Medicinrådet

Baggrund for Medicinrådets anbefaling vedrørende encorafenib i kombination med cetuximab til behandling af patienter med metastatisk kolorektalkræft, der har $BRAF^{V600E}$-mutation

Anb

Version 1.0

Om Medicinrådet

Medicinrådet er et uafhængigt råd etableret af Danske Regioner.

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

Om baggrunden for Medicinrådets anbefaling

Baggrund for Medicinrådets anbefaling er en sammenfatning af lægemidlets værdi for patienterne, omkostninger for samfundet og en gengivelse af de vurderinger, der er grundlag for Medicinrådets anbefaling.

Anbefalingen er Medicinrådets vurdering af, om omkostningerne vedrørende brug af lægemidlet er rimelige, når man sammenligner dem med lægemidlets værdi for patienterne. I nogle tilfælde spiller sygdommens alvorlighed en særlig rolle i vurderingen.

Anbefalingen er et klinisk og økonomisk baseret råd til regionerne til brug for deres beslutning om at anvende et givet lægemiddel.

Læs eventuelt mere i Håndbog for Medicinrådets proces og metode vedr. nye lægemidler og indikationsudvidelser – version 2, som du kan finde på Medicinrådets hjemmeside under siden Metoder.

Dokumentoplysninger	
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1. Anbefaling vedrørende encorafenib i kombination med cetuximab til behandling af patienter med metastatisk kolorektalkræft, der har $BRAF^{V600E}$-mutation

Medicinrådet anbefaler encorafenib i kombination med cetuximab til behandling af patienter med metastatisk kolorektalkræft, der har $BRAF^{V600E}$-mutation, og som har modtaget mindst én tidligere behandling.

Medicinrådet anbefaler encorafenib i kombination med cetuximab, fordi behandlingen både giver patienterne længere levetid og færre bivirkninger end den behandling, de får i dag. Samtidig vurderer Medicinrådet at sundhedsvæsenets omkostninger til lægemidlet vil være rimelige i forhold til effekten af behandlingen.

2. Medicinrådets konklusion vedrørende lægemidlets værdi

Medicinrådet vurderer, at encorafenib i kombination med cetuximab til metastatisk kolorektalkræft med $BRAF^{V600E}$-mutation giver en **moderat merværdi** sammenlignet med FOLFIRI eller IRI, begge i kombination med cetuximab. Vurderingen er baseret på evidens af lav kvalitet, som betyder, at nye studier med moderat sandsynlighed vil ændre konklusionen.

Høringen har ikke givet anledning til ændringer i vurderingen af lægemidlet (se ansøgers høringssvar i bilag 3).

Læs mere i Medicinrådets vurdering af lægemidlets værdi og den bagvedliggende protokol (se bilag 4 og bilag 7).

3. Resultater af sundhedsøkonomiske analyser

Medicinrådet har vurderet, at det vil koste ca. 288.000 kr. mere at behandle én patient med encorafenib i kombination med cetuximab end med den behandling, man bruger i dag. Meromkostningerne er i høj grad drevet af lægemiddelpriserne på encorafenib og cetuximab. Medicinrådet har også vurderet, at regionerne vil skulle bruge ca. 29 mio. kr. mere i det femte år efter en evt. anbefaling. Beløbene er baseret på de officielle listepriser for lægemidlerne. Rådets beslutning er truffet på baggrund af priser på lægemidlerne, som Amgros har forhandlet med lægemiddelfirmaerne. De forhandlede priser er fortrolige efter firmaernes ønske, og derfor må Medicinrådet ikke offentliggøre hverken de reelle priser eller omkostninger.

Læs mere i den sundhedsøkonomiske afrapportering (se bilag 1).

4. Alvorlighed

Sygdommens alvorlighed er altid medtaget i Medicinrådets vurdering af et lægemiddels værdi. Det sker i forbindelse med valget af effektmål og den vægt, Medicinrådet tillægger effektestimaterne, hvilket er forskelligt alt efter typen af effektmål. Derudover har Medicinrådet formuleret et alvorlighedsprincip, som Medicinrådet kan inddrage i helt særlige situationer. Dette har ikke været nødvendigt i denne sag.

5. Anbefalingen betyder

Anbefalingen betyder, at Medicinrådet råder regionerne til at bruge encorafenib i kombination med cetuximab til patienter med metastatisk kolorektalkræft med $BRAF^{V600E}$-mutation, men ikke nødvendigvis som førstevalg til alle patienter. Encorafenib i kombination med cetuximab har indikation til patienter, som har modtaget førstelinjebehandling, Medicinrådet forventer, at behandling med encorafenib i kombination med cetuximab primært vil anvendes i andenlinjebehandling i dansk klinisk praksis.

6. Sagsbehandlingstid

Medicinrådet har brugt 15 uger på arbejdet med encorafenib i kombination med cetuximab til behandling af patienter med metastatisk kolorektalkræft, der har $BRAF^{V600E}$-mutation.

7. Kontaktinformation til Medicinrådet

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

8. Versionslog

Versionslog		
Version	**Dato**	**Ændring**
1.0	27. januar 2021	Godkendt af Medicinrådet

9. Bilag

1. Medicinrådets sundhedsøkonomiske afrapportering vedr. encorafenib i kombination med cetuximab, version 1.0
2. Forhandlingsnotat fra Amgros vedr. encorafenib i kombination med cetuximab
3. Høringssvar fra ansøger, inkl. eventuel efterfølgende dialog vedr. lægemidlets værdi
4. Medicinrådets vurdering vedr. encorafenib i kombination med cetuximab til behandling af patienter med metastatisk kolorektalkræft, der har $BRAF^{V600E}$-mutation, version 1.0
5. Ansøgers endelige ansøgning
6. Ansøgers tekniske dokument til den sundhedsøkonomiske ansøgning
7. Medicinrådets protokol for vurdering vedr. encorafenib i kombination med cetuximab til behandling af patienter med metastatisk kolorektalkræft, der har $BRAF^{V600E}$-mutation, version 1.0

Medicinrådet

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Medicinrådet

Sundhedsøkonomisk afrapportering

Encorafenib i kombination med cetuximab

Metastatisk kolorektalkræft med $BRAF^{V600E}$-mutation

Version 1.0

Om Medicinrådet

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

Dokumentets formål

Dette dokument indeholder en beskrivelse af den sundhedsøkonomiske analyse, som ligger til grund for ansøgningen for encorafenib i kombination med cetuximab til metastatisk kolorektalkræft med $BRAF^{V600E}$-mutation, samt en gennemgang af ansøgers modelantagelser til den sundhedsøkonomiske model. Sekretariatet vil kommentere på ansøgers modelantagelser under afsnittene "Sekretariatets vurdering". Her vil sekretariatets vurdering fremgå sammen med eventuelle ændrede modelantagelser og begrundelser herfor.

Afsnit 4.4 indeholder en tabel, der opsummerer både ansøgers og sekretariatets modelantagelser med det formål tydeligt at vise, hvordan sekretariatets sundhedsøkonomiske analyse afviger fra ansøgers sundhedsøkonomiske analyse. Resultatafsnittet baserer sig på sekretariatets modelantagelser og sundhedsøkonomiske analyse.

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Indholdsfortegnelse

1. Liste over forkortelser

AIP	Apotekernes indkøbspris
BRAF	*Proto-oncogene B-Raf*
BSA	Kropsfladeareal *(body surface area)*
DKK	Danske kroner
DRG	Diagnose Relaterede Grupper
EGFRi	*Epidermal Growth Factor Receptor inhibitor*
FOLFIRI	Folinsyre, fluorouracil, irinotecan
FOLFOX	Folinsyre, fluorouracil, oxaliplatin
IRI	Irinotecan
KM	Kaplan-Meier
KRC	Kolorektalkræft
mKRC	Metastatisk kolorektalkræft
OS	Samlet overlevelse
PD	Progredieret sygdom
PFS	Progressionsfri overlevelse
RDI	Relativ dosisintensitet
SAIP	Sygehusapotekernes indkøbspris
SmPC	Produktresumé
TTD	*Time to treatment discontinuation*

2. Opsummering

Baggrund

Encorafenib i kombination med cetuximab er indiceret til voksne patienter med metastatisk kolorektalkræft med $BRAF^{V600E}$-mutation. Omkring 110 patienter kandiderer årligt til behandling af den ansøgte indikation i Danmark. Sekretariatets vurdering tager udgangspunkt i dokumentation indsendt af Pierre Fabre.

Analyse

Den sundhedsøkonomiske analyse estimerer de inkrementelle omkostninger pr. patient ved behandling med encorafenib + cetuximab over en tidshorisont på 15 år. Encorafenib + cetuximab sammenlignes med FOLFIRI eller FOLFOX ± bevacizumab eller cetuximab til patienter med metastatisk kolorektalkræft med $BRAF^{V600E}$-mutation.

Inkrementelle omkostninger og budgetkonsekvenser

I det scenarie, sekretariatet mener er mest sandsynligt, er de inkrementelle omkostninger for encorafenib + cetuximab ca. [redacted] DKK sammenlignet med FOLFIRI eller FOLFOX ± bevacizumab eller cetuximab. Hvis analysen udføres med AIP, bliver de inkrementelle omkostninger til sammenligning 288.000 DKK pr. patient.

Sekretariatet vurderer, at budgetkonsekvenserne for regionerne ved anbefaling af encorafenib + cetuximab som standardbehandling vil være ca. [redacted] DKK i år 5. Hvis analysen udføres med AIP, er budgetkonsekvenserne ca. 29 mio. DKK i år 5.

Konklusion

De inkrementelle omkostninger er i høj grad drevet af lægemiddelomkostningerne for encorafenib og cetuximab. Der er usikkerhed forbundet med komparatorerne, da effektestimaterne er baseret på data fra et studie, hvor kontrolarmen udgør behandlinger, som ikke er de hyppigst anvendte i dansk klinisk praksis.

3. Baggrund for den sundhedsøkonomiske analyse

Pierre Fabre (herefter omtalt som ansøger) er markedsføringstilladelsesindehaver af encorafenib og har den 15. oktober 2020 indsendt en ansøgning til Medicinrådet om anbefaling af encorafenib + cetuximab som standardbehandling på danske hospitaler af den nævnte indikation. Som et led i denne ansøgning vurderer Medicinrådets sekretariat, på vegne af Medicinrådet, den sundhedsøkonomiske analyse, ansøger har indsendt. Denne rapport er sekretariatets vurdering af den fremsendte sundhedsøkonomiske analyse (herefter omtalt som analysen).

3.1 Patientpopulation

Kræft i tyk- og endetarm (kolorektalkræft herefter forkortet KRC) er en af de hyppigste kræftsygdomme i Danmark. I 2018 blev i alt 4.433 personer diagnosticeret med KRC, størstedelen med tyktarmskræft. Hyppigheden stiger med alderen. KRC ses sjældent før 40-års alderen, og de fleste tilfælde ses først efter 60 års-alderen. Omkring 20-30 % af patienterne har allerede metastatisk KRC (mKRC) ved diagnosetidspunktet, og yderligere 20 % udvikler mKRC inden for fem år. Patienter med BRAF-mutationer har den dårligste prognose, da standardbehandlingen ofte har begrænset effekt med en median overlevelse på 4-6 måneder efter førstelinjebehandling. BRAF-mutationer findes i ca. 10 % af patienter med mKRC. Fagudvalget skønner, at ca. 110 patienter med $BRAF^{V600E}$-positiv mKRC årligt vil være kandidater til behandling med encorafenib i kombination med cetuximab efter førstelinjebehandling [1].

3.1.1 Komparator

Medicinrådet har defineret FOLFIRI (folinsyre, fluorouracil, irinotecan) ± bevacizumab eller cetuximab og FOLFOX (folinsyre, fluorouracil, oxaliplatin) ± bevacizumab eller cetuximab som komparatorer til encorafenib + cetuximab for populationen specificeret i afsnit 3.1, se Tabel 1.

Tabel 1: Definerede populationer og komparatorer.

Population	Komparator
Patienter med metastatisk kolorektalkræft med $BRAF^{V600E}$-mutation, som tidligere har modtaget systemisk terapi i form af kemoterapi i 1.- og/eller 2. linje	FOLFIRI ± bevacizumab eller cetuximab FOLFOX ± bevacizumab eller cetuximab

3.2 Problemstilling

Formålet med analysen er at estimere de gennemsnitlige inkrementelle omkostninger pr. patient og de samlede budgetkonsekvenser for regionerne ved anbefaling af encorafenib + cetuximab som standardbehandling på danske hospitaler af den nævnte indikation.

Medicinrådet har vurderet den kliniske merværdi af encorafenib + cetuximab og specificeret følgende kliniske spørgsmål:

Klinisk spørgsmål 1*:*
Hvilken værdi har encorafenib i kombination med cetuximab sammenlignet med FOLFIRI ± bevacizumab eller EGFRi eller FOLFOX ± bevacizumab eller EGFRi for patienter med metastatisk kolorektalkræft, som har BRAF^{V600E}-mutation?

4. Vurdering af den sundhedsøkonomiske analyse

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

4.1 Antagelser og forudsætninger for model

Den sundhedsøkonomiske model har til formål at estimere de inkrementelle omkostninger pr. patient ved 2. eller 3. linjebehandling af metastatisk kolorektalkræft med BRAF^{V600E}-mutation. Encorafenib + cetuximab sammenlignes med FOLFIRI + cetuximab eller IRI + cetuximab i et randomiseret, open-label, fase III-studie (BEACON) [2]. Valget mellem FOLFIRI + cetuximab eller IRI + cetuximab var op til den behandlende læge (klinikers valg af kemoterapi). Ansøgers analyse bygger på effektdata fra BEACON-studiet. Ansøger antager, at FOLFIRI effektmæssigt kan ligestilles med IRI, og sammenligner derfor omkostningerne forbundet med behandling med encorafenib + centuximab med omkostningerne forbundet med FOLFIRI + cetuximab.

Ansøgers model gør det muligt at vælge andre komparatorer end klinikers valg af kemoterapi fra studiet. Der er tale om følgende komparatorer:

- Trifluridin + tipiracil
- FOLFOX. Sammenligningen bygger på en antagelse om, at effekten er den samme som ved behandling med FOLFIRI. Effektdata fra kontrolarmen i BEACON-studiet anvendes derfor, og kun lægemiddelomkostningerne adskiller sig dermed fra sammenligningen med FOLFIRI
- FOLFIRI, hvor ansøger har udarbejdet en indirekte sammenligning for at estimere effektestimaterne for FOLFIRI alene.

Det er i modellen muligt at definere den specifikke andel af patienter, der modtager hhv. cetuximab eller bevacizumab i kombination med FOLFIRI eller FOLFOX. Dette har kun betydning for de inkluderede lægemiddelomkostninger, da ansøger antager, at effekten af regimerne vil være den samme, uanset om bevacizumab eller cetuximab indgår i kombinationerne eller ej.

Sekretariatets vurdering

Fagudvalget vurderer, at effekten af behandlingen i kontrolarmen i BEACON-studiet svarer til effekten af behandlingen i dansk klinisk praksis på trods af, at IRI + cetuximab indgår som en del af kontrolarmen. Fagudvalget vurderer, at danske patienter oftest behandles med FOLFIRI i 1. linje og FOLFOX i 2. linje, og har tidligere ligestillet FOLFIRI og FOLFOX. I BEACON-studiet kan klinikeren vælge mellem IRI og FOLFIRI i kontrolarmen. Der foreligger ikke studier, der viser differentieret respons mellem IRI og FOLFIRI, og fagudvalget vurderer derfor, at de er klinisk ligeværdige. Derfor antages effektestimaterne for behandling med komparator at være ens, uanset hvilket regime der benyttes.

Fagudvalget vurderer, at cetuximab kun tillægges i omkring 10 % af behandlingerne i Danmark, mens bevacizumab tillægges i omkring 80 % af behandlingerne. Der er usikkerhed forbundet med effekten ved at tillægge cetuximab eller bevacizumab til FOLFIRI og FOLFOX for denne patientpopulation grundet mangel på studier, der undersøger den specifikke mKRC-population med $BRAF^{V600E}$-mutation. Det er muligt, at FOLFOX + bevacizumab er et bedre valg af behandling end irinotecan-holdig behandling suppleret med cetuximab, men størrelsesordenen er meget vanskelig at vurdere.

I sekretariatets hovedanalyse er både FOLFIRI og FOLFOX komparatorer. Det antages, at andelen af patienter, der modtager FOLFIRI er 20 %, og andelen, der modtager FOLFOX er 80 %. Effektestimaterne for FOLFIRI og FOLFOX antages at være ens, og bygger på data fra BEACON-studiet. Ændringen i andelene af patienter, der modtager hhv. FOLFIRI og FOLFOX, har derfor kun betydning for lægemiddelomkostningerne forbundet med oxaliplatin og irinotecan. Ændringen har minimal betydning for analysens resultat. Sekretariatet ændrer også andelen af patienter, der modtager cetuximab eller bevacizumab i kombination med FOLFIRI eller FOLFOX. I sekretariatets hovedanalyse antages det, at 10 % af patienterne modtager cetuximab i kombination med FOLFIRI eller FOLFOX, mens 80 % modtager bevacizumab i kombination med FOLFIRI eller FOLFOX. Se Tabel 2 for en oversigt over de valgte komparatorer i hhv. ansøgers analyse og sekretariatets hovedanalyse.

