of Rozlytrek (entrectinib). Costs of chemotherapy are not expected to have a considerable impact on the budget impact analyses.

For this budget impact analysis NoMA considers all other costs beyond drug costs of Rozlytrek (entrectinib) and the drug costs related to chemotherapies as part of best supportive care to be negligible. Consequently, NoMA has not included wastage, compliance rate and dose adjustements in the simplified budget impact analysis.

Table 12 shows the drug acquisition costs for Rozlytrek (entretinib).

Table 12: Drug acquisition costs AUP including VAT

Drug	Concentration (ml or tablets)	Pack volume	Cost per pack (NOK)	Source
Rozlytrek	100 mg	30	11 555,90	Legemiddelsøk
Rozlytrek	200 mg	90	69 154,00	Legemiddelsøk
Pemetrexed	500 mg/vial		12 949,50	Legemiddelsøk
Carboplatin	450mg/vial		2 800,90	Legemiddelsøk
Cisplatin	100mg/vial		421,30	Legemiddelsøk

Treatment costs for Rozlytrek (entrectinib) in NOK per patient per year after treatment initiation are presented in Table 13.

NoMA used the following parameters to estimate the drug costs for Rozlytrek (entrectinib) per patient per year:

- Dose: 600mg per day
- Treatment duration: 365 days. NoMA uses 12 months as a proxy in these calculations. This is based on the median observed time on treatment in the integrated analysis (8.6 months, data cut-off in October 2018). Transforming the median to mean time on treatment results in about 12 months[3].
- Price 90-pack (200mg): 69 154 NOK

In this simplified budget impact analyses, NoMA used the following parameters as a rough approximation to chemotherapy drug costs used in the comparator arm:

- Dose:
  - pemetrexed: 500 mg/m^2 per 21 dag syklus
  - carboplatin: 450 mg/m^2 per 21 dag syklus
  - cisplatin: 100 mg/m^2 per 21 dag syklus
- Treatment duration: undiscounted PFS of 6 months as a proxy.

List prices, including VAT for carboplatin, cisplatin and pemetrexed as shown in table 13.

NoMA chose to use the same types of chemotherapy and proxy for treatment duration as Roche. NoMA expects that patients in the comparator arm will not receive chemotherapy until progression in Norwegian clinical practice due to high toxicity. It can therefore be expected that the chemotherapy costs assumed in this budget impact analyses are slightly larger than in clinical practice. Due to chemotherapy being associated with low costs, applying Roche's assumption that patients receive chemotherapy until progression won't have a significant impact on the budget impact analyses.

[3] In order to estimate the mean treatment duration, we have chosen to assume an exponential distrubution. For exponential distributions, the relationship between median and mean is the mean is 1.44 times greater than the median.

Table 13: Drug costs per patient per year after treatment initiation. List price, including VAT

Rozlytrek (entrectinib)	841 604 NOK
BSC (simplification based on pemetrexed and carboplatin/cisplatin)	240 988 NOK

4.3 BUDGET IMPACT

The budget impact analyses for Rozlytrek (entrectinib) can only result in a very rough estimate due to the unknown number of identified patients. Consequently, NoMA chose to simplify the following parameters used in the budget impact analyses:

- Costs of BSC: NoMA uses a cost proxy based on pemetrexed and carboplatin
- Time on treatment: NoMA uses 12 months as a proxy for time on treatment.
- Compliance rate: NoMA assumed 100% compliance rate for Rozlytrek (entrectinib).
- Wastage and dose adjustments: NoMA has not included wastage and dose adjustments in this simplified budget impact analysis.

The estimated budget impact in NOK as a result of drug costs for lower and upper ranges of eligible patients is presented in Table 14.

Table 14: Estimated budget impact of drug costs for the eligible patient population for a lower and upper range. List price, including VAT and undiscounted.