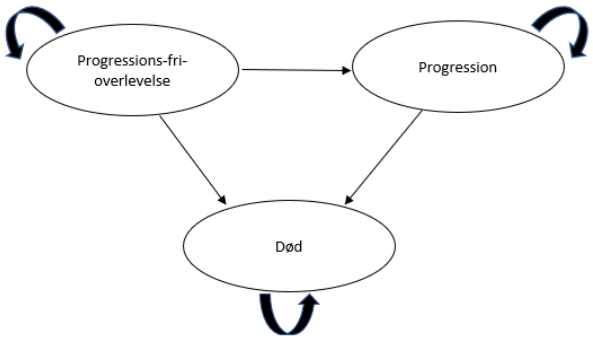
Tabel 2: Oversigt over ansøgers valg af komparator og sekretariatets valg af komparator.

BEACON	Ansøgers analyse	Sekretariatets hovedanalyse
Kontrolarm: Klinikers valg af kemoterapi (FOLFIRI + cetuximab eller IRI + cetuximab).	Komparator: FOLFIRI + cetuximab. Analysen bygger på effektestimater fra BEACON-studiet. Ansøger antager, at FOLFIRI + cetuximab kan ligestilles med IRI + cetuximab.	Komparator: FOLFIRI eller FOLFOX ± bevacizumab eller cetuximab. Fagudvalget har ligestillet FOLFIRI og FOLFOX, og vurderer, at FOLFIRI og IRI er klinisk ligeværdige. Sekretariatets hovedanalyse bygger på effektdata fra BEACON-studiet. 10 % af patienterne antages at få cetuximab, og 80 % antages at få bevacizumab i kombination med FOLFIRI eller FOLFOX. Det er usikkert hvilken betydning cetuximab og bevacizumab har for den samlede effekt.

Sekretariatet vælger FOLFIRI og FOLFOX som komparatorer, hvoraf det antages, at 20 % af patienterne modtager FOLFIRI, og 80 % af patienterne modtager FOLFOX. Yderligere antages det, at 10 % af patienterne vil modtage cetuximab i kombination med FOLFIRI eller FOLFOX, mens 80 % vil modtage bevacizumab i kombination med FOLFIRI eller FOLFOX.

4.1.1 Modelbeskrivelse

Ansøger har indleveret en *partitioned survival model*, der estimerer omkostninger baseret på den tid, patienten er i de tre stadier: progressionsfri overlevelse (PFS), progression (PD) og død. Figur 1 viser modellens struktur. En cyklus i modellen er en måned, og ansøger har benyttet *half-cycle correction*.



Figur 1: Beskrivelse af modelstrukturen i omkostningsanalysen.

Ansøger anvender Kaplan-Meier (KM)-data til beregning af tiden, patienterne befinder sig i stadierne. KM-data er benyttet til at lave ekstrapoleringer for PFS og den samlede overlevelse (OS) og tid til behandlingsophør (*time to treatment discontinuation*, TTD). Til

ekstrapolering af PFS og OS er log-logistisk anvendt som parametrisk funktion for begge arme, se Figur 2 og Figur 3. Modellen estimerer, at omkring [redacted] % af patienterne, der modtog encorafenib + cetuximab, vil være i live efter 60 måneder, og at det vil gælde for ca. [redacted] % af patienterne, der modtog FOLFIRI + cetuximab eller IRI + cetuximab. Effektdata kommer fra BEACON-studiet, og det antages, at effekten af FOLFIRI eller FOLFOX er den sammen som effekten i kontrolarmen i studiet.

Figur 2: PFS-kurve og OS-kurve for encorafenib + cetuximab.

Figur 3: PFS-kurve og OS-kurve for FOLFIRI + cetuximab eller IRI + cetuximab.

Behandlingslængden bygger på TTD, og ansøger antager, at nogle af de patienter, der har progredieret, kan fortsætte behandling med encorafenib + cetuximab, hvis der er en forventet effekt ved at fortsætte behandlingen. Til ekstrapolering af TTD er gamma anvendt som parametrisk funktion. Den gennemsnitlige behandlingslængde for patienter, der modtog encorafenib + cetuximab, var ca. [redacted], mens den var ca. [redacted] for patienter, der modtog FOLFIRI + cetuximab eller IRI + cetuximab. Det antages, at behandlingslængden ved behandling med FOLFIRI eller FOLFOX ± bevacizumab eller cetuximab er den samme som behandlingslængden for kontrolarmen i BEACON-studiet.

Sekretariatets vurdering
Fagudvalget vurderer, at patienter ikke vil fortsætte behandling efter progression. Sekretariatet ændrer derfor modellen således, at andelen af patienter i behandling, ikke overstiger andelen af patienter, der ikke er progredieret.

Sekretariatet accepterer ansøgers modelantagelser, men ændrer modellen således, at andelen af patienter, der er i behandling, ikke overstiger andelen af patienter, der ikke er progredieret.

4.1.2 Analyseperspektiv

Ansøgers omkostningsanalyse har et begrænset samfundsperspektiv og en tidshorisont på 15 år. Tidshorisonten afspejler ikke, at patienterne er under behandling i 15 år, men i stedet er formålet at sikre, at alle omkostninger, der falder efter behandlingen er ophørt, er inkluderet i analysen. Ansøger argumenterer for, at alle patienter vil være døde inden for 15 år, og alle relevante økonomiske forskelle, der måtte være mellem patienter, der behandles med encorafenib + cetuximab, og patienter, der behandles med FOLFIRI eller FOLFOX ± bevacizumab eller cetuximab, vil derfor komme til udtryk i denne tidsperiode. Omkostninger, der ligger efter det første år, er diskonteret med en rente på 4 %.

Sekretariatets vurdering
Sekretariatet accepterer ansøgers valg vedr. analyseperspektiv.

4.2 Omkostninger

I det følgende præsenteres ansøgers antagelser for omkostningerne i den sundhedsøkonomiske analyse af encorafenib + cetuximab sammenlignet med FOLFIRI + cetuximab. I sekretariatets hovedanalyse er både FOLFIRI eller FOLFOX ± bevacizumab eller cetuximab komparatorer, som beskrevet i afsnit 4.1. De inkluderede omkostninger i ansøgers analyse er lægemiddelomkostninger, hospitalsomkostninger, bivirkningsomkostninger, patientomkostninger og omkostninger til efterfølgende behandling.

4.2.1 Lægemiddelomkostninger

De anvendte doser er hentet i de respektive lægemidlers produktresuméer (SmPC'er) på nær doseringen for cetuximab, se Tabel 3. Ansøger antager, på baggrund af en udtalelse fra en dansk klinisk ekspert, at cetuximab gives ved 500 mg/m^2 hver anden uge. Ifølge SmPC'et skal cetixumab gives ved 250 mg/m^2 hver uge. Cetuximab eller bevacizumab kan gives i tillæg til FOLFIRI og FOLFOX. Ansøger antager, at 100 % af patienterne modtager cetuximab i tillæg til behandling med FOLFIRI. Ansøgers model giver mulighed for at estimere omkostningerne, når bevacizumab gives i tillæg. Her antages en dosis på 7,5 mg/kg hver tredje uge.

Encorafenib + cetuximab:

- Encorafenib: 300 mg dagligt
- Cetuximab: 400 mg/m^2 ved indledende dosis, herefter 500 mg/m^2 hver anden uge

FOLFIRI + cetuximab:

- Calciumfolinat: 400 mg/m^2 hver anden uge
- Fluorouracil: 2.800 mg/m^2 hver anden uge
- Irinotecan: 180 mg/m^2 hver anden uge
- Cetuximab: 400 mg/m^2 ved indledende dosis, herefter 500 mg/m^2 hver anden uge

FOLFOX + cetuximab:

- Calciumfolinat: 400 mg/m^2 hver anden uge
- Fluorouracil: 2.800 mg/m^2 hver anden uge
- Oxaliplatin: 85 mg/m^2 hver anden uge
- Cetuximab: 400 mg/m^2 ved indledende dosis, herefter 500 mg/m^2 hver anden uge

Til beregning af lægemiddelomkostninger benytter ansøger kropsfladearealet (BSA) på 1,79 m^2 og gennemsnitsvægten 70,7 kg fra BEACON-studiet [2]. Alle lægemidler gives ved intravenøs infusion på nær encorafenib, der er formuleret som kapsler. Ansøgers estimering af lægemiddelomkostninger bygger på AIP, hvilket sekretariatet udskifter med SAIP.

Tabel 3: Anvendte lægemiddelpriser, SAIP (oktober 2020).

Lægemiddel	Styrke	Pakningsstørrelse	Pris [DKK]	Kilde
Encorafenib	75 mg	42 stk.	[redacted]	Amgros
Cetuximab	5 mg/ml	100 ml	[redacted]	Amgros
Calciumfolinat	10 mg/ml	10 x 100 ml	[redacted]	Amgros
Fluorouracil	50 mg/ml	100 ml	[redacted]	Amgros
Irinotecan	20 mg/ml	25 ml	[redacted]	Amgros
Oxaliplatin	5 mg/ml	40 ml	[redacted]	Amgros
Bevacizumab	25 mg	16 ml	[redacted]	Amgros

Inden behandling med cetuximab, antages det, at patienter præmedicineres med tetracyclin (500 mg) og hydrokortison (8 mg). Tetracyclin gives på tabletform, og listeprisen er 19,32 DKK. Hydrokortison er en creme, og listeprisen er 95,84 DKK.

Ansøger har medregnet den relative dosisintensitet (RDI), der blev fundet i BEACON-studiet [2], se Tabel 4. Der tages dermed højde for dosisreduktion og midlertidige afbrydelser i behandlingen i beregningerne af lægemiddelomkostningerne. RDI for bevacizumab antages at være 1, da lægemidlet ikke indgik i studiet. Der er ligeledes ikke fundet RDI for præmedicineringen.

Tabel 4: Relative dosisintensiteter fra BEACON-studiet.

Lægemiddel	RDI
Encorafenib	[redacted]
Cetuximab	[redacted]
Calciumfolinat	[redacted]
Fluorouracil	[redacted]
Irinotecan	[redacted]
Oxaliplatin	[redacted]
Bevacizumab	1

Sekretariatets vurdering

Fagudvalget vurderer, at patienter, som modtager encorafenib + cetuximab, vil modtage 250 mg/m^2 cetuximab hver uge og ikke 500 mg/m^2 hver anden uge, som ansøger antager. Dog vurderer fagudvalget, at hvis patienten modtager FOLFIRI/FOLFOX + cetuximab, er det dansk klinisk praksis at give cetuximab hver anden uge. Fagudvalget vil ikke afvise, at cetuximab (i kombination med encorafenib) i fremtiden vil blive administreret hver anden uge, men da der endnu ikke er erfaring med administrationen af encorafenib + cetuximab, vurderer fagudvalget, at man vil følge SmPC'et. Sekretariatet ændrer hovedanalysen, så cetuximab (i kombination med encorafenib) vil blive administreret hver uge, men præsenterer en følsomhedsanalyse, hvor det antages, at cetuximab vil blive administreret hver anden uge.

Sekretariatet accepterer ansøgers antagelser vedr. lægemiddelomkostninger men ændrer administrationsfrekvensen for cetuximab, så det administreres hver uge, når det gives i kombination med encorafenib. Sekretariatet præsenterer en følsomhedsanalyse, hvor cetuximab antages at blive administreret hver anden uge.

4.2.2 Hospitalsomkostninger

Ansøger har inkluderet administrationsomkostninger på 835 DKK til intravenøs infusion baseret på en artikel, som har undersøgt omkostningerne for IV-administration til behandling af HER2-positiv brystkræft [3]. Encorafenib administreres oralt, og der er derfor ikke medregnet administrationsomkostninger. Ansøger antager, at patienter, der ikke er progredieret, uanset behandlingsregime vil have en konsultation med en onkolog én gang om måneden og vil få foretaget en CT-scanning hver anden måned. Patienter,

der er progredieret, antages at have to sygeplejerskekonsultationer om måneden og ét besøg hos en praktiserende læge hver fjerde måned.

Ansøger antager yderligere, at patienter, der behandles med FOLFIRI + cetuximab skal have lagt en veneport fire gange om måneden hos en sygeplejerske, når patienterne ikke er progredieret, og to gange om måneden, når patienterne er progredieret. Se Tabel 5 for ansøgers antagelser vedrørende monitorering og opfølgning.

Tabel 5: Omkostninger til lægemiddeladministration.

	Encorafenib + cetuximab	FOLFIRI + cetuximab	Enhedsomkostning [DKK]	Kilde
Præ-progression				
CT-scanning	0,5	0,5	1.862	DRG 2020: 30PR07
Konsultation med onkolog	1	1	451,95	Medicinrådets værdisætning af enhedsomkostninger
Sygeplejerskebesøg	0	4	544	Medicinrådets værdisætning af enhedsomkostninger
Post-progression				
Sygeplejerskebesøg	2	4	544	Medicinrådets værdisætning af enhedsomkostninger
Konsultation med praktiserende læge	0,25	0,25	1.176	Medicinrådets værdisætning af enhedsomkostninger

Ansøger har inkluderet terminalomkostninger på 118.782 DKK. Denne omkostning er baseret på et studie, der undersøgte terminalomkostninger i Danmark, England, Frankrig, Tyskland, Japan, Nederlandene, Taiwan, USA og Canada [4]. Ansøger har omregnet til danske kroner og benyttet forbrugerprisindekset til at beregne omkostningen i 2020.

Sekretariatets vurdering

Ansøger benytter en administrationsomkostning for intravenøs infusion, som er fundet i et studie, der undersøgte administrationsomkostningerne ved behandling for HER2-positiv brystkræft [3]. Ansøger har benyttet DRG-koden 04MA98 med taksten 1.799 DKK for et ambulant besøg i en følsomhedsanalyse. Sekretariatet vælger at benytte DRG-taksten for at undgå, at der kan være sygdomsspecifikke faktorer fra studiet, der har haft betydning for estimeringen af omkostningerne.

Ansøger antager, at patienter, der behandles med FOLFIRI + cetuximab, skal have lagt en veneport fire gange om måneden, når patienten ikke er progredieret, og to gange om måneden, når patienten er progredieret. Fagudvalget vurderer, at patienter, der

behandles med FOLFIRI + cetuximab eller FOLFOX + cetuximab, kun vil få lagt én veneport i forbindelse med opstart af behandling, som er funktionel resten af behandlingsforløbet.

Ansøger har inkluderet terminalomkostninger, som bygger på et studie, der inkluderer omkostninger fra en række forskellige lande [4]. Eftersom studiet bygger på flere landes kliniske praksis, er det usikkert, hvorvidt terminalomkostningerne vil være de samme i dansk klinisk praksis. Sekretariatet vælger derfor at ekskludere terminalomkostningerne men præsenterer en følsomhedsanalyse, hvor ansøgers estimat af terminalomkostninger inkluderes.

Sekretariatet vælger at benytte DRG-taksten fra ansøgers følsomhedsanalyse til beregning af administrationsomkostninger. Derudover ændrer sekretariatet analysen således, at patienter, der modtager FOLFIRI + cetuximab eller FOLFOX + cetuximab, får lagt én veneport i forbindelse med opstart af behandlingen. Sekretariatet ekskluderer terminalomkostninger fra hovedanalysen men præsenterer en følsomhedsanalyse, hvor terminalomkostningerne er inkluderet.

4.2.3 Bivirkningsomkostninger

Ansøger estimerer bivirkningsomkostningerne på baggrund af bivirkningsfrekvenserne fundet i BEACON-studiet [2]. Bivirkninger af grad 3 eller 4 er inkluderet i analysen, hvis de forekom hos minimum 2 % af patienterne i bare én af armene i studiet. Ansøger har benyttet 2020 DRG-takster til at estimere bivirkningsomkostningerne. Se Tabel 6.

Tabel 6: Bivirkningsfrekvenser (grad 3-4) ved behandling med encorafenib + cetuximab og FOLFIRI + cetuximab.

	Encorafenib + cetuximab	FOLFIRI + cetuximab	Enhedsomkostning [DKK]	Kilde
Mavesmerter	3,2 %	5,2 %	2.343	06MA98
Anæmi	5,6 %	6,7 %	4.732	16PR02
Svækkelse	3,7 %	5,2 %	2.343	06MA98
Smerte	2,3 %	0,5 %	2.343	06MA98
Diarré	2,8 %	10,4 %	5.297	06MA11
Svimmelhed	4,2 %	4,7 %	2.343	06MA98
Febril neutropeni	0,0 %	2,6 %	3.149	16MA98
Hypertension	1,4 %	2,6 %	14.415	05MA11
Intestinal obstruktion	4,6 %	2,6 %	5.297	06MA11

Leukopeni	0,0 %	4,1 %	3.149	16MA98
Kvalme	0,0 %	1,6 %	2.343	06MA98
Neutropeni	0,9 %	10,4 %	3.149	16MA98
Mundbetændelse	0,0 %	2,1 %	2.343	06MA98
Urinvejsinfektion	2,3 %	0,0 %	2.343	06MA98
Opkast	1,4 %	3,1 %	2.343	06MA98

Sekretariatets vurdering
Sekretariatet accepterer ansøgers tilgang vedr. bivirkningsomkostninger men gør opmærksom på, at grundet valg af komparator i sekretariatets hovedanalyse, er det usikkert, om bivirkningsprofilen er helt korrekt. Bivirkninger relateret til bevacizumab indgår ikke i analysen, og FOLFOX-regimet blev ikke undersøgt i BEACON-studiet. Fagudvalget vurderer, at FOLFOX har flere neurologiske bivirkninger end FOLFIRI, hvorfor klinikerne foretrækker at benytte FOLFIRI i 1. linje og FOLFOX i 2. linje. Bivirkningsomkostningerne kan derfor være underestimeret for komparatorarmen.

Sekretariatet accepterer ansøgers tilgang vedr. bivirkningsomkostninger.

4.2.4 Patientomkostninger

Ansøger har inkluderet patient- og transportomkostninger for hospitalsbesøg i forbindelse med behandling med encorafenib + cetuximab og FOLFIRI + cetuximab og for monitorering og opfølgning. Ansøger antager, at patienter bruger 0,5 timer ved hvert hospitalsbesøg, og benytter enhedsomkostningen på 179 DKK per time for patienttid og 98,56 DKK for transportomkostninger per hospitalsbesøg, jf. Medicinrådet værdisætning af enhedsomkostninger.

Sekretariatets vurdering
Ansøger antager, at samtlige hospitalsbesøg tager 0,5 timer, uanset hvilken behandling patienterne modtager. Sekretariatet bemærker, at en administrationstid på 0,5 timer af cetuximab, bevacizumab, FOLFIRI og FOLFOX ikke er et præcist estimat baseret på lægemidlernes produktresuméer. Eksempelvis administreres cetuximab over minimum 2 timer ved indledende dosis, og 1 time ved efterfølgende doser. Patientomkostningerne for administration af cetuximab er derfor underestimeret. I sekretariatets hovedanalyse vil 10 % af patienterne, der modtager FOLFIRI eller FOLFOX, også modtage cetuximab i kombination, og 100 % vil modtage cetuximab i kombination med encorafenib. Dermed har underestimeringen størst betydning for encorafenib + cetuximab. Sekretariatet accepterer dog ansøgers tilgang til beregning af patientomkostninger, da det har mindre betydning for analysens resultat.

Sekretariatets accepterer ansøgers tilgang vedr. patientomkostninger.

4.2.5 Efterfølgende behandling

Ansøger antager, at 20 % af patienterne, der er progredieret uanset behandlingsregime, vil modtage behandling med trifluridin + tipiracil, som doseres ved 35 mg/m^2 én gang hver fjerde uge. Det antages, at patienterne i gennemsnit vil modtage to cyklusser. Ansøger antager, at de resterende 80 % af patienterne vil modtage best supportive care, og at der ikke medregnet nogen omkostninger for denne behandling.

Sekretariatets vurdering
Trifluridin + tipiracil er ikke standardbehandling i Danmark, og fagudvalget vurderer, at danske patienter derfor ikke vil modtage denne behandling. Fagudvalget vurderer, at langt størstedelen af patienterne, der er progredieret, ikke vil modtage yderligere behandling grundet dårlig almentilstand og grundet mangel på efterfølgende behandlingsmuligheder. Sekretariatet ekskluderer derfor efterfølgende behandling fra sekretariatets hovedanalyse. Det har minimal betydning for analysens resultat.

Sekretariatet accepterer ikke ansøgers antagelser vedr. efterfølgende behandling og ekskluderer omkostningerne fra hovedanalysen.

4.3 Følsomhedsanalyser

Formålet med følsomhedsanalyserne er at undersøge usikkerhederne i analysen. Ansøger har udført følgende følsomhedsanalyser:

- Patienttid per hospitalsbesøg: 2 timer
- Omkostning for intravenøs infusion sættes til 1.799 DKK efter DRG-koden: 04MA98
- Spild medregnes

Sekretariatets vurdering
Sekretariatet vurderer, at det har lille betydning for analysens resultat, om patienttiden per hospitalsbesøg sættes til 2 timer, og præsenterer derfor ikke følsomhedsanalysen. Sekretariatet anvender ansøgers følsomhedsanalyse for omkostning for intravenøs infusion i hovedanalysen og præsenterer derfor ikke denne følsomhedsanalyse. Lægemiddelomkostningerne har stor betydning for analysens resultat, og sekretariatet præsenterer derfor følsomhedsanalysen, hvor spild medregnes. Der er usikkerhed forbundet med terminalomkostningerne, og sekretariatet vælger at ekskludere omkostningerne i hovedanalysen, men præsenterer en følsomhedsanalyse, hvor terminalomkostningerne inkluderes.

Der er usikkerhed forbundet med administrationsfrekvensen for cetuximab, når det gives i kombination med encorafenib. Grundet mangel på erfaring med behandling med encorafenib + cetuximab, vurderer fagudvalget, at man i dansk klinisk praksis vil følge SmPC'et og give cetuximab én gang om ugen (250 mg/m^2). Fagudvalget vurderer, at man i fremtiden formentlig vil give cetuximab en gang hver anden uge (500 mg/m^2), som ansøger antager. Sekretariatet præsenterer derfor en følsomhedsanalyse, hvor det

antages, at cetuximab administreres hver anden uge, når det gives i kombination med encorafenib.

Ansøger antager, at ingen af patienterne vil modtage bevacizumab i tillæg til FOLFIRI, men fagudvalget vurderer, at størstedelen af de danske patienter (80 %) vil modtage bevacizumab i tillæg til FOLFIRI eller FOLFOX. Sekretariatet vælger derfor at præsentere følsomhedsanalyser, hvor det antages, at 0 % og 100 % af patienterne modtager bevacizumab i tillæg til FOLFIRI eller FOLFOX.

Sekretariatet præsenterer følsomhedsanalyser, hvor spild medregnes og terminalomkostningerne inkluderes. Yderligere præsenteres en følsomhedsanalyse, hvor cetuximab antages at blive administreret hver anden uge, når det gives i kombination med encorafenib, og en følsomhedsanalyse hvor andelen af patienter, der modtager bevacizumab i kombination med FOLFIRI eller FOLFOX, sættes til hhv. 0 % og 100 %.

4.4 Opsummering af basisantagelser

I Tabel 7 opsummeres basisantagelserne for ansøgers hovedanalyse sammenlignet med de ændringer, som sekretariatet har lavet i egen hovedanalyse.

Tabel 7: Basisantagelser for ansøgers og sekretariatets hovedanalyse.

Basisantagelser	Ansøger	Sekretariatet
Komparator	FOLFIRI + cetuximab eller IRI + cetuximab (klinikers valg af kemoterapi)	FOLFIRI (20 %) eller FOLFOX (80 %) ± cetuximab (10 %) eller bevacizumab (80 %)
Tidshorisont	15 år	15 år
Diskonteringsrate	4 %	4 %
Inkluderede omkostninger	Lægemiddelomkostninger Hospitalsomkostninger Bivirkningsomkostninger Patient- og transportomkostninger Efterfølgende behandling	Lægemiddelomkostninger Hospitalsomkostninger Bivirkningsomkostninger Patient- og transportomkostninger
Behandlingslinje	2. og 3. linjebehandling	2. og 3. linjebehandling
Administrationsfrekvens for cetuximab (når det gives i kombination med encorafenib)	Hver anden uge	Hver uge
Parametriske funktioner for PFS og OS:		
Encorafenib + cetuximab	Log-logistisk	Log-logistisk

Basisantagelser	Ansøger	Sekretariatet
FOLFIRI/FOLFOX ± bevacizumab eller cetuximab	Log-logistisk	Log-logistisk

5. Resultater

5.1 Resultatet af sekretariatets hovedanalyse

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

- Komparator er FOLFIRI eller FOLFOX ± cetuximab (10 %) eller bevacizumab (80 %)
- Andelen af patienter, der modtager FOLFIRI: 20 % og FOLFOX: 80 %
- Omkostninger til efterfølgende behandling ekskluderes
- Cetuximab administreres hver uge, når det gives i kombination med encorafenib
- Omkostning for intravenøs infusion sættes til 1.799 DKK efter DRG-koden: 04MA98
- Én veneport bliver lagt ved opstart af behandling og er funktionel resten af behandlingsforløbet

Den inkrementelle omkostning pr. patient bliver ca. [redacted] DKK i sekretariatets hovedanalyse. Udføres analysen med AIP bliver den inkrementelle omkostning pr. patient ca. 288.000 DKK. Resultaterne fra sekretariatets hovedanalyse præsenteres i Tabel 8.

Tabel 8: Resultatet af sekretariatets hovedanalyse, DKK, diskonterede tal.

	Encorafenib + cetuximab	FOLFIRI/FOLFOX ± bevacizumab eller cetuximab	Inkrementelle omkostninger
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Hospitalsomkostninger	79.080	29.580	49.500
Bivirkningsomkostninger	1.287	2.441	-1.154
Patientomkostninger	6.488	4.495	1.993
Totale omkostninger	[redacted]	[redacted]	[redacted]

5.1.1 Resultatet af sekretariatets følsomhedsanalyser

Ved samme antagelser som i sekretariatets hovedanalyse for meromkostninger, udfører sekretariatet følsomhedsanalyser på følgende: andelen af patienter, der modtager bevacizumab i tillæg til FOLFIRI eller FOLFOX, administrationsfrekvensen for cetuximab, når det gives i kombination med encorafenib, spild og på terminalomkostninger, der inkluderes, se Tabel 9.

Tabel 9: Resultatet af sekretariatets følsomhedsanalyse sammenlignet med hovedanalysen, DKK

Scenarie	Inkrementelle omkostninger
Resultatet af hovedanalysen	[redacted]
0 % bevacizumab i tillæg til FOLFIRI/FOLFOX	[redacted]
100 % bevacizumab i tillæg til FOLFIRI/FOLFOX	[redacted]
Cetuximab administreres hver anden uge, når det gives i kombination med encorafenib	[redacted]
Spild medregnes	[redacted]
Terminalomkostninger inkluderes	[redacted]

6. Budgetkonsekvenser

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

- Encorafenib + cetuximab bliver anbefalet som standardbehandling af Medicinrådet til indikationen, som denne analyse omhandler
- Encorafenib + cetuximab bliver ikke anbefalet som standardbehandling

Budgetkonsekvenserne bliver differencen mellem budgetkonsekvenserne i de to scenarier.

6.1 Ansøgers estimat af patientantal og markedsandel

Ansøger antager, at 143 patienter kandiderer til behandling med encorafenib + cetuximab. Hvis encorafenib + cetuximab anbefales som standardbehandling, antager ansøger et markedsoptag på 5 % i år 1, som stiger til 25 % i år 5, og det giver dermed en årlig stigning i markedsoptag på 5 %-point. Tabel 10 viser estimatet af antal patienter årligt i budgetkonsekvenserne.

Tabel 10: Ansøgers estimat af antal nye patienter pr. år.

	År 1	År 2	År 3	År 4	År 5
Anbefales					
Encorafenib + cetuximab	7	14	21	29	36
FOLFIRI/FOLFOX ± bevacizumab eller cetuximab	136	129	122	115	107
Anbefales ikke					
Encorafenib + cetuximab	0	0	0	0	0
FOLFIRI/FOLFOX ± bevacizumab eller cetuximab	143	143	143	143	143

Sekretariatets vurdering

Sekretariatet estimerer budgetkonsekvenserne med samme antagelser omkring komparator, som er antaget i hovedanalysen, der estimerer omkostninger per patient. Fagudvalget har anslået i protokollen, at omkring 110 patienter kandiderer til behandling med encorafenib + cetuximab som 2. linjebehandling. Fagudvalget vurderer, at det er realistisk, at 143 patienter kandiderer til behandlingen i år 1, når det også inkluderer patienter, der skal starte 3. linjebehandling. Dog vurderer fagudvalget, at patienter fremover vil modtage encorafenib + cetuximab i 2. linje, hvis behandlingen anbefales. Dermed falder patientantallet til 110 efter år 1 og frem. Sekretariatet ændrer derfor patientantallet til 110 efter år 1.

Fagudvalget vurderer, at markedsoptaget vil være højere end ansøgers estimat ved en anbefaling. Fagudvalget estimerer, at encorafenib + cetuximab vil have et markedsoptag på 50 % i år 1 og på 90 % i de efterfølgende år. Sekretariatet ændrer derfor patientantallet jævnfør fagudvalgets vurdering, se Tabel 11.

Tabel 11: Sekretariatets estimat af antal nye patienter pr. år.

	År 1	År 2	År 3	År 4	År 5
Anbefales					
Encorafenib + cetuximab	72	99	99	99	99
FOLFIRI/FOLFOX ± bevacizumab eller cetuximab	72	11	11	11	11
Anbefales ikke					

	År 1	År 2	År 3	År 4	År 5
Encorafenib + cetuximab	0	0	0	0	0
FOLFIRI/FOLFOX ± bevacizumab eller cetuximab	143	110	110	110	110

Der er usikkerhed forbundet med antallet af patienter, der vil kandidere til behandling med encorafenib + cetuximab. Da patienternes almentilstand ofte ikke er forenelig med yderligere behandling efter 1. linje, tilbydes kun ca. 50 % af patienterne på nuværende tidspunkt 2. linje-kemoterapi. Fagudvalget vurderer, at det er sandsynligt, at flere patienter vil kunne tilbydes encorafenib + cetuximab, da denne kombination har en favorabel bivirkningsprofil sammenlignet med kemoterapi-kombinationerne. Da det kun er patienter, som kandiderer til behandling med FOLFIRI eller FOLFOX, som indgår i analysen, er det ikke muligt at vurdere, i hvilket omfang budgetkonsekvenserne er underestimeret, hvis patienter med dårligere almentilstand også tilbydes encorafenib + cetuximab.

Sekretariatet udfører egen budgetkonsekvensanalyse, hvor patientantallet sættes til 110 efter år 1, og hvor markedsoptaget sættes til 50 % i år 1 og 90 % i de efterfølgende år.

6.2 Sekretariatets budgetkonsekvensanalyse

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

- Patientantallet reduceres til 110 efter år 1
- Markedsoptaget sættes til 50 % i år 1 og 90 % i de efterfølgende år

Sekretariatet estimerer, at anvendelse af encorafenib + cetuximab vil resultere i budgetkonsekvenser på ca. [redacted] DKK i år 5. Resultatet er præsenteret i Tabel 12.

Hvis analysen udføres med AIP, bliver budgetkonsekvenserne ca. 29 mio. DKK i år 5.

Tabel 12: Sekretariatets analyse af totale budgetkonsekvenser, mio. DKK, ikke-diskonterede tal.

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

7. Diskussion

Behandling med encorafenib + cetuximab er forbundet med betydelige meromkostninger sammenlignet med behandling med FOLFIRI eller FOLFOX ± bevacizumab eller cetuximab. De inkrementelle omkostninger er i høj grad drevet af lægemiddelomkostningerne for encorafenib og cetuximab.

7.1 Usikkerheder

Fagudvalget vurderer, at data for komparator i BEACON-studiet, som er klinikers valg af kemoterapi (FOLFIRI + cetuximab eller IRI + cetuximab) kan bruges som proxy for effekten for FOLFIRI eller FOLFOX ± bevacizumab eller cetuximab. Dog er det usikkert, hvilken betydning bevacizumab og cetuximab har for den samlede effekt af FOLFIRI/FOLFOX-regimerne. I studiet fik patienterne i kontrolarmen cetuximab i kombination med FOLFIRI eller IRI, og det er uvist, om effekten ville have været anderledes, hvis patienterne havde modtaget bevacizumab i stedet for cetuximab. Fagudvalget vurderer, at det er muligt, at FOLFOX + bevacizumab er et bedre valg af behandling end irinotecan-holdig behandling suppleret med cetuximab, men størrelsesordenen er meget vanskelig at vurdere.

Da der er forskel på kontrolarmen i BEACON-studiet og komparatorerne i sekretariatets hovedanalyse, er det også usikkert om bivirkningsprofilen, der indgår i analysen er i overensstemmelse med det, der reelt ses i dansk klinisk praksis. Ifølge fagudvalget giver FOLFOX flere neurologiske bivirkninger end FOLFIRI, men da FOLFOX ikke indgik i BEACON-studiet, er disse bivirkninger ikke medregnet i analysen.

Da analysens resultat i høj grad er drevet af lægemiddelomkostningerne, har det en vis betydning, om spild medregnes, og om bevacizumab gives i kombination med FOLFIRI/FOLFOX eller ej.