(I NOK)	Year 1 (5-10 patients)	Year 2 (5-20 patients)	Year 3 (5-30 patients)	Year 4 (5-40 patients)	Year 5 (5-50 patients)
Entrectinib recommended for use	4,2 mil-8,4 mil	4,2 mil - 16,8 mil	4,2 mil – 25,2 mil	4,2 mil-33,6 mil	4,2 mil-42 mil
Entrectinib not recommended for use (simplified)	1,2 mil-2,4 mil	1,2 mil-4,8 mil	1,2 mil-7,2 mil	1,2 mil-9,6 mil	1,2 mil-12 mil
Budget impact of recommendation	3 mil – 6 mil	3 mil – 12 mil	3 mil – 18 mil	3 mil – 24 mil	3 mil – 30 mil

To illustrate the uncertainty in the budget impact analyses NoMA presents budget impact in the fifth year after introduction for 5, 20 and 50 patients. The presented budget impact is highly uncertain due to the aspects listed above in addition to the unknown numbers of patients with NTRK-fusions that can be identified in Norwegian clinical practice.

In the fifth year after introduction, a rough estimate of the budget impact of a positive recommendation for Rozlytrek (entrectinib) for eligible patient populations of different size are estimated to be around:

- 30 million NOK including VAT for 50 patients
- 12 million NOK including VAT for 20 patients
- 3 million NOK including VAT for 5 patients.

With LIS-prices for the comparators, the budget impact in the fifth year after introduction is estimated to be around:

- [redacted] NOK including VAT for 50 patients
- [redacted] NOK including VAT for 20 patients
- [redacted] NOK including VAT for 5 patients.

5 SUMMARY AND CONCLUSION

Health service interventions are evaluated against three priority-setting criteria – the benefit criterion, the resource criterion and the severity criterion. The priority-setting criteria are assessed and weighed against one another. The more severe the condition or the more extensive the benefit of the intervention, the more acceptable higher resource use will be. Quality and uncertainty associated with the documentation and the budget impact are included in the overall assessment of interventions.

Histology independent indications are a novel concept. While novel consepts might require novel approaches, the submitted documentation would likely not be sufficient even if all patients had the same histology.

The submitted documentation shows the different requirements of the regulatory process and the HTA-process. The submitted documentation was deemed sufficient to indicate a postive benefit/risk by EMA, even though it was not considered comprehensive, and further documentation will need to be submitted to EMA at a later stage. NoMA concludes that the submitted documentation does not allow to establish a credible estimate of relative effectiveness of entrectinib compared to best supportive care. As a consequence, cost-effectiveness of entrectinib could not be assessed in a health economic model and no ICER could be calculated.

NoMA's assessment of the benefit criterion:

Entrectinib is a promising treatment for patients with solid tumours harbouring NTRK-fusion who are without other satisfactory treatment options. The available efficacy data indicate that patients whose solid tumours are harbouring NTRK-fusions are likely to benefit from the treatment.

Entrectinib is also reasonably well-tolerated, in comparison to other cancer treatments, in particular chemotherapy. This benefit is supported by stable HRQoL scores for the time periode before treatment and while patients received treatment.

NoMA concludes that the submitted documentation is not adequate to establish a reasonably credible estimate for the benefit of entrectinib over best supportive care. The documentation submitted on the relative effectiveness of entrectinib does not allow NoMA to evaluate the benefit criterion, due to following major restrains:

- No direct treatment comparison is available, and the submitted indirect treatment comparison does not correct for prognositic or effect modifying factors other than tumour histology.
- In particular, the submitted comparison does not account for the prognostic and predictive value of NTRK-fusions in these patients.
- A significant proportion of the patients included in the clinical trial would not be eligible for treatment with entrectinib according to the approved indication, as they had not exhausted all available treatment options.

- There is a large diversity in the patient population studied, both with regard to histology, previous treatment and other patient characteristics.
- The generalizability to patients in the Norwegian clinical pratice is questionable, and it is difficult establish which patients will be treated in Norway. This can also change over time, as more patients will be tested for NTRK-fusions.
- Health-related quality of life data from the clinical trial are only available for the intervention arm. These data are are based on very few patients per histology and do not allow robust conclusions about how entrectinib improves patients' health-related quality of life compared to comparator treatment.