Hospitalsomkostningerne udgør en væsentlig andel af de samlede omkostninger for både encorafenib + cetuximab-regimet og FOLFIRI/FOLFOX-regimerne. Fagudvalget vurderer, at man i dansk klinisk praksis potentielt vil give patienter cetuximab hver anden uge i stedet for hver uge, når det gives i kombination med encorafenib. Dog mangler der erfaring med behandlingen, og det vurderes derfor, at man indledningsvist vil følge SmPC'et. Antages det, at cetuximab gives hver anden uge i stedet for hver uge, når det gives i kombination med encorafenib, falder de inkrementelle omkostninger pr. patient med ca. [redacted] DKK. Det har minimal betydning, om terminalomkostninger er inkluderet i analysen.

Der er usikkerhed forbundet med antallet af patienter, der vil modtage behandling med encorafenib + cetuximab, hvis behandlingen anbefales. Fagudvalget vurderer, at det er sandsynligt, at flere patienter vil kunne tilbydes encorafenib + cetuximab, da denne kombination har en favorabel bivirkningsprofil sammenlignet med FOLFIRI og FOLFOX, men størrelsesordenen er svær at vurdere. Dermed er budgetkonsekvenserne sandsynligvis underestimeret. Da det kun er patienter, som kandiderer til behandling

med FOLFIRI eller FOLFOX, som indgår i analysen, er det ikke muligt at vurdere, i hvilket omfang budgetkonsekvenserne er underestimeret, hvis patienter med dårligere almentilstand også tilbydes encorafenib + cetuximab.

8. Referencer

1. Medicinrådets protokol for vurdering af encorafenib i kombination med cetuximab til patienter med metastatisk kolorektalkræft , der har BRAF V600E- mutation. :0–15.

2. Kopetz S, Grothey A, Yaeger R, Van Cutsem E, Desai J, Yoshino T, et al. Encorafenib, Binimetinib, and Cetuximab in BRAF V600E–Mutated Colorectal Cancer . N Engl J Med. 2019;381(17):1632–43.

3. Olsen J, Jensen KF, Olesen DS, Knoop A. Costs of subcutaneous and intravenous administration of trastuzumab for patients with HER2-positive breast cancer. J Comp Eff Res. 2018;7(5):411–9.

4. French EB, McCauley J, Aragon M, Bakx P, Chalkley M, Chen SH, et al. End-of-life medical spending in last twelve months of life is lower than previously reported. Health Aff. 2017;36(7):1211–7.

9. Bilag

9.1 Resultatet af ansøgers hovedanalyse

I ansøgers hovedanalyse bliver den inkrementelle omkostning pr. patient [redacted] DKK over en tidshorisont på 15 år. Resultaterne fra ansøgers hovedanalyse er præsenteret i Tabel 13.

Tabel 13: Resultatet af ansøgers hovedanalyse, DKK, diskonterede tal.

	Encorafenib + cetuximab	FOLFIRI + cetuximab	Inkrementelle omkostninger
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Hospitalsomkostninger	160.358	153.950	6.408
Bivirkningsomkostninger	1.287	2.441	-1.154
Patientomkostninger	10.267	10.401	-134
Efterfølgende behandling	4.000	5.431	-1.431
Totale omkostninger	[redacted]	[redacted]	[redacted]

9.2 Ansøgers budgetkonsekvensanalyse

Ansøger har inkluderet de samme omkostninger i budgetkonsekvensanalysen, som der er inkluderet i omkostningsanalysen. Med de ovenstående antagelser om patientantal og markedsandel, estimerer ansøger, at anvendelse af encorafenib + cetuximab vil resultere i budgetkonsekvenser på ca. [redacted] DKK i år 5.

Ansøgers estimat af budgetkonsekvenserne fremgår af Tabel 14.

Tabel 14: Ansøgers hovedanalyse for totale budgetkonsekvenser, mio. DKK, ikke-diskonterede tal.

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

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Forhandlingsnotat

Dato for behandling i Medicinrådet	27-01-2021
Leverandør	Pierre-Fabre
Lægemiddel	Encorafenib (Braftovi)
Ansøgt indikation	Encorafenib i kombination med cetuximab til behandling af voksne patienter med $BRAF^{V600E}$-pisitiv kolorektalkræft, som tidligere har modtaget behandling for deres sygdom.

Forhandlingsresultat

Amgros har følgende pris på encorafenib:

Lægemiddel	Styrke/dosis	Pakningsstørrelse	AIP	Tidligere SAIP	Forhandlet SAIP
Encorafenib	300 mg	42 stk.	11.960,00 kr.	[redacted]	[redacted]

Encorafenib er en del af et udbud på malignt melanom. Aftalen løber frem til d. 30.06.2021 med mulighed for 2*6 måneders forlængelse. Firmaet har mulighed for at byde ind med en ny pris i det næste udbud.

Vurdering af forhandlingsresultatet

Det er Amgros' vurdering at vi **har** den bedst mulige pris på encorafenib.

[redacted]

Konklusion

Der er ikke blevet foretaget nogen forhandling på dette lægemiddel, da det er med i et eksisterende udbud. [redacted].

Pierre Fabre

Stockholm 2020-12-04

Pierre Fabre Pharma Norden ABs comments to: ref# document 98718

The Medical Council assessment regarding encorafenib in combination with cetuximab in patients with metastatic colorectal cancer that has BRAFV600E mutation.

Pierre Fabre agree with the categorization of relative treatment effect as a large added benefit.
Encorafenib + cetuximab offers significant improvement in treatment effect to this patient population with severe prognosis and limited current treatment options available.

However, Pierre Fabre are surprised that the overall rating has been reduced to moderate added benefit based on uncertainty of median OS and 12 months survival as well as the representativeness of the control arm.

- With regards to the median and 12 months survival the effect difference, is as pointed out by Fagudvalget significant and clinically meaningful.
- Further, Fagudvalget points out that based on confirmation of results with the latest data cut the results are credible and unlikely to change in future data cuts.
  Pierre Fabre agrees with this assessment.

However, Pierre Fabre cannot see that these findings has been accounted for in Fagudvalget final assessment, where it is argued that there is still uncertainty due to censoring of the data.
As Fagudvalget, Pierre Fabre believes that the data has shown that current results are robust and shows a large added benefit throughout. Therefore, there would not be a rational for reducing the added benefit due to uncertainty in the data available.

For the representativeness of the trial data to current treatments in Denmark, Pierre Fabre would like to point out the following.

- First of all, Fagudvalget concludes in their report that the BEACON control arm is relevant for the Danish treatment situation and that they cannot point to a treatment arm that would have been more optimal for the decision.

Based on this, Pierre Fabre doesn't fully agree with that the conclusion around the control arm is that the effect could be overestimated and that this leads to a downgrading of the added benefit.

- Further, as pointed out by Fagudvalget, the control arm of the BEACON trail slightly overperforms compared to current treatments and they attribute this difference in survival to the trial patient population.

Pierre Fabre

Pierre Fabre acknowledge that the patient population could contribute to a difference. However, we would also like to point out that given the poor evidence available for alternative treatments in this population the difference could also be attributed to the control arm of the BEACON trial providing better treatment effect than current standard of care.

- If so, the treatment effect of the BEACON trial could potentially be underestimated rather than over estimated as argued by Fagudvalget.

Based on the above Pierre Fabre, one could argue that the overall assessment of OS benefit should be “large added benefit” and not downgraded to “moderate added benefit”. This as the results seen in the BEACON trial are robust and results in a large added benefit to this patient population.

As a concluding remark we would like to thank the DMC for a very transparent and professional attitude during the process.

Yours sincerely

Erik Arver

Pierre Fabre
Taking care, living better

Erik Arver
Market Access Director Nordics
Market Access
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Medicinrådet

Medicinrådets vurdering vedrørende encorafenib i kombination med cetuximab til patienter med metastatisk kolorektalkræft, der har $BRAF^{V600E}$-mutation

Version 1.0

Om Medicinrådet

Medicinrådet er et uafhængigt råd etableret af Danske Regioner.

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

Om vurderingsrapporten

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

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

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

Dokumentoplysninger	
Godkendelsesdato	9. december 2020
Dokumentnummer	100815
Versionsnummer	1.0

Indholdsfortegnelse

1. Medicinrådets konklusion

Medicinrådet vurderer, at encorafenib i kombination med cetuximab til metastatisk kolorektalkræft med $BRAF^{V600E}$-mutation giver en moderat merværdi sammenlignet med FOLFIRI eller IRI begge i kombination med cetuximab. Vurderingen er baseret på evidens af lav kvalitet.

Sprog: dansk
Format: pdf
Udgivet af Medicinrådet, 9. december 2020

MEDICINRÅDET KATEGORISERER LÆGEMIDLERS VÆRDI I EN AF FØLGENDE KATEGORIER:

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

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

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

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

2. Begreber og forkortelser

AE	*Adverse event*
BRAF:	*Proto-oncogene B-Raf*
BID:	Dosering to gange dagligt
CI:	Konfidensinterval
DCCG:	Dansk Colorektal Cancer Gruppe
dMMR:	Defekter i *mismatch repair*-systemet
ECOG:	*Eastern Cooperative Oncology Group*
EMA:	Det Europæiske Lægemiddelagentur (*European Medicines Agency)*
EPAR:	*European Public Assessment Report*
GRADE:	System til at vurdere evidens (*Grading of Recommendations, Assessment, Development and Evaluation*)
HR:	*Hazard ratio*
IRI	Irinotecan
ITT:	*Intention-to-treat*
IV:	Intravenøs
K-RAS:	*Kirsten Rat Sarcoma Viral Oncogene Homologue*
KRC:	Kolorektalkræft
MAPK:	*Mitogen-activated protein kinases*
mKRC:	Metastaseret kolorektalkræft
N-RAS	*Neuroblastoma RAS Viral Oncogene Homolog*
OR:	*Odds ratio*
ORR:	Objektiv respons rate
PICO:	Population, intervention, komparator og effektmål (*Population, Intervention, Comparator and Outcome)*
PP:	*Per-protocol*
PS:	*Performance status*
RCT:	Randomiseret kontrolleret studie *(Randomised Controlled Trial)*

RR:	Relativ risiko
SMD:	*Standardized Mean Difference*
QD:	Dosering en gang dagligt
QW:	Dosering en gang ugentligt
Q2W:	Dosering to gange ugentligt

3. Introduktion

Formålet med Medicinrådets vurdering af encorafenib i kombination med cetuximab til BRAF^{V600E}-positiv metastatisk kolorektalkræft er at vurdere den værdi, lægemidlet har sammenlignet med dansk standardbehandling. Vurderingen er udarbejdet, fordi Medicinrådet har modtaget en endelig ansøgning fra ansøger, Pierre-Fabre. Vi modtog ansøgningen den 15. oktober 2020

Det kliniske spørgsmål er:
Hvilken værdi har encorafenib i kombination med cetuximab sammenlignet med FOLFIRI ± bevacizumab eller EGFR-hæmmer eller FOLFOX ± bevacizumab eller EGFR-hæmmer for *patienter med metastatisk kolorektalkræft, som har BRAF^{V600E}-mutation?*

3.1 Kolorektalkræft

Kræft i tyk- og endetarmen (kolorektalkræft herefter forkortet KRC) er en af de hyppigste kræftsygdomme i Danmark. I 2018 blev i alt 4433 patienter diagnosticeret med KRC, størstedelen med tyktarmskræft. Hyppigheden af KRC stiger med alderen. KRC diagnosticeres sjældent før 40-års alderen, og de fleste tilfælde diagnosticeres først efter 60 års-alderen [1]. Siden 2014 er alle i aldersgruppen 50-74 år i Danmark blevet tilbudt screening for KRC [2]. Femårsoverlevelsen for endetarmskræft er hhv. 66 og 69 % for mænd og kvinder, mens den for tyktarmskræft er hhv. 63 og 65 % [3,4]. Årsagen til sygdommen er ofte ukendt.

Symptomerne ved KRC manifesterer sig hyppigt ved ændringer i afføringsmønsteret, herunder slim og blod i afføringen, anæmi samt uforklarlige almene symptomer heriblandt vægttab, mavesmerter og svækkelse. De uspecifikke og sene symptomer medfører, at patienter først sent i sygdomsudviklingen opsøger læge. Som konsekvens heraf har omkring 20-30 % af patienterne allerede metastatisk KRC (mKRC) ved diagnosetidspunktet, og yderligere 20 % udvikler mKRC inden for fem år [5]. Overlevelsen for patienter med metastatisk sygdom er forbedret i takt med introduktionen af nye målrettede behandlingsformer og mere aggressiv metastasekirurgi [6].

Identifikation af prognostiske og prædiktive mutationer anvendes med henblik på at planlægge og målrette behandlingen. Derfor undersøges tumorvævet for mutationer i *epidermal growth factor receptor* (EGFR)-signaleringsvejen (K-RAS, BRAF og N-RAS-mutationer) og for defekter i *mismatch repair*-systemet (dMMR). Patienter med BRAF-mutationer har den dårligste prognose med en median overlevelse på 4-6 måneder efter førstelinjebehandling [6–8].

BRAF er en proteinkinase, som er involveret i MAPK-signaleringskaskaden (*mitogen-activated protein kinase*), som driver celledeling. Næsten alle BRAF-mutationer er af typen BRAF^{V600E} (herefter omtalt BRAF-mutationer), som overaktiverer BRAF, hvilket resulterer i, at maligne celler deler sig hastigt, og tumor vokser sig større med mulig spredning [9]. Ca. 10 % af patienter med mKRC har BRAF-mutationer [7].

De senere år har der været tiltagende akkumuleret evidens for, at også tumors placering i tarmen (højre side versus venstre side) kan have en prognostisk og prædiktiv betydning, og at højre- og venstresidige tumorer adskiller sig på en række væsentlige punkter med hensyn til patogenese, patologi, mutationsstatus, mikrosattelit instabilitet m.m. Denne viden er dog kun gradvist begyndt at få indflydelse på design af studier og på den kliniske behandling af patienter med KRC [10].

3.2 Nuværende behandling

Behandlingen for mKRC med BRAF-mutationer følger retningslinjer fra Dansk Colorektal Cancer Gruppe (DCCG) [11]. Målet med behandlingen afhænger af udbredelsen af primær tumor og metastaser, samt lokation af den primære tumor og dermed hvorvidt det vurderes muligt at opnå kirurgisk fjernelse.

De mulige behandlinger i første- og andenlinje består overordnet set af de samme lægemidler. Behandlingsrækkefølgen tilrettelægges efter den enkelte patients behov, ønsker og sygdomskarakteristika. Nedenfor gennemgås samtlige linjer for mKRC.

Førstelinjebehandling
For alle patienter, hvor kirurgi ikke er mulig initielt, består førstelinjebehandlingen af kemoterapi. Formålet med behandlingen er at forlænge patienternes liv og lindre eventuelle sygdomssymptomer.

Valg af førstelinje kemoterapi til patienter med BRAF-muteret mKRC er en individuel vurdering. Dette skyldes, at hidtidige studier af førstelinjebehandling, samt øvrige linjer til patienter med mKRC, ikke er selekteret på baggrund af BRAF-mutationsstatus. Evidens for behandling af patienter med BRAF-muterede tumorer bygger derfor på subgruppeanalyser, hvor antallet af patienter med BRAF-mutationer ofte er meget beskedent.

Førstelinjebehandling er en af følgende kemoterapi-kombinationer:

- To-stof kemoterapi i form af **FOLFIRI** (folinsyre, fluorouracil (5-FU), irinotecan) *eller* **FOLFOX** (folinsyre, 5-FU, oxaliplatin).
- Triple kemoterapi i form af FOLFOXIRI (folinsyre, 5-FU, oxaliplatin og ironotecan).
- Capecitabine i kombination med bevacizumab eller capecitabine i kombination med oxaliplatin (CAPEOX).

FOLFIRI samt FOLFOX anses som ligeværdige behandlingsalternativer, hvad angår deres effekt. I Danmark er der praksis for at tilbyde størstedelen af patienterne FOLFIRI i førstelinje, da oxaliplatin i FOLFOX er kendetegnet ved neurologiske bivirkninger, der kan være irreversible, i fx USA er praksis dog at starte med FOLFOX. Effekten af behandling vurderes hver 2. til 3. måned med CT-scanninger. Ophør af behandling skyldes typisk progression af sygdom, eller at patienten får intolerable bivirkninger af behandlingen. Der findes derfor ikke en fast behandlingslængde.

Behandling med FOLFOXIRI anses som en mere aggressiv men samtidig også mere bivirkningsfuld. Behandlingen tilbydes kun til en mindre gruppe patienter, der har særlig god almen tilstand. Typisk er det yngre patienter, der har symptomgivende sygdom, og/eller som vurderes at have en tumor, som potentielt kan blive resektabel. Formålet med behandlingen er således tumorreduktion, enten for at gøre tumor resektabel eller for at opnå symptomlindring.

Capecitabine i kombination med bevacizumab er en mindre aggressiv behandling, som bl.a. benyttes til patienter, der ikke kan tåle flerstofs kemoterapi-kombinationer. Derfor bruges det i mindre grad end de øvrige muligheder.

Targeteret antistofbehandling

FOLFIRI, FOLFOX og FOLFOXIRI kan gives i kombination med targeteret antistofbehandling. Targeteret antistofbehandling kan enten være en EGFR-hæmmer (cetuximab eller panitumumab) eller angiogenesehæmmeren bevacizumab. EGFR-hæmmere har kun effekt, hvis patientens tumor er K- og N-RAS-wildtype. Da RAS mutation meget sjældent forekommer sammen med BRAF-mutation, har det været praksis at behandle patienter med BRAF-mutation som værende K- og N-RAS-wildtype, dvs. at behandling med EGFR-hæmmere derfor benyttes til denne patientgruppe. I flere posthoc-analyser af randomiserede fase-III-studier har man forsøgt at bestemme den prædiktive værdi af BRAF-mutation i forhold til effekt af behandling med EGFR-hæmmer. Resultatet af disse studier har ikke kunnet opnå statistisk signifikans til at afklare dette spørgsmål. Endvidere har man i to metaanalyser forsøgt at belyse dette men med modstridende konklusioner [12–14]. Det er derfor fortsat usikkert, om BRAF-mutationer er en prædiktiv markør for effekt af behandling med EGFR-hæmmer. Der er ingen kendt prædiktiv biomarkør for effekt af behandling med bevacizumab.

Der foretages en individuel vurdering af, hvorvidt der skal tillægges targeteret antistofbehandling. For BRAF-muterede patienter er det kun en mindre andel, hvor targeteret behandling anvendes i førstelinje. Det er oftest patienter, hvor det vurderes, at tumor kan gøres resektabel. Typen af antistofbehandling afhænger af lokalisation af tumor; EGFR-hæmmere anvendes oftest ved venstresidige tumorer uden RAS-mutationer og bevacizumab oftest ved højresidige tumorer, da der ses differentieret respons [15].

Andenlinjebehandling

Ved progression under eller efter endt førstelinjebehandling tilbydes patienterne andenlinjebehandling, hvis patienternes performance status og almentilstand tillader det. Således anslås det, at ca. 50 % af patienter, der gennemgår førstelinjebehandling vil være i stand til at starte andenlinjebehandling. Andenlinjebehandling afhænger af, hvad patienten fik som førstelinjebehandling. Er der givet FOLFIRI i førstelinje, tilbydes der efterfølgende FOLFOX i andenlinje og omvendt. Da FOLFIRI oftest benyttes i førstelinje, vurderer fagudvalget, at størstedelen af patienter i dansk klinisk praksis modtager FOLFOX i andenlinje.

I andenlinjebehandling kan targeteret antistofbehandling anvendes, hvis det ikke blev givet i førstelinjebehandling.

Som anført er der ingen klar international konsensus vedrørende behandling med EGFR-hæmmere til patienter med BRAF-muterede mKRC. Fagudvalget vurderer, at der er en større del af patienter, der modtager bevacizumab i tillæg til kemoterapi som andenlinjebehandling, men behandling med EGFR-hæmmer kan også anvendes.

Eksempler på dansk praksis i første- og andenlinjebehandling af patienter med BRAFmut-tumorer:

- Hvis en patient med BRAFmuteret tumor modtager FOLFOXIRI + bevacizumab i førstelinje, og patienten har almen tilstand til yderligere behandling, vil irinotecan-holdig behandling med EGFR-hæmmer være en mulighed i andenlinjebehandling.
- Hvis en tilsvarende patient har modtaget FOLFIRI i førstelinje vil behandling med FOLFOX + bevacizumab være en mulighed som andenlinjebehandling.
- Hvis en tilsvarende patient har modtaget capecitabine + bevacizumab i førstelinje vil FOLFOX + bevacizumab eller FOLFIRI + EGFR-hæmmer være muligheder som andenlinjebehandling

Tredjelinjebehandling
Der er relativt få patienter, som har så god almenstatus, at de kan modtage tredjelinjebehandling, og der er derfor ikke nogen veletableret tredjelinjebehandling af BRAF-muterede mKRC-patienter. Eneste mulighed vil, som udgangspunkt, være eksperimentel behandling. Hvis patienterne ikke er progredieret under et tidligere behandlingsregime, kan behandling i få tilfælde reinduceres, hvis bivirkningerne tillader det, og patienten ud fra en helhedsbetragtning vurderes som egnet.

3.3 Encorafenib

Encorafenib er af Det Europæiske Lægemiddelagentur (*European Medicines Agency,* EMA) godkendt i kombination med cetuximab. Behandlingen har indikation til voksne patienter med mKRC, der udtrykker $BRAF^{V600E}$-mutation.

Encorafenib er en potent BRAF-kinasehæmmer, som hæmmer MAPK-signaleringsvejen i tumorceller, der udtrykker $BRAF^{V600E}$-mutationer, hvorved tumorvækst hæmmes.

Encorafenib gives i kombination med EGFR-hæmmeren cetuximab (herefter encorafenib + cetuximab), da monoterapi med en BRAF-hæmmer i KRC medfører aktivering af en feedback-mekanisme, som leder til aktivering af EGFR, hvilket bevirker at der ingen effekt ses af behandlingen. Kombinationsbehandlingen sikrer at dette ikke sker. Encorafenib + cetuximab har indikation til patienter, der tidligere har modtaget første- eller andenlinjebehandling jf. afsnit 3.2. Encorafenib + cetuximab kan dermed anvendes som anden- og tredjelinjebehandling og udgør en ny virkningsmekanisme.

Encorafenib er formuleret som kapsler. Den anbefalede dosis af encorafenib er fire kapsler af 75 mg (300 mg) én gang dagligt. Encorafenib skal administreres i kombination med cetuximab, som gives i forhold til gældende produktresumé (intravenøst (IV) én gang ugentlig, initialdosis 400 mg/m2, efterfølgende doser er 250 mg/m2).

Behandling bør fortsættes indtil progression, eller indtil patienten udvikler uacceptable bivirkninger/toksicitet.

Encorafenib + cetuximab er af EMA allerede godkendt til behandling af ikke-resektabel og/eller metastatisk modermærkekræft.

Fagudvalget forventer, at såfremt encorafenib + cetuximab anbefales, vil det primært få plads i andenlinjebehandling. Det forventes dog, at behandlingen i det første år både vil blive tilbudt patienter i anden- og tredjelinje indtil behandlingen er indfaset.

Fagudvalget skønner, at ca. 110 patienter med $BRAF^{V600E}$-muteret mKRC årligt vil være kandidater til encorafenib + cetuximab i anden linje. Dette er baseret på følgende estimater; 4433 diagnosticeret med KRC om året, 50 % af dem vil udvikle mKRC (ca. 2217 patienter), og 10 % af disse har $BRAF^{v600E}$ (ca. 221 patienter). Der forventes et stort frafald fra første til anden linje, derfor er det sandsynligt, at ca. 50 % kan tilbydes andenlinjebehandling (ca. 110 patienter).

Fagudvalget gør opmærksom på, at flere immunterapi-behandlinger er under godkendelse i EMA til en subgruppe af patienterne med mKRC, som har dMMR. Disse udgør ca. 30 % af de 110 patienter, som forventes at være kandidater til encorafenib + cetuximab. Immunterapi forventes at blive indplaceret som behandlingsmulighed i anden linje, og derfor kan der forventes et frafald af kandidater til encorafenib + cetuximab, hvis disse immunterapier godkendes.

4. Metode

Medicinrådets protokol for vurdering af encorafenib i kombination med cetuximab beskriver sammen med Håndbog for Medicinrådets proces og metode vedr. nye lægemidler og indikationsudvidelser, hvordan vi vil vurdere lægemidlets værdi for patienterne.

Det kliniske spørgsmål er:
Hvilken værdi har encorafenib i kombination med cetuximab sammenlignet med FOLFIRI ± bevacizumab eller EGFR-hæmmer eller FOLFOX ± bevacizumab eller EGFR-hæmmer for patienter med metastatisk kolorektalkræft, som har $BRAF^{v600E}$-mutation?

Population
Patienter med mKRC, der har $BRAF^{v600E}$-mutation, og som tidligere har modtaget systemisk terapi i form af kemoterapi i første- og/eller andenlinjebehandling, jf. afsnit 3.2.

Intervention
300 mg oralt administreret encorafenib én gang dagligt i kombination med intravenøst cetuximab én gang ugentligt, initialdosis 400 mg/m2, efterfølgende doser er 250 mg/m2.

Komparator

- FOLFOX (folinsyre, 5-FU, oxaliplatin) ± bevacizumab eller EGFR-hæmmer.
- FOLFIRI (folinsyre, 5-FU, irinotecan) ± bevacizumab eller EGFR-hæmmer.

Andenlinje kemoterapi afhænger af, hvad patienten fik som førstelinjebehandling. Er der givet FOLFIRI i førstelinje, tilbydes der efterfølgende FOLFOX i andenlinje og omvendt. I protokollen var det derfor specificeret, at ansøger blot skulle belyse én af de to komparatorer i deres kliniske ansøgning, eftersom de anses som klinisk ligestillede. I den sundhedsøkonomiske analyse er der forskellige omkostninger forbundet med FOLFOX og FOLFIRI. Derfor belyses de separat i den sundhedsøkonomiske analyse.

Effektmål
Se Tabel 1.

Tabel 1. Effektmålstabel, som angivet i protokollen

Effektmål	Vigtighed	Effektmålsgruppe	Måleenhed	Mindste klinisk relevante forskel
Overlevelse (OS)	Kritisk	Dødelighed/ overlevelse	Median OS	3 måneder
			Andel, som er i live efter 12 måneder	5 %-point
Livskvalitet	Vigtig	Livskvalitet, alvorlige symptomer og bivirkninger	Forskel i gennemsnitlig ændring fra baseline i EORTC-QLQ-C30	10 point
Bivirkninger	Vigtig	Livskvalitet, alvorlige symptomer og bivirkninger	Andel af patienter, der får én eller flere grad 3-4 uønskede hændelser	5 %-point
			Kvalitativ gennemgang af uønskede hændelser	-

For alle effektmål har fagudvalget bedt om data med længst mulig opfølgningstid, med mindre andet er angivet.

5. Resultater

5.1 Klinisk spørgsmål 1

5.1.1 Litteratur

Nedenfor beskriver og vurderer vi den litteratur, som ansøger har anvendt i sin endelige ansøgning. Til besvarelse af det kliniske spørgsmål baserer ansøgningen sig på ét fase-III-studie, der også var angivet i protokollen:

- Kopetz et al. 2019 (BEACON CRC); Encorafanib, Binimetinib and Cetuximab in BRAF V600E-mutated Colorectal Cancer; N Engl. J Med. [16]

BEACON-studiet indeholder en direkte sammenligning mellem intervention og komparator for effektmålene *samlet overlevelse (OS) og bivirkninger*. Fagudvalget efterspurgte i protokollen også data for livskvalitet og opfølgende data på overlevelse. Ansøger har for disse effektmål indsendt *data on file* for at besvare det kliniske spørgsmål. Fagudvalget vil vurdere relevansen af de upublicerede data, jf. Medicinrådets kriteriepapir vedrørende upublicerede data [17].

Studiekarakteristika
BEACON-studiet [16] er et randomiseret, ublindet, fase-III-studie, som undersøgte effekt og sikkerhed af encorafenib i kombination med cetuximab eller encorafenib i kombination med både cetuximab og binimetinib hos patienter med $BRAF^{V600E}$-muteret mKRC, hvis sygdom har progredieret efter én eller to tidligere behandlinger. Studiet undersøgte, hvorvidt behandlingen kunne øge overlevelsen sammenlignet med FOLFIRI eller irinotecan (IRI), begge i kombination med cetuximab.

Patienter blev inkluderet fra 221 klinikker i 28 lande, hvoraf 111 af klinikkerne lå i Europa. Studiet inkluderede patienter ≥ 18 år, med $BRAF^{V600E}$-muteret mKRC, som havde progredieret på enten førstelinje eller andenlinjebehandling, og som havde en *European Cancer Oncogenic Group* (ECOG) *performancestatus* (PS) på 0-1.
I studiet blev 665 patienter randomiseret i en ratio 1:1:1 til en af følgende arme:

- Encorafenib 300 mg én gang dagligt (QD) + cetuximab IV én gang om ugen (QW) (N = 220)
- Encorafenib 300 mg QD + binimetinib 45 mg to gange dagligt (BID) + cetuximab IV QW (N = 224)
- Klinikers valg af kemoterapi (N=221)
    - IRI IV hver 2. uge (Q2W) + cetuximab IV QW, eller
    - FOLFIRI (folinsyre IV Q2W + 5-FU Q2W + IRI IC Q2W) + cetuximab IV QW

Ingen overkrydsning var tilladt mellem armene.

Hvert center skulle forud for randomiseringen oplyse, hvilken kemoterapi man ville behandle med. Randomiseringen var stratificeret i forhold til følgende faktorer: ECOG PS, tidligere behandling med IRI, hvorvidt cetuximab blev givet jf. amerikansk eller EMA's indikation, og om patienterne stod til at skulle modtage hhv. anden- eller tredjelinjebehandling.

De primære endepunkter i studiet inkluderede OS og objektiv respons rate (ORR) for encorafenib + binimetinib + cetuximab-armen. Sekundære endepunkter inkluderede OS for encorafenib + cetuximab-armen samt ORR, progressionsfri overlevelse (PFS), *duration of respons* (DOR), *time to response* (TRR), hvor de to interventionsarme blev sammenlignet med komparator, og indbyrdes. Derudover blev der også foretaget analyser af bivirkninger og livskvalitet. Analyse af bivirkninger blev foretaget baseret på en *safety* populationen, som inkluderede alle patienter, der havde modtaget mindst én behandlingsdosis i enten interventions- eller kontrolarmen, og som var blevet evalueret mindst én gang efter behandling.

Baseline karakteristika

Tabel 2 lister baselinekarakteristika for populationen i BEACON-studiet. I studiet indgår en interventions-arm med triplet-regimet, encorafenib + binimetinib + cetuximab. Resultatet fra denne arm vil ikke indgå i fagudvalgets vurdering, da der ikke er ansøgt om godkendelse af denne kombination i EMA.

Tabel 2. Baseline karakteristika fra BEACON-studiet

	Encorafenib + cetuximab (n = 220)	Kontrol (n = 221)
Køn, n (%)		
Mænd	115 (52,3)	94 (42,5)
Kvinder	105 (47,7)	127 (57,5)
Alder (år)		
Mean (SD)	60.2 (11,7)	58.4 (12,1)
Median	61	60
Min, max	30, 91	27, 91
Etnicitet, n (%)		
Asiatisk	25 (11,4)	39 (17,6)
Kaukasisk	183 (83,2)	172 (77,8)
Sorte/afroamerikaner	0 (0,0)	0 (0,0)
Andre	3 (1,4)	3 (1,4)
Ikke rapporteret som følge af konfidentielle årsager	8 (3,6)	7 (3,2)
ECOG PS ved baseline, n (%)		
0	112 (50,9)	108 (48,9)
1	104 (47,3)	113 (51,1)
2	4 (1,8)	0 (0,0)
Antal tidligere systemiske regimer for metastatisk, n (%)		

1	146 (66,4)	145 (65,6)
2	74 (33,6)	75 (33,9)
> 2	0 (0,0)	1 (0,5)
Tidligere IRI	114 (51,8)	117 (52,9)
Tidligere oxaliplatin	210 (95,5)	201 (91,0)
Primær tumor lokation, n (%)		
Ventre colon, inklusiv rectum	83 (37,7)	68 (30,8)
Højre colon	110 (50,0)	119 (53,8)
Ventre og højre colon	11 (5,0)	22 (10,0)
Ukendt	16 (7,3)	12 (5,4)
Primær tumor fjernet, n (%)		
Fuldstænding resekteret	123 (55,9)	122 (55,2)
Delvist resekteret/ikke resekteret	97 (44,1)	99 (44,8)
Antal organer involveret		
Gennemsnit (SD)	3 (1,4)	3 (1,3)
Median	2	2
Min, max	0, 7	1, 8
Antal organer involveret, n (%)		
≤ 2	117 (53,2)	123 (55,7)
≥ 3	103 (46,8)	98 (44,3)
Lokation af metastase, n (%)		
Lever	134 (60,9)	128 (57,9)
Lunge	83 (37,7)	86 (38,9)
Lymfeknuder	82 (37,3)	88 (39,8)
Peritoneum/omentum	97 (44,1)	93 (42,1)
Microsatellite instability status (polymerase chain reaction), n (%)		
Abnormal høj	19 (8,6)	12 (5,4)
Abnormal lav	1 (0,5)	1 (0,5)
Normal	157 (71,4)	147 (66,5)
Ikke evaluerbar	16 (7,3)	10 (4,5)
Manglende data	27 (12,3)	51 (23,1)
Carcinoembryonisk antigen (CEA) ved baseline, n (%)		
> 5 µg/L	153 (69,5)	178 (80,5)
≤ 5 µg/L	67 (30,5)	42 (19,0)
Manglende data	0 (0,0)	1 (0,5)

Forkortelser: CEA = Carcinoembryonisk antigen; ECOG = European Cancer Oncogenic Group; IRI = irinotecan; PS = performance status; SD = standard deviation.