Roche has provided the outline of a plan for how relative effectiveness and cost-effectiveness can be established after the launch of entrectinib using updated trial data, and data from regristries. Even though assessement will have to be done after submission, the suggested package and approach could be sufficient for a re-evaluation of the data once available.

NoMA's assessment of the resource criterion:

The documentation submitted on the relative effectiveness and cost-effectivness of entrectinib submitted by Roche does not allow NoMA to evaluate the resource criterion.

The cost-effectiveness of entrectinib could not be assessed with the submitted health economic model. While the model type chosen by Roche might have been appropriate, NoMA cannot approve the input used in the model as sufficient to establish relative effectiveness. Consequently, NoMA could not estimate an ICER to quantify cost-effectivness of introducing entrectinib.

NoMA's assessment of the severity criterion:

Metastatic solid tumours without satifactory treatment options are clearly severe conditions, regardless of the mutational status of the tumour.

NoMA lacks a credible estimate remaining QALYs for patients with NTRK-positive fusions that receive currently available treatment (BSC), and could not quantify severity in terms of absolute shortfall. Describing severity based on average age of the patient population in the clinical trials and the corresponding expected remaining QALYs in the general Norwegian population, NoMA assumes that patients with NTRK-positive fusions loose on averagde around 20 QALYs. This description of severity is based on assumptions and it should be interpreted with caution.

NoMA's assessment of budget impact:

There is high uncertainty about how many patients will be tested for NTRK-fusions, and which criteria will be used for testing in Norwegian clinical practice. The testing of tumours for NTRK-fusions is being assessed by The Norwegian Institue of Public Health in a separate report.

Uncertainty about the number of patients clearly influences the budget impact analyses. The prevalence and the testing strategy will impact the number of cases found, and hence the number of patients

treated. We therefore present a simplified budget impact with a wide range, which could be somewhere between 3 million NOK for 5 patients and for 30 million NOK for 50 patients per year in a stable market. Budget impact with LIS-prices is between [redacted] NOK for 5 patients and [redacted] NOK for 50 patients per year.

Norwegian Medicines Agency, 12-02-2021

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APPENDIX 1: DISCUSSION ON COMPARATORS

According to the approved indication, entrectinib should be used in patients with no other satisfactory treatment options. The excact placement in the treatment algorithm for entrectinib will vary the histology of the tumour, and there is no clear guidelines available. Based on the available guidelines, and some feedback from clincal experts, we attempt to discuss the placement of entrectinib in different histologies.

Breast cancer

According to the Norwegian guidelines, patients with triple negative breast cancer who are BRCA-negative are treated with chemotherapy. Based on the guidelines, patients seems likely to benefit from at least two lines of chemotherapy, and there are several available treatment options, including regimens containing antracyclins and taxans. Given the multitude of available chemotherapy regimens available for breast cancer, the exact placement of chemotherapy is depending on patient preference. Roche placed entrectinib in the 3rd and later treatment lines which NoMA considers as appropriate. However, NoMA consideres the provided comparator data in breast cancer as little representative for the breast cancer patient population in Norwegian clinical practice as 4 of the 6 patients with breast cancer had secretory breast cancer, which has a different prognosis from non-secretory breast cancer.

Non-small lung cancer

According to feedback from Norwegian clinicians, patients with non-small cell lung cancer will clearly benefit from treatment with platinumbased chemotherapy, either sequentially or in combination. The benefit of docetaxel is rather limited, and the clinicians assume that entrectinib will be used before docetaxel in eligible patients. Nintinib is not used in Norwegian clinical practice.

Colorectal cancer

Norwegian guidelines on colorectal cancer recommend two lines of chemotherapy, while the benefit of a third line and beyond is considered to be limited. Consequently, it seems reasonable that patients with colorectal cancer who have received two lines of chemotherapy would be considered candidates for treatment with entrectinib.