Fagudvalget har sammenlignet baselinekarakteristika fra studiepopulationen med den forventede danske patientpopulation. Fagudvalget noterer, at mange af patienterne i studiet har PS 0, hvilket er bedre, end der kan forventes i dansk klinisk praksis. Dertil modtager ca. 1/3 af patienterne tredjelinjebehandling i studiet, hvilket er flere, end fagudvalget forventer i dansk klinisk praksis. Fagudvalget vurderer, at dette indikerer, at patienterne overordnet set har haft en god prognose fra start, i og med at de kan håndtere så mange behandlingslinjer. Selvom der er flere patienter med venstresidige tumorer i encorafenib + cetuximab-armen, noterer fagudvalget, at der i begge arme er omkring 50 % af patienterne, som har primær tumorlokalisation i højre side af tarmen, hvilket er det mest almindelige ved BRAF-muterede tumorer og tilsvarende danske patienter. Højresidige tumorer opdages oftest senere end venstresidige tumorer, og derfor kan disse patienters sygdom være mere fremskreden. Fagudvalget noterer, at patienterne i studiet er yngre end den gennemsnitlige danske KRC-patient. Dog ses det, at patienter med BRAF-muterede tumorer er yngre end den samlede population af mKRC [8], hvilket, fagudvalget mener, stemmer godt overens med patienterne i dansk klinisk praksis. Fagudvalget finder ikke, at der er betydende forskelle mellem populationerne i behandlingsarmene.

Kontrolarmen modtager potentielt samme regime kemoterapi i anden-/tredjelinjebehandling som i første-/andenlinjebehandling
Jf. tabel 2, havde 65,6 % af patienterne i studiets kontrolarm tidligere modtaget én systemisk behandling og skulle dermed modtage andenlinjebehandling. 33,9 % havde modtaget to tidligere systemiske behandlinger og skulle derfor modtage tredjelinjebehandling. Tabel 2 angiver desuden, at 52,2 % i kontrolarmen tidligere havde modtaget IRI. Fagudvalget er opmærksomme på, at patienter, som indgik i studiets kontrolarm forud for studiet, kunne have modtaget en irinotecan-holdig behandling i enten første- eller andenlinjebehandling. Dette kan teoretisk forringe effektresultaterne i kontrolarmen og deraf overestimere effektforskellene mellem armene. Det er dog normal praksis at give irinotecan-holdig behandling sammen med EGFR-hæmmer trods tidligere progression på irinotecan-holdigt regime. Det skyldes at chancen for respons forøges væsentligt sammenlignet med cetuximab monoterapi [18].

Sammenligning af kontrolarmen i studiet med dansk klinisk praksis
I studiet modtager patienterne i kontrolarmen FOLFIRI eller IRI i kombination med cetuximab.

I dansk klinisk praksis anvendes oftere FOLFIRI i førstelinje og dermed FOLFOX i anden linje, selvom de to behandlinger er vurderet som klinisk ligestillet. Fagudvalget forventer ikke, at det ville have haft nogen betydning for studiets resultater, hvis FOLFOX blev anvendt i førstelinje i stedet for FOLFIRI.

I studiet kan investigator vælge mellem IRI og FOLFIRI i kontrolarmen. Der foreligger ikke studier, der viser differentieret respons mellem IRI og FOLFIRI [19], og fagudvalget vurderer derfor, at de to behandlinger er klinisk ligeværdige.

Det er lidt vanskeligere at drage paralleller til dansk klinisk praksis i forhold til targeteret behandling. Argumentet for at tillægge cetuximab (som man gør i kontrolarmen i

BEACON-studiet, men sjældent i dansk klinisk praksis) er en viden om, at BRAF-mutation udelukker K- og N-RAS-mutation og omvendt, og at EGFR-hæmmere har effekt for patienter som er RAS-wildtype. I Danmark er man mere tilbageholdende med at anvende EGFR-hæmmere i førstelinje i kombination med kemoterapi til BRAF-muteret sygdom. Det skyldes bl.a. stigende opmærksomhed på tumors placering i forhold til en række parametre for prognose og prædiktivitet, hvor BRAF-mutationer overvejende ses i højresidige tumorer, og hvor EGFR-hæmmere synes at have bedre effekt i venstresidige tumorer. Derfor er det i dansk klinisk praksis vurderet, at behandling med FOLFOX + bevacizumab er en relevant andenlinjebehandling til disse patienter.

Fagudvalget finder det vanskeligt med stor sikkerhed at vurdere, om der er væsentlige forskelle i effekten af andenlinjebehandling med enten FOLFOX + bevacizumab eller irinotecan-holdig behandling med tillæg af EGFR-hæmmere til patienter med BRAF-muterede tumorer.

På baggrund af de beskrevne usikkerheder, vurderer fagudvalget, at BEACON-studiets kontrolarm er relevant.

Det er muligt, at FOLFOX + bevacizumab er et bedre valg af behandling end irinotecan-holdig behandling suppleret med EGFR-hæmmere, men det er meget vanskeligt at vurdere, hvor stor forskellen er.

Fagudvalget anerkender de forskelle, der kan være mellem studiet og dansk klinisk praksis, som potentielt kan betyde, at effektforskelen mellem interventions- og kontrolarmen overestimeres. Fagudvalget understreger, at da dette er det første studie, der undersøger effekten af et lægemiddel i en population udelukkende bestående af BRAF-muterede patienter, er det svært at sammenligne med resultater fra tidligere studier samt effekten af nuværende behandling i dansk klinisk praksis. Eftersom der ikke findes en etableret international konsensus vedrørende anden- og tredjelinjebehandling for patienter med BRAF-mutation, og da der er flere muligheder for førstelinjebehandling afhængig af bl.a. den enkelte patients sygdomskarakteristika og målet med behandling og patientens præferencer, så mener fagudvalget, at det er vanskeligt at pege på en mere optimal kontrolarm.

5.1.2 Databehandling og analyse

Nedenfor beskriver vi ansøgers datagrundlag, databehandling og analyse for hvert effektmål. Ansøger har indsendt data fra BEACON-studiet, som indeholder en direkte sammenligning mellem intervention og komparator, hvilket er i overensstemmelse med protokollen. I den endelige ansøgning præsenterer ansøger data fra BEACON-studiet fra tre forskellige analysetidspunkter.

Den første analyse af BEACON-studiet blev foretaget i februar 2019 (præspecificeret interimanalyse) med 7,8 måneders median opfølgningstid [16]. Her er der data for OS og bivirkninger, som efterspurgt i protokollen. Derudover indeholder analysen også publicerede livskvalitetsdata [20], dog opgjort anderledes end efterspurgt i protokollen.

Fagudvalget vil benytte data for effektmålene livskvalitet og bivirkninger fra dette analysetidspunkt.

Den anden analyse af BEACON-studiet blev foretaget i august 2019 med 12,8 måneders median opfølgningstid. Analysen er også prædefineret. Data for median OS fra denne analyse indgår i *European Public Assessment Report* (EPAR) [20]. Overlevelsesraten ved 12 måneder forventes publiceret i januar 2021 og vil derfor indgå i kategoriseringen af encorafenib + cetuximab. Data vedrørende livskvalitet og bivirkninger indgår som *data on file*, der er konfidentielt. Jf. Medicinrådets kriteriepapir, skal data kunne publiceres minimum 12 måneder efter vurderingsrapportens offentliggørelse. Da ansøger ikke har kunnet bekræfte, at dette kan lade sig gøre for livskvalitetsdata og bivirkninger, kan fagudvalget ikke benytte disse data i vurderingen. Fagudvalget vil således kun anvende overlevelsesdata[1] fra dette opfølgningstidspunkt.

Den tredje analyse af BEACON-studiet blev foretaget i maj 2020 med ca. 21 måneders median opfølgningstid. Det er en post-hoc overlevelsesanalyse, som ikke er præspecificeret. OS-data fra dette opfølgningstidspunkt indgår som *data on file*, der er konfidentielt. Fagudvalget kan derfor ikke benytte data fra denne opfølgning i forbindelse med kategorisering af OS men benytter data som supplerende information.

Data for livskvalitet, opgjort i overensstemmelse med Medicinrådets protokol, er på nuværende tidspunkt fortroligt og indgår derfor ikke i kategoriseringen. Ansøger har i deres ansøgning suppleret med publiceret data på EORTC QLQ-C30 fra BEACON-studiet, opgjort som tid til 10 % forringelse i livskvalitet for hhv. encorafenib + cetuximab-armen og for kontrolarmen. Data stammer fra analysetidspunktet i februar 2019. Fagudvalget vurderer, at dette data kan benyttes kvalitativt i vurderingen af livskvalitet.

Ansøger har præsenteret data for bivirkninger fra BEACON-studiet baseret på en *safety* populationen (n = 409 patienter, heraf n = 216 i encorafenib + cetuximab-armen og n = 193 i kontrolarmen).

Fagudvalget vurderer, at det indsendte datagrundlag er tilstrækkeligt til at vurdere det kliniske spørgsmål, der er opstillet i Medicinrådets protokol.

5.1.3 Evidensens kvalitet

Fagudvalget har anvendt GRADE til at foretage en systematisk og transparent vurdering af kvaliteten af evidensen. Nedenfor følger en beskrivelse af vurderingen af de væsentligste domæner for hvert klinisk spørgsmål. Den fuldstændige GRADE-vurdering og begrundelserne er samlet i en GRADE-profil (bilag 1).

Der er nedgraderet for inkonsistens, da der kun foreligger et sammenlignende studie. For livskvalitet er der yderligere nedgraderet for indirekthed, da data var opgjort på en

[1] Data fra andelen, der er i live efter 12 måneder, er ikke publiceret for dette analysetidspunkt. Ansøger forventer denne data publiceret i januar 2021, og det forventes derfor at kunne inddrages i kategoriseringen.

anden måde end efterspurgt i protokollen. Derudover er der for dette effektmål også nedgraderet for risk of bias, eftersom studiet var ublindet, hvilket kan have haft en indflydelse på patienternes besvarelse af livskvalitetsspørgeskemaet.
For effektmålet samlet overlevelse, er der nedgraderet for indirekthed, da komparator-armen i studiet er forskellige fra dansk klinisk praksis, hvilket kan påvirke effektestimaterne.

Fagudvalget er opmærksomme på, hvilke usikkerheder et ublindet design medfører, men vurderer, at det vil være vanskeligt med et blindet design til denne behandling. Dels fordi det ville kræve, at alle patienter fik anlagt et centralt venekateter med dertilhørende risiko for blødning, pneumothorax, thrombedannelse og infektioner og dels ville det kræve en meget høj administrationsfrekvens for patienterne.

Fagudvalget vægter højt, at BEACON-studiet er det første studie, hvor den samlede population er patienter med BRAF-muterede tumorer. Det er derfor et særdeles væsentligt studie i forhold til tidligere studier, der næsten udelukkende baserer sig på subgruppeanalyser i uselekterede patientpopulationer. Det er desuden det første studie på mKRC-patienter, hvor man behandler targeteret i forhold til denne BRAF-mutation.

Evidensens kvalitet er lav, hvilket betyder, at nye studier med moderat sandsynlighed kan ændre konklusionen.

5.1.4 Effektestimater og kategorier

I tabel 3 herunder fremgår de absolutte og relative effektforskelle, de foreløbige og aggregerede kategorier, den samlede kategori og den samlede kvalitet af evidensen for det kliniske spørgsmål.

Tabel 3. Resultater for klinisk spørgsmål 1

Effektmål	Målenhed (MKRF)	Vigtighed	Forskel i absolutte tal		Forskel i relative tal		Aggregeret værdi for effektmålet
			Forskel (95 % CI)	Foreløbig værdi	Forskel (95 % CI)	Foreløbig værdi	
Overlevelse (OS)	Median OS (MKRF: 3 mdr.)	Kritisk	3,4 mdr.^	Kan ikke kategoriseres	HR: 0,61 [0,48; 0,77]	Stor merværdi	Moderat merværdi
	Andel, som er i live efter 12 måneder (MKRF: 5 %-point)		16,7 %-point^*	Kan ikke kategoriseres			
Livskvalitet	Forskel i gennemsnitlig ændring fra baseline i EORTC-QLQ-C30 (MKRF: 10 point)	Vigtig	Ingen data	Kan ikke kategoriseres	Ingen data	Kan ikke kategoriseres	Kan ikke kategoriseres
Bivirkninger	Andel af patienter, der får én eller flere grad 3-4 uønskede hændelser (MKRF: 5 %-point)	Vigtig	-11 %-point [-21; -1 %]†	Ingen dokumenteret merværdi	RR: 0,82 [0,69; 0,98]	Merværdi af ukendt størrelse	Merværdi af ukendt størrelse
	Kvalitativ gennemgang af uønskede hændelser		IR, se side 21 for gennemgang af bivirkningsprofil				
Konklusion							
Samlet kategori for lægemidlets værdi	Moderat merværdi						
Kvalitet af den samlede evidens	Lav						

*CI = konfidensinterval, HR = Hazard Ratio, MKRF = mindste klinisk relevante forskel, IR = ikke relevant, mdr. = måneder, OR = Odds Ratio, RR = relativ risiko. *Data stammer fra data on file. Ansøger forventer denne data bedømt i et fagfællebedømt tidsskrift januar 2021. ^Data stammer fra analysetidspunktet den 15. august 2019. †Data stammer fra analysetidspunktet den 11. februar 2019.*

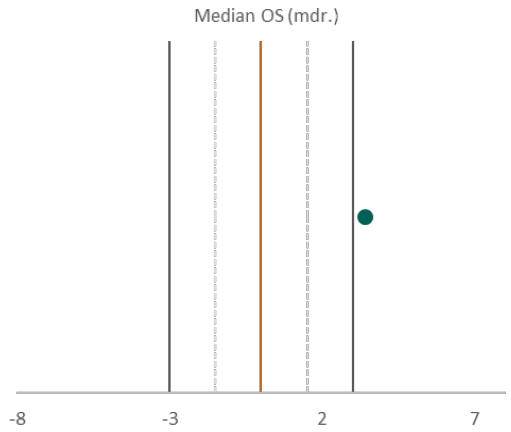
Overlevelse

Som beskrevet i protokollen er effektmålet overlevelse kritisk for vurderingen af lægemidlets værdi for patienterne, fordi kræftsygdommen er forbundet med høj dødelighed. Det er derfor afgørende, at behandlingen kan forlænge patienternes levetid. Fagudvalget ønskede effektmålet opgjort som median OS, hvilket afspejler OS for den samlede patientpopulation samt overlevelsesrate ved 12 måneder, som viser, hvor stor en gruppe af patienterne der opnår længerevarende effekt af behandlingen. Medicinrådet fastsatte i protokollen, at tre måneders median overlevelse var en klinisk relevant forskel i patientgruppen, fagudvalget pointerer dog, at dette er en patientgruppe med særdeles dårlig prognose, hvor patienterne forventes at overleve 4-6 måneder efter førstelinjebehandling.

I vurderingen af effektmålet tages der udgangspunkt i data fra august 2019 som den nyeste publicerede opgørelse. Median opfølgningstid var 12,8 måneder.

Median OS

Median OS var 9,3 måneder for patienter behandlet med encorafenib + cetuximab sammenlignet med 5,9 måneder i komparatorarmen. Dette resulterer i en absolut effektforskel for median OS på 3,4 måneder, se figur 1, hvilket afspejler en klinisk relevant effektforskel, da estimatet overstiger den mindste klinisk relevante forskel. Fagudvalget understreger, at dette er en forbedring på ca. 50 % ift. patienternes nuværende prognose (4-6 måneder). Derfor vurderer fagudvalget at 3,4 måneders yderligere overlevelse er en betydelig forbedring.



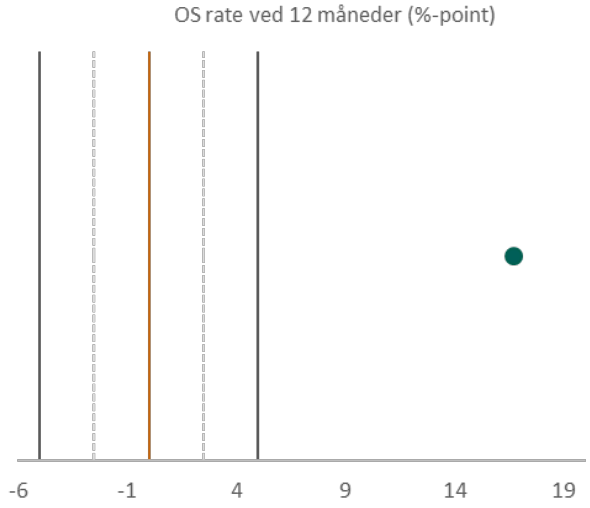
Figur 1. Punktestimat for den absolutte forskel for median overlevelse. De optrukne linjer indikerer den mindste klinisk relevante forskel. De stiplede linjer indikerer grænserne for Medicinrådets kategorier svarende til halvdelen af MKRF.