Neuroendocrine tumours (NET)

According to the Norwegian guidelines, everolimus is recommended as first or second line treatment for gastroenteropancreatic NET, and sunitinib might be used in the same line in patients who have a tumour with origin in the pancreas. Patients with NET would probably have received one or two lines of treatment before receiving entrectinib. The proposed comparator for entrectinib is best supportive care in patients with no previous treatment. While best supportive care is in general appropriate, it is considered problematic that the patients were less heavily pretreated than the patients should be according to the apporoved indication.

Pancreatic cancer

Roche is proposing gemcitabine with or without paclitaxel, or FOLFORI, in previously untreated patients as comparator for patients with pancreatic cancer. The Norwegian guidelines mention either of these therapies as first-line treatment, and consider them well documented alternatives. It seems appropriate to position entrectinib after first line chemotherapy in these patients.

Thyroid cancer
Roche has used best supportive care in second line after radioactive iodine as the comparator for patients with thyroid cancer. According to Norwegian guidelines, lenvatinib is considered first line treatment and sorafenib is second line treatment in patients refractive to radioactive iodine. Thus, patients have at least two satisfactory treatment lines, that should be used before entrectinib.

Soft tissue sarcoma
Roche is proposing doxorubicin or trabectedin as comparator. Both of these treatments are recommended by ESMO, with a anthracyclins including doxorubicin recommended in the first line, and trabectedin considered a position in the second line and beyond (34). Soft tissue sarcomas are heterogenous, and the exact treatment given will depend on the specific subgroup. However it seems that patients have at least two satisfactory treatment lines, that should be used before entrectinib.

MASC
Given the high prevalence of NTRK-fusions it seems likely that entrectinib will be used as first-line treatment for these patients. It is noted that despite the clear histological definition of MASC, Roche has submitted a control arm containing different forms of salivary gland histologies.

Others
Patients with other histologies (5 different histologies) are included in the submitted comparator data. For those patients, the same comparator effect as the average of the other patients included in the comparator arm, have been assumed. This approach excludes these patients from the analysis. As these patients are still included in the intervention arm, NoMA is concerned about the imbalance regarding histology this generates in the arms.

APPENDIX 2: HEALTH-RELATED QUALITY OF LIFE

In this appendix NoMA presentes the health ulitity values submitted by Roche in a more detailed way.

The following table shows EQ-5D health utility values for the intervention arm as collected in STARTRK-2.

The resulting utility value for PF averaged across all histologies (0.823) is lower than the utility value for PD averaged across all histologies.

EQ-5D-3L utility values from STARTRK-2

Tumor type	State	Number of Observa-tions	Mean	Mini-mum	Maximum	Median
ALL	Baseline	48	0.702	-0.003	1.000	0.796
ALL	PFS	409	0.823	-0.086	1.000	0.848
ALL	PPS	44	0.839	0.587	1.000	0.796
BREAST	Baseline	6	0.820	0.293	1.000	0.907
BREAST	PFS	48	0.956	0.710	1.000	1.000
BREAST	PPS	4	0.924	0.812	1.000	0.942
CRC	Baseline	3	0.464	0.082	0.689	0.620
CRC	PFS	5	0.469	-0.086	0.639	0.639
CRC	PPS	4	0.949	0.796	1.000	1.000
MASC	Baseline	4	0.797	0.189	1.000	1.000
MASC	PFS	58	0.837	0.189	1.000	1.000
MASC	PPS	2	0.778	0.760	0.796	0.778
NEURO-ENDO-CRINE	Baseline	3	0.772	0.708	0.848	0.760