Overlevelsesrate ved 12 måneder

Efter 12 måneder var OS-raten 41,5 % [34,2; 48,7] i encorafenib + cetuximab-armen mod 24,8 % [18,5; 31,5] i kontrolarmen[2]. Punktestimatet for den absolutte effektforskel er

[2] Dette data er pt. *data on file*, men ikke fortroligt. Resultaterne forventes publiceret i januar 2021.

16,7 %-point, se figur 2, hvilket afspejler en klinisk relevant effektforskel (defineret i protokollen som værende 5 %-point). Der foreligger publicerede data for overlevelses-raten fra et tidligere opgørelsestidspunkt (februar 2019). Dette data vurderes dog som umodent med mange censureringer, før medianen nås, hvilket betyder, at 12-måneders raten herfra ikke kan benyttes. Her viser overlevelsesraten ved 6 måneder, at 65 % af patienterne er i live i encorafenib + cetuximab-armen, mens 47 % af patienterne var i live i kemoterapi-armen, som giver en absolut effektforskel på 18 %-point.



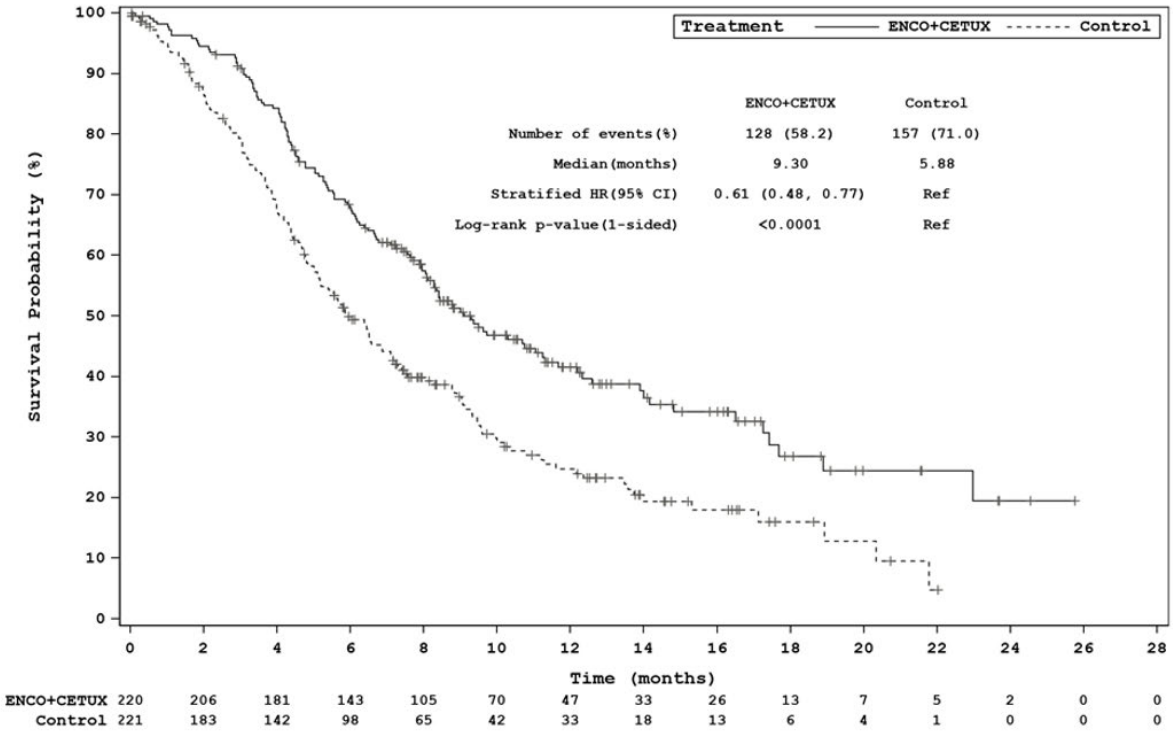
Figur 1. Punktestimat og 95% konfidensinterval for den absolutte forskel for 12 måneders overlevelsesraten. De optrukne linjer indikerer den mindste klinisk relevante forskel. De stiplede linjer indikerer grænserne for Medicinrådets kategorier svarende til halvdelen af MKRF.

De absolutte forskelle for de to opgørelser af OS er afbildet i figur 1 og figur 2. Der er ikke noget konfidensinterval på de absolutte effektforskelle, da der ikke findes veletablerede metoder til beregning af et konfidensinterval baseret på Kaplan-Meier kurver. Derfor har encorafenib + cetuximab en foreløbig værdi, **som ikke kan kategoriseres** for OS.

Den relative effektforskel er opgjort som en Hazard Ratio (HR) på 0,61 (0,48; 0,77). Baseret på den relative effektforskel har encorafenib + cetuximab **en stor merværdi** for OS.

Overlevelseskurve
I ansøgers ansøgning indgår en overlevelseskurve fra august 2019 med en median opfølgningstid på 12,8 måneder, se figur 3.

Figur 3. Overlevelseskurve fra BEACON-studiet analysetidspunkt fra august 2019 [21,22]



Fagudvalget vurderer, at overlevelseskurverne indikerer, at *proportional hazard* antagelsen er opfyldt, da det ses, at kurverne allerede deler sig efter 2 måneder og forbliver adskilte over tid. Fagudvalget vurderer dog, at der er mange censureringer før median OS, især efter 6 måneder. Derfor er der betydelige usikkerheder ved at vurdere kurven i forbindelse med 12-måneders overlevelsesraten samt usikkerhed ift. median OS for encorafenib + cetuximab. Derudover er der få patienter tilbage ved 12 måneder, hvorfor datagrundlaget for at vurdere 12-måneders overlevelsesraten er sparsomt. Ansøger har indsendt overlevelsesdata fra et senere analysetidspunkt med længere opfølgningstid (maj 2020), som dog er fortrolige[3]. [redacted]

[3] Ansøger har oplyst om, at dette data forventes publiceret ca. maj 2021. Indtil data er publiceret, vil denne information være blændet. Data vil dog blive offentliggjort senest 27. januar 2022, jf. Medicinrådets kriteriepapir for anvendelse af publiceret data.

Samlet OS

Der ses en stor merværdi for den relative effektforskel, hvilket fagudvalget vægter tungt. Dertil ses der absolutte effektforskelle for hhv. median overlevelse (3,4 måneder) og overlevelsesraten ved 12-måneder (16,7 %-point), som begge er større end MKRF. Fagudvalget finder, at alle disse resultater viser, at encorafenib + cetuximab forlænger overlevelsen for patientgruppen. Fagudvalget understreger dog, at datagrundlaget indeholder mange censureringer omkring median OS og 12-måneders overlevelsesraten, hvilket gør estimaterne usikre. Desuden er der tvivl om, hvorvidt behandlingen i kontrolarmen er dårligere end dansk klinisk praksis. Dette kan betyde, at forskellen mellem de to behandlingsarme overvurderes. Fagudvalget vurderer at median OS i kontrolarmen er høj sammenlignet med hvad fagudvalget ellers ser i patientpopulationen (4-6 måneder), hvilket kan skyldes at populationen i studiet har en bedre almen tilstand end danske patienter. Samlet vurderer fagudvalget, at encorafenib + cetuximab aggregeret har en **moderat merværdi** for effektmålet overlevelse sammenlignet med komparatoren FOLFIRI eller IRI i kombination med cetuximab vedr. effektmålet overlevelse.

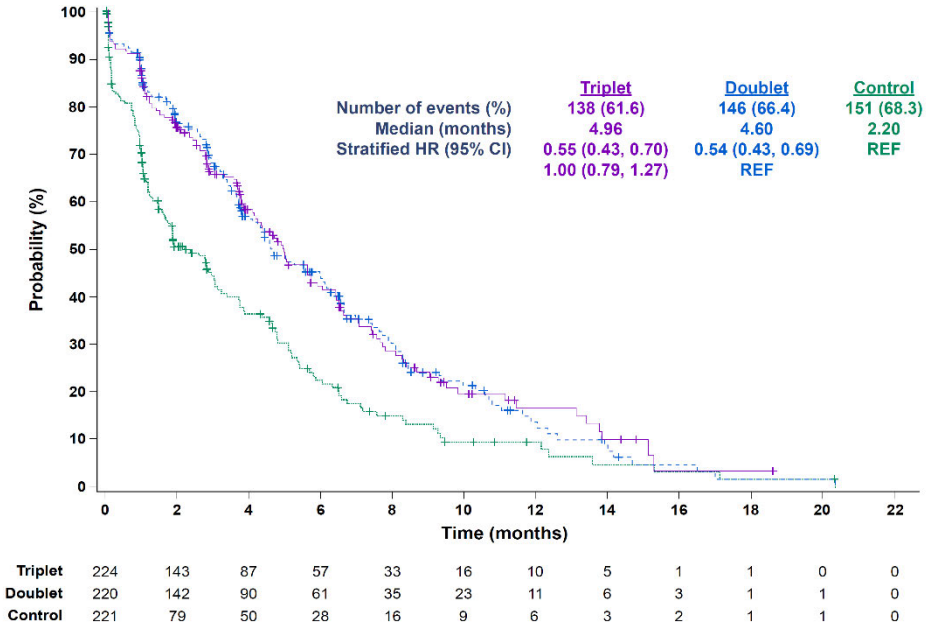
Livskvalitet

Som beskrevet i protokollen er effektmålet livskvalitet vigtig for vurderingen af lægemidlets værdi, eftersom det er vigtigt, at behandling med encorafenib + cetuximab ikke forringer patienternes livskvalitet yderligere, da patienterne allerede har forringet livskvalitet som følge af sygdommen og tidligere behandling(er).

Livskvalitet blev i protokollen efterspurgt som gennemsnitlig ændring fra baseline på EORTC-QLQ-C30. Der foreligger på nuværende tidspunkt intet data for dette, da data ikke er udgivet og er fortroligt, jf. afsnit 5.1.2. Effektmålet kan dermed ikke kategoriseres.

Ansøger har indleveret data for livskvalitet opgjort som tid til 10 % forringelse på EORTC QLQ-C30, se figur 4. Fagudvalget vurderer, at data kan benyttes til en narrativ vurdering af livskvalitet og dermed til en vis grad belyse effektmålet.

Figur 4. Tid til 10 % forringelse i EORTC QLQ-C30 fra BEACON-studiet, analysetidspunkt: Februar 2019 [20]



Det ses, at median tid til 10 % forringelse i EORTC-QLQ-C30 er 4,6 måneder i encorafenib + cetuximab-armen og 2,2 måneder komparator-armen, hvilket resulterer i en absolut forskel på 2,4 måneder. Den relative forskel er opgjort som en HR på 0,54 [0,43; 0,69]. Resultaterne indikerer, at patienter i behandling med encorafenib + cetuximab formår at opretholde deres livskvalitet i længere tid, sammenlignet med standard kemoterapi.

Fagudvalget vurderer, at data er modne, eftersom mange patienter allerede har oplevet en 10 % forværring af livskvalitet ved analysetidspunktet.

Fagudvalget vurderer, at den narrative gennemgang indikerer, at encorafenib + cetuximab har en bedre effekt ift. effektmålet livskvalitet, end komparator. Fagudvalget kan ikke udelukke, at et ublindet design af studiet kan medvirke til en bedre oplevelse af livskvalitet, hvorfor data skal tolkes med forbehold. Fagudvalget finder det plausibelt, at patienternes livskvalitet forbedres, da der er færre bivirkninger forbundet med encorafenib + cetuximab sammenlignet med kemoterapi (se næste afsnit), og fordi patienterne oplever at være i en effektiv behandling.

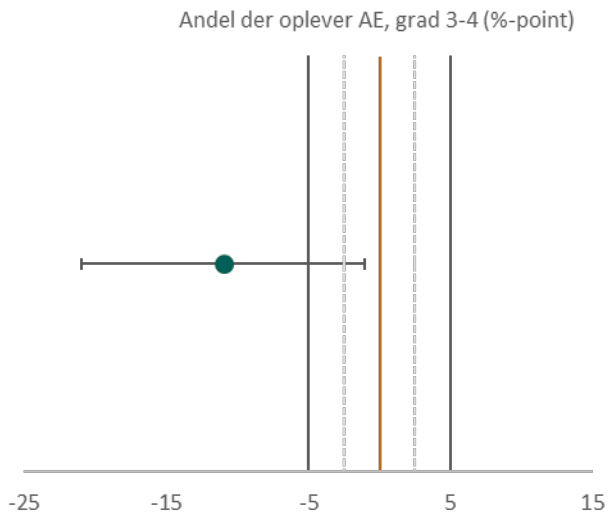
Bivirkninger

Som beskrevet i protokollen er effektmålet bivirkninger vigtig for vurderingen af lægemidlets værdi, dette skyldes, at bivirkninger har betydning for patientens compliance og livskvalitet i behandlingsforløbet. Derudover er det væsentligt, at encorafenib + cetuximab ikke medfører flere alvorlige bivirkninger end nuværende standardbehandling, da patienternes almene tilstand kan være svækket som følge af både sygdommen og tidligere behandling. I protokollen ønskede fagudvalget bivirkninger

opgjort som andelen, der oplevede grad 3-4 uønskede hændelser (adverse event (AE)) samt en kvalitativ gennemgang af bivirkningsprofilen. Ansøger har indsendt bivirkningsdata foretaget på safety-populationen.

Grad 3-4 uønskede hændelser
Punktestimatet for den absolutte effektforskel (-11 %-point i encorafenibs favør, se figur 5) afspejler en klinisk relevant effektforskel, da det overstiger mindste klinisk relevante forskel på 5 %-point. Dvs. at færre patienter oplever grad 3-4 uønskede hændelser ved behandling med encorafenib + cetuximab end ved behandling med komparator. Konfidensintervallet er bredt (-21; -1) og indeholder både værdier, som indikerer, at encorafenib + cetuximab medfører færre bivirkninger men også værdier, som indikerer, at der ingen forskel er imellem encorafenib + cetuximab og komparator. Derfor er den foreløbige værdi af encorafenib + cetuximab **ingen dokumenteret merværdi** vedr. grad 3-4 uønskede hændelser.

Den absolutte forskel er afbildet i figur 5 nedenfor.



Figur 5: Punktestimat og 95 % konfidensinterval for den absolutte forskel for bivirkninger. De optrukne linjer indikerer den mindste klinisk relevante forskel. De stiplede linjer indikerer grænserne for Medicinrådets kategorier svarende til halvdelen af MKRF.

Den relative effektforskel er opgjort som en Risk Ratio (RR) på 0,82 (0,69; 0,98). Baseret på den relative effektforskel, som fremgår af tabel 2, har encorafenib + cetuximab foreløbigt en **merværdi af ukendt størrelse** vedr. bivirkninger.

Kvalitativ gennemgang af bivirkninger
Bivirkningsdata baserer sig på *safety* populationen i studiet, derudover er EMA's produktresumé også blevet konsulteret [23]. Af tabel 4 fremgår det, hvilke uønskede hændelser som forekom i studiet. Median behandlingsvarighed var for encorafenib + cetuximab 19 uger og behandlingsvarigheden var 7 uger i kontrolarmen.