NEURO-ENDO-CRINE	PFS	11	0.791	0.620	1.000	0.743
NEURO-ENDO-CRINE	PPS	11	0.832	0.691	1.000	0.796
NSCLC	Baseline	9	0.763	0.088	1.000	0.796
NSCLC	PFS	69	0.918	0.228	1.000	1.000
NSCLC	PPS	2	0.805	0.796	0.814	0.805
OTHER	Baseline	3	0.633	0.208	1.000	0.691
OTHER	PFS	47	0.806	0.150	1.000	0.796
OTHER	PPS	7	0.956	0.691	1.000	1.000
PANCRE-ATIC	Baseline	3	0.796	0.796	0.796	0.796
PANCRE-ATIC	PFS	32	0.756	0.159	1.000	0.796
PANCRE-ATIC	PPS	8	0.798	0.691	0.883	0.796
SARCOMA	Baseline	12	0.648	-0.003	0.850	0.708
SARCOMA	PFS	93	0.763	0.516	1.000	0.760
SARCOMA	PPS	6	0.674	0.587	0.691	0.691
THYROID	Baseline	5	0.589	0.024	1.000	0.743
THYROID	PFS	46	0.752	0.137	1.000	0.814
THYROID	PPS	0				

Roche argues that a higher average utility value in the post-progression stadium compared to progression-free stadium is implausible. This led to adjustments of the utility values for PF and PD:

- PF: Roche chose to use a nested random effects model that adjusted the utility values for PF for sex, tumour type, age and time and assumed that tumours were randomly sampled from a population of possible tumours and that patients were then sampled randomly from within this tumour pool. The model provided a utility value of 0.8119 (95% CI: 0.76, 0.86) for PF which Roche used in its base case.

- PD: Roche chose to set post-progression utility for entrectinib to be equal to the PD utility values estimated for the comparator arm in their health economic model.

The following tables show two alternative sets of health utility values that Roche submitted for the comparator arm. This table presents comparator health utility values based on NICE-technology appraisals in which the assessed intervention received reimbursement.

Selected utility sources for comparator tumour types

Tumour type	N	Utility estimate – PFS	Measure of uncertainty (SE)	Utility estimate – PD	Measure of uncertainty (SE)	Sourced from NICE Technology appraisal guidances
Colorectal cancer	4	0.73	0.14	0.64	0.14	TA405
MASC	7	0.725	0.14	0.60	0.14	Assumption: average of known
Thyroid cancer (papillary and anaplastic)	5	0.72	0.14	0.64	0.14	TA535
Non-small-cell lung cancer (squamous and non-squamous)	10	0.74	0.18	0.59	0.06	TA428
Pancreatic cancer	3	0.70	0.14	0.65	0.14	TA476
Sarcoma	13	0.72	0.14	0.56	0.14	TA465
Neuroendocrine tumours	3	0.767	0.14	0.725	0.14	TA539
Breast cancer (including secre-tory)	6	0.705	0.14	0.496	0.14	TA515
Other (average of known)	3	0.725	0.14	0.65	0.14	Assumption: average of known
Weighted average		**0.73**		**0.59**		Calculation

The presented utility values are averaged and weighted by the prevalence of each tumour type in STARTRK-2. In this estimation an average PF-utility value of 0.775 and an average PD-utility value of 0.652 was estimated by Roche.

This table presents comparator health utility values based on a review of the literature.

Alternative utility values applied in the model per tumour type as derived from the literature. Source: Roche submission.

Tumour Type	**Utility on PFS**	**Utility on PPS**	**Source**
CRC	0.835	0.82	(35)
MASC	0.830	0.62	(36)*
Papillary thyroid	0.870	0.52	(37)
Anaplastic thyroid	0.870	0.52	(37)
Squamous NSCLC	0.710	0.67	(38)
Non-squamous NSCLC	0.710	0.67	(38)
Pancreatic	0.810	0.73	(39)
Sarcoma	0.690	0.56	(40)
Neuroendocrine	0.776	0.73	(41)
Secretory Breast	0.812	0.77	(42)
Non-secretory Breast	0.812	0.77	(42)
Other	0.780	0.67	(43)**
Weighted average	**0.775**	**0.652**	**Calculation**

**as proxy (assumption) | **for PPS utility, the average of all other tumours PPS utility is employed.*

ATTACHMENT 1: COMMENTS FROM THE COMPANY

Vedlegg fra Roche: Rozlytrek for treatment of NTRK fusion positive tumors

Vi ønsker å takke Statens Legemiddelverk for gjennomforing av metodevurderingen, og for muligheten under prosessen til å gi innspill med flere gode diskusjoner.