Tabel 4. Bivirkningstabel for encorafenib + cetuximab samt kontrolarmen

	Encorafenib + cetuximab (n = 216)		Kontrolarm (n = 193)	
	Alle grader n (%)	Grad 3+ n (%)	Alle grader n (%)	Grad 3+ n (%)
Diarré	83 (38,4)	6 (2,8)	94 (48,7)	20 (10,4)
Kvalme	82 (38,0)	1 (0,5)	84 (43,5)	3 (1,6)
Træthed	72 (33,3)	9 (4,2)	54 (28,0)	9 (4,7)
Nedsat appetit	67 (31,0)	3 (1,4)	56 (29,0)	6 (3,1)
Aknieform dermatitis	65 (30,1)	1 (0,5)	77 (39,9)	5 (2,6)
Mavesmerter	60 (27,8)	7 (3,2)	54 (28)	10 (5,2)
Opkastning	59 (27,3)	3 (1,4)	61 (31,6)	6 (3,1)
Kraftløshed	52 (24,1)	8 (3,7)	53 (27,5)	10 (5,2)
Ledsmerter	49 (22,7)	3 (1,4)	3 (1,6)	0 (0)
Hovedpine	43 (19,9)	0 (0)	5 (2,6)	0 (0)
Anæmi	42 (19,4)	12 (5,6)	36 (18,7)	13 (6,7)
Pyreksi	40 (18,5)	3 (1,4)	28 (14,5)	1 (0,5)
Forstoppelse	39 (18,1)	0 (0)	39 (20,2)	2 (1)
Modermærkeforandring	34 (15,7)	0 (0)	0 (0)	0 (0)
Myalgi	33 (15,3)	1 (0,5)	4 (2,1)	0 (0)
Udslæt	32 (14,8)	0 (0)	28 (14,5)	3 (1,6)
Muskuloskeletale smerter	29 (13,4)	0 (0)	5 (2,6)	0 (0)
Tør hud	28 (13,0)	0 (0)	16 (8,3)	1 (0,5)
Rygsmerter	28 (13,0)	3 (1,4)	27 (14)	2 (1,0)
Stakåndethed	28 (13,0)	2 (0,9)	20 (10,4)	6 (3,1)
Hypomagnesiæmi	25 (11,6)	1 (0,5)	19 (9,8)	3 (1,6)
Smerte i ekstremiteterne	25 (11,6)	0 (0)	2 (1)	0 (0)
Hudkløe	24 (11,1)	0 (0)	10 (5,2)	0 (0)
Vægtforøgning	24 (11,1)	1 (0,5)	12 (6,2)	0 (0)
Søvnløshed	24 (11,1)	0 (0)	13 (6,7)	0 (0)
Perifert ødem	23 (10,6)	0 (0)	14 (7,3)	1 (0,5)
Smerte i øvre del af maven	22 (10,2)	2 (0,9)	15 (7,8)	1 (0,5)
Urinvejsinfektion	17 (7,9)	5 (2,3)	6 (3,1)	2 (1)
Forhøjet alanin aminotransferase	14 (6,5)	1 (0,5)	14 (7,3)	4 (2,1)
Tarmobstruktion	14 (6,5)	10 (4,6)	8 (4,1)	5 (2,6)
Mundbetændelse	13 (6,0)	0 (0)	45 (23,3)	4 (2,1)
Hypokalæmi	13 (6,0)	2 (0,9)	27 (14,0)	6 (3,1)
Alopeci	9 (4,2)	0 (0)	21 (10,9)	0 (0)
Hypertension	8 (3,7)	3 (1,4)	6 (3,1)	5 (2,6)
Forhøjet alkalin fosfatase I blodet	7 (3,2)	4 (1,9)	10 (5,2)	4 (2,1)

Kræftsmerter	6 (2,8)	5 (2,3)	2 (1,0)	1 (0,5)
Hypocalcæmi	4 (1,9)	0 (0)	9 (4,7)	5 (2,6)
Lungeemboli[a]	3 (1,4)	3 (1,4)	10 (5,2)	9 (4,7)
Tyndtarmobstruktion	3 (1,4)	3 (1,4)	6 (3,1)	5 (2,6)
Neutropeni	3 (1,4)	2 (0,9)	36 (18,7)	20 (10,4)
Subileus (tarmslyng)	2 (0,9)	0 (0)	4 (2,1)	4 (2,1)
Fysisk almen svækkelse	1 (0,5)	1 (0,5)	4 (2,1)	4 (2,1)
Fald i neutrofile celler	1 (0,5)	1 (0,5)	21 (10,9)	16 (8,3)
Fald i hvide blodceller	1 (0,5)	0 (0)	14 (7,3)	8 (4,1)
Febril neutropeni	0 (0)	0 (0)	5 (2,6)	5 (2,6)

De hyppigste bivirkninger (alle grader > 25 %) forbundet ved behandling med encorafenib + cetuximab er træthed, kvalme, diarré, akne (dermatitis acneiform), mavesmerter, nedsat appetit og opkast. For kontrolarmen ses en lidt højere andel, som oplever hyppige typer af bivirkninger, heriblandt diarré, kvalme, træthed, nedsat appetit, akne, opkastning, kraftløshed og mavesmerter.

De hyppigste grad 3+ bivirkninger i encorafenib + cetuximab-armen er tarmobstruktion, anæmi og træthed, disse adskiller sig dog ikke fra kontrolarmen, hvori der tilmed ses en del andre typer grad 3+ bivirkninger. Fagudvalget bemærker, at der i kontrolarmen ses flere tilfælde af febril neutropeni samt større risiko for lungeemboli og tarmslyng, hvilket kan være forbundet med indlæggelse for patienten.

Det er angivet, at flere i behandling med encorafenib + cetuximab oplever modermærkeforandringer (15,7 %, grad 1 + 2). Desuden er det i produktresuméet angivet, at ny primær melanom er en mulig bivirkning ved behandling med encorafenib + cetuximab [23]. Fagudvalget finder dog ikke dette bekymrende taget patienternes forventede restlevetid i betragtning.

Encorafenib + cetuximab medfører overordnet set betydeligt færre bivirkninger sammenlignet med kemoterapi af alle grader. Der er dog visse typer af bivirkninger såsom tør hud, dyspnøe, søvnløshed og ødemer, som er hyppigere ved behandling med encorafenib + cetuximab. Fagudvalget understreger dog, at dette primært handler om bivirkninger af grad 1-2, og at der ikke er tegn på, at encorafenib + cetuximab medfører flere tilfælde af grad 3+ bivirkninger. Fagudvalget understreger, at der er tale om et ublindet klinisk studie, hvilket betyder, at der kan være forskelle i, hvor tilbøjelige patienterne i hver arm er til at indrapportere bivirkninger. Fagudvalget vurderer, at de få bivirkninger der er forbundet ved behandling med encorafenib + cetuximab reflekteres i, at få patienter ophører med behandlingen grundet bivirkninger. 8,3 % af patienterne, som modtog encorafenib og cetuximab, ophørte behandling grundet bivirkninger, hvorimod der var 11,4 % af patienterne i kontrolarmen, som måtte ophøre behandlingen.

Fagudvalget konkluderer, at encorafenib + cetuximab har en favorabel bivirkningsprofil sammenlignet med FOLFIRI eller IRI i kombination med cetuximab.

Behandling med encorafenib + cetuximab anbefales ikke til patienter med moderat-svær leverpåvirkning (Child-Pugh Class B og C).

Dosisreduktion og seponering grundet bivirkninger
Der er særlige bivirkninger forbundet med encorafenib + cetuximab, som kan håndteres ved dosisreduktion eller pausering af behandling. Fagudvalget henviser til EMA's produktresumé i forhold til dosisreduktion og seponering.

Fagudvalgets konklusion vedr. effektmålet bivirkninger
Fagudvalget vurderer, at encorafenib + cetuximab aggregeret har en **merværdi af ukendt størrelse** vedr. bivirkninger. Fagudvalget vægter den relative effektforskel tungest ved grad 3-4 uønskede hændelser, som viser en merværdi af ukendt størrelse. Punktestimatet for den absolutte effektforskel for grad 3-4 uønskede hændelser indikerer en klinisk relevant effektforskel (MKRF 5 %-point) til fordel for encorafenib + cetuximab, men grundet det brede konfidensinterval er der usikkerheder forbundet med dette estimat. Fagudvalget finder det klinisk plausibelt, at encorafenib + cetuximab har færre bivirkninger end den nuværende standardbehandling med kemoterapi, som patienterne modtager i dansk klinisk praksis. Dette understøttes af den narrative gennemgang af bivirkninger, hvor fagudvalget konkluderer, at encorafenib + cetuximab har en favorabel bivirkningsprofil sammenlignet med FOLFIRI eller IRI i kombination med cetuximab.

5.1.5 Fagudvalgets konklusion

Fagudvalget vurderer, at encorafenib i kombination med cetuximab giver en **moderat merværdi** sammenlignet med FOLFIRI eller IRI i kombination med cetuximab, til patienter med metastatisk kolorektalkræft, der har $BRAF^{V600E}$-mutation.
I den samlede vurdering af værdien af encorafenib i kombination med cetuximab vægter fagudvalget den betydelige effekt på overlevelse højt. Overlevelseseffekten skal ses i lyset af en ellers forventet overlevelse i størrelsesordenen 4-6 måneder efter progression på førstelinje kemoterapi. Endvidere ses en favorabel bivirkningsprofil ved behandlingen.

For det kritiske effektmål *overlevelse* havde encorafenib i kombination med cetuximab en foreløbig stor merværdi ift. den relative effektforskel. Ligeledes var de absolutte effektforskelle for hhv. median overlevelse (3,4 måneder) og overlevelsesraten ved 12-måneder (16,7 %-point) større end MKRF. Fagudvalget vægter den relative effektforskel højt i den samlede vurdering af effektmålet men vurderer, at de usikkerheder der er forbundet med overlevelsesdata, skal trække den samlede værdi for overlevelse ned på moderat merværdi for encorafenib i kombination med cetuximab sammenlignet med FOLFIRI eller IRI i kombination med cetuximab.

For det vigtige effektmål *bivirkninger* har encorafenib i kombination med cetuximab en merværdi af ukendt størrelse i forhold til uønskede hændelser grad 3-4. Fagudvalget konkluderer baseret på den narrative gennemgang af bivirkninger, at encorafenib i

kombination med cetuximab har en favorabel bivirkningsprofil sammenlignet med FOLFIRI eller IRI i kombination med cetuximab.

For det vigtige effektmål *livskvalitet* kunne effektmålet ikke kategoriseres, da data ikke var opgjort som angivet i protokollen. Fagudvalget har dog foretaget en narrativ gennemgang af effektmålet vha. tid til 10 % forringelse af patienternes livskvalitet. Denne gennemgang underbygger, at encorafenib i kombination med cetuximab har bedre effekt på livskvalitet sammenlignet med FOLFIRI eller IRI i kombination med cetuximab. Fagudvalget finder det plausibelt, at patienternes livskvalitet forbedres, da der er færre bivirkninger forbundet med encorafenib sammenlignet med FOLFIRI eller IRI i kombination med cetuximab.

I den samlede vurdering af værdien af encorafenib i kombination med cetuximab vægter fagudvalget den betydelige effekt på overlevelse højt samtidig med, at der ses en favorabel bivirkningsprofil ved behandlingen.

Fagudvalget pointerer, at det er første gang, man har et studie, som udelukkende inkluderer BRAF-muterede mKRC-patienter. Behandlingen er et vigtigt skridt i retningen mod at kunne tilbyde en effektiv behandling til en patientgruppe, som har en meget dårlig prognose og dårligere effekt af standardbehandling end andre patienter med mKRC.

6. Andre overvejelser

Fordeling mellem FOLFIRI og IRI i komparatorarmen for studiet
Fagudvalget ønskede i protokollen en redegørelse ift. fordelingen af patienter mellem valg af komparator; dvs. IRI + cetuximab eller FOLFIRI + cetuximab samt oplysninger om, hvor mange patienter der allerede i første eller anden linje har modtaget et regime med et af stofferne. Ansøger har givet disse informationer i ansøgningen, men de er fortrolige og kan derfor ikke beskrives i vurderingsrapporten.

Patienter, som kan modtage encorafenib + cetuximab som andenlinjebehandling
Fagudvalget vurderer, at hvis lægemidlet anbefales, vil anvendelsen hovedsageligt finde sted i andenlinje.

Som nævnt i afsnit 3.3, tilbydes kun ca. 50 % af patienterne på nuværende tidspunkt andenlinje kemoterapi, da patienternes almentilstand ofte ikke er forenelig med yderligere behandling. Fagudvalget vurderer, at det er sandsynligt, at flere patienter vil kunne tilbydes encorafenib + cetuximab, da denne kombination har en favorabel bivirkningsprofil sammenlignet med kemoterapi-kombinationerne.

7. Relation til behandlingsvejledning

Der findes ikke en relevant behandlingsvejledning fra Medicinrådet, men der findes en behandlingsvejledning fra Rådet for Anvendelse af Dyr Sygehusmedicin (RADS), men her er det faglige grundlag forældet. Der er planlagt en opdatering af behandlingsvejledningen på området.

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9. Sammensætning af fagudvalg og kontaktinformation til Medicinrådet

Medicinrådets fagudvalg vedrørende tyk- og endetarmskræft

Sammensætning af fagudvalg	
Formand	Indstillet af
Lone Nørgård Petersen *Overlæge*	Lægevidenskabelige Selskaber
Medlemmer	Udpeget af
René Olesen *Overlæge*	Region Nordjylland
Anders Kindberg Boysen *Overlæge*	Region Midtjylland
Torben Frøstrup Hansen *Overlæge*	Region Syddanmark
Lars Simon Reiter *Overlæge*	Region Sjælland
Jacob Hagen Vasehus Schou *Konstitueret overlæge*	Region Hovedstaden
Gabor Liposits *Overlæge*	Dansk Colorectal Cancer gruppe
Anita Grant *Patient/patientrepræsentant*	Danske Patienter
Jette Lyngholm *Patient/patientrepræsentant*	Danske Patienter
Solvej Wandy Pedersen *Klinisk farmaceut*	Dansk Selskab for Sygehusapoteksledelse
Jesper Sonne *Overlæge*	Dansk Selskab for Klinisk Farmakologi

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10. Versionslog

Versionslog		
Version	**Dato**	**Ændring**
1.0	9. december 2020	Godkendt af Medicinrådet

11. Bilag 1: Evidensens kvalitet

11.1 Cochrane – risiko for bias

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

Tabel 2 Vurdering af risiko for bias Kopetz et al. 2019, Encorafenib, Binimetinib, and Cetuximab in BRAF V600E-Mutated Colorectal Cancer, NCT-02928224

Bias	Risiko for bias	Uddybning
Risiko for bias i randomiserings-processen	**Lav**	Patienterne blev randomiseret i en ratio 1:1:1 via et *interactive web response system*.
Effekt af tildeling til intervention	**Lav**	Studiet var ublindet, dvs. patienter og investigator var klar over den tildelte intervention. Sponsor var blindet. Der ses dog ikke nogen variationer mellem interventionerne. Analyserne var baseret på *intention-to-treat*-princippet.
Manglende data for effektmål	**Lav**	Effektivitetsanalyser blev foretaget på *full analysis set*, dvs. alle randomiserede patienter, der modtog minimum en dosis af tildelte intervention. Imputering blev foretaget ved manglende data.
Risiko for bias ved indsamlingen af data	**Forbehold**	Investigator og patienter var ublindet. Det kan have haft en effekt på opgørelsen af livskvalitet, da patienterne selv skulle stå for det. Scanningsdata blev udført retrospektivt (4 uger efter initialt respons) af blindet *readers*. Incidens og sværhedgrad af alvorlige hændelser blev vurderet ift. bestemte kriterier (National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03)
Risiko for bias ved udvælgelse af resultater, der rapporteres	**Lav**	Alle effektmål defineret i Medicinrådets protokol var præspecificeret. Dog er det lidt uklart ud fra clinicaltrials.gov, om EORTC-QLQ livskvalitetsmåling blev tilføjet senere. Valget af effektmål er dog, hvad man kan forvente i populationen.
Overordnet risiko for bias	**Lav**	Den største bekymring var studiets ublindede design. Det vurderes dog at have en minimal betydning taget sygdommen og aktuel behandling i betragtning, da patienter i kontrolarmen stort set får den behandlin,g de ellers vil kunne have fået. Desuden vil det være svært at rekruttere til et dobbeltblindet studie, som følge af karakteristiske bivirkninger i armene, og som følge af at administrationsfrekvensen af både placebo og behandling ellers vil være meget høj.

11.2 GRADE

Det kliniske spørgsmål – encorafenib + cetuximab sammenlignet med FOLFIRI eller IRI begge + cetuximab til behandling af BRAF^{V600E}-muteret mKRC

Tabel 3. GRADE evidensprofil for det kliniske spørgsmål

Sikkerhedsvurdering							Antal patienter		Effekt			
Antal studier	Studie-design	Risiko for bias	Inkonsistens	Indirekthed	Unøjagtighed	Andre overvejelser	Encorafenib + cetuximab	FOLFIRI + cetuximab eller IRI + cetuximab	Relativ (95 % CI)	Absolut (95 % CI)	Sikkerhed	Vigtighed
Overlevelse (OS), follow up: median 12,8 måneder												
1	RCT	Ikke alvorlig	Alvorlig[a]	Alvorlig[b]	Ikke alvorlig	Ingen	128/220 (58,2 %)	157/221 (71,0 %)	HR 0,61 (0,48; 0,77)	3,4 måneder	⨁⨁◯◯ LOW	KRITISK
Livskvalitet (EORTC-QLQ-C30), follow up: median 7,8 måneder												
1	RCT	Alvorlig[c]	Alvorlig[a]	Alvorlig[d]	Ikke alvorlig	Ingen	146/220 (66,4 %)	151/221 (68,3 %)	HR 0,54 (0,43; 0,69)	2,4 måneder	⨁◯◯◯ VERY LOW	VIGTIGT
Uønskede hændelser, follow up: mediain 7,8 måneder												
1	RCT	Ikke alvorlig	Alvorlig[a]	Ikke alvorlig	Ikke alvorlig	Ingen	108/216 (50,0 %)	117/193 (60,6 %)	RR 0,82 (0,69; 0,98)	-11 %-point (-21; -1)	⨁⨁⨁◯ MODERATE	VIGTIGT
Kvalitet af den samlede evidens	LAV											

CI: Konfidens interval; HR: Hazard