Vi har forståelse for at det er utfordrende å metodevurdere denne typen behandlinger for sjeldne sykdommer, hvor datagrunnlaget er begrenset. Prognoser viser at det vil ta et sted mellom 17 og 105 år å gjennomføre studier med tilfredsstillende evidens- og styrkegrad i de ulike kreftformene undersøkt for Rozlytrek, noe som understreker at tradisjonelle data ikke lar seg generere raskt i så sjeldne kreftformer. Vi skulle imidlertid ønsket oss at rapporten i større grad fokuserte på fordelene ved en målrettet tumor-agnostisk behandling, de lovende resultatene fra den kliniske studien og hvilken verdi det kan gi for pasientene å motta en mer persontilpasset kreftbehandling.

Vi innser at det er begrenset kunnskap om NTRK sin prognostiske rolle, og dermed også hvordan behandling med Rozlytrek ville stilt seg sammenlignet med konvensjonell behandling for pasienter med NTRK fusjonsprotein. Samtidig mener vi det hadde vært en fordel om SLV i denne saken hadde vist eksplorative resultater på kostnad-nytte forholdet, enten gjennom egne analyser eller ved å vise det som har blitt presentert av Roche gjennom innsendelsen fra mai 2020. Selv om det er stor usikkerhet i flere av estimatene som brukes for kost-nytte vurderingen mener vi det ville vært mulig å presentere eksplorative analyser med resultater fra de mest troverdige utfallene. Vi ønsker også å bemerke at flere av usikkerhetsmomentene nevnt av SLV har blitt adressert gjennom innsendelsen av en fleksibel modellstruktur som enkelt tillater endringer rundt nettopp disse parameterne. Roche har også presentert gjennom innsendelsen flere scenarioanalyser som belyser disse mer usikre parameterne og hvordan de påvirker resultatene fra modellen.

Basert på overnevnte punkter har vi derfor valgt å ta opp noen av SLV sine punkter til diskusjon, presentere noen resultater, og mulige fremtidige løsninger som kan utforskes.

1. ***Ukjent prognostisk verdi av NTRK-fusjon:***

Usikkerhetene rundt NTRK-fusjoner som en prognostisk faktor kan ha stor innvirkning på de helseøkonomiske resultatene, som påpekt av SLV. Det finnes imidlertid svært lite informasjon om den "naturlige historikken" til NTRK+ -pasienter, og det er derfor også veldig lite data på den prognostiske verdien av NTRK-fusjoner. De fleste studier identifisert tyder imidlertid på at pasienter med NTRK fusjons-positive tumorer har en dårligere prognose sammenlignet med pasienter uten NTRK-fusjon (1,2,3). Dersom NTRK-fusjoner er en **negativ** prognostisk faktor kan det tyde på at effekten i kontrollarmen av modellen er konservativ, da denne er basert på populasjoner som **ikke** er NTRK-testet og derfor antatt NTRK-negativ.

I basecaset innsendt fra Roche er ikke prognostiske implikasjoner av en NTRK-fusjon inkludert. Som indikert i scenarioanalysene bør dette betraktes som en konservativ antagelse, tatt i betraktning at de fleste tilgjengelige publikasjoner har identifisert NTRK-fusjoner som en negativ prognostisk faktor.

Det bør også bemerkes at det er mulig å utforske hvordan NTRK-fusjon som en prognostisk faktor vil påvirke resultatene i kost-nytte modellen. Dette ble presentert til SLV i rapporten innsendt fra mai 2020. Resultatene fra vår seneste innsendte kostnad-nytte modell kan vise mulige scenarioer angående NTRK+ som en prognostisk faktor, noe som i så fall gir et ICER-spekter fra NOK 687,000 (dersom NTRK er en **negativ** prognostisk faktor - HR: 2.33 (1)) til NOK 1,300,000 (dersom NTRK er en **positiv** prognostisk faktor - antatt HR: 0.8) basert på dagens listepris.

Selv om vi ikke kan helt utelukke at NTRK-fusjon er en positiv prognostisk faktor, mener vi imidlertid at dette er er mindre sannsynlig basert på dagens kunnskap. Om man tar dette i betraktning viser Roche sin modell at forventet ICER vil være innenfor hva som normalt anses som kostnadseffektivt med dagens listepriser.

2. Ukjent effekt av Rozlytrek

Grunnet liten pasientpopulasjon og stor heterogenitet mellom de forskjellige pasientgruppene er det utfordrende å finne gode tall for estimering av langtidseffekten av Rozlytrek. Den 2. oktober 2020 delte vi med SLV en intra-pasientanalyse som gjør det mulig å sammenligne progresjonsfri overlevelse (PFS) og tid til ny behandling i pasientene behandlet med Rozlytrek sammenlignet med de samme pasientene men i tidligere behandlingslinjer (4). Denne viser at, til tross for at Rozlytrek har blitt gitt i senere linjer, så ser man en bedre effekt av å stå på Rozlytrek sent i forløpet, enn man gjorde på de tidligere behandlingslinjene for den enkelte pasient. Analysen viser også at pasientene i studiene ikke er høyt selekterte pasienter med stor sannsynlighet for god respons. Intra-pasientanalysen sier også noe om størrelsesforholdet av effekten, og viser at analyser fra innsendt modell ikke er urimelige. I tillegg til dette har omfattende scenarioanalyser blitt presentert for å ta høyde for alternative langtids-effektestimater.

3. Videre kunnskapsgenerering

Når vi fremover vil samle inn mer data om både NTRK-fusjonspasienter og pasienter som behandles med Rozlytrek, mener vi at det er plausibelt at vi over tid kan besvare en del av de utfordringene knyttet til usikkerhet som SLV har påpekt. Fremtidige analyser med real-world registerdata (Flatiron) kan trolig benyttes til en indirekte sammenligning og dermed til estimering av den vektede kontrollarmen i kost-nytte modellen. Dette kan bidra til å gi bedre estimater på den relative effekten av Rozlytrek. Denne typen data kan også bidra med å si noe om hvordan NTRK-pasientgruppen ser ut med tanke på alder og andre pasientkarakteristika, og muligens dermed også indirekte den prognostiske verdien til NTRK. I tillegg er det planlagt nye datakutt fra STARTRK-studiene, som dermed vil gi data fra flere pasienter og lengre oppfølgingningstid. Samlet sett burde dette bidra til en betydelig reduksjon i usikkerheten knyttet til kostnad-nytte beregningene.

Oppsummering:

I prosessen rundt implementeringen av persontilpasset kreftbehandling i Norge har flere aktører pekt på utfordringene med dagens system ift. innføring av behandling til stadig mindre pasientgrupper, der det finnes mindre data egnet for kostad-nytte beregninger. Disse innovative legemidlene vil som kjent kreve mer fleksible løsninger enn hva som tidligere har blitt akseptert i dagens system. Selv om vi mener det med vår modell er mulig å beregne en ICER har vi forståelse for utfordringene knyttet til dette og diskuterer derfor gjerne alternative løsninger for innføring, for å redusere usikkerhet og fordele risiko.

Kilder:

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2. Musholt TJ et al. Surgery 2000; Prognostic significance of RET and NTRK1 rearrangements in sporadic papillary thyroid carcinoma
3. Manju L et al., NTRK fusion oncogenes in pediatric papillary thyroid carcinoma in northeast United States
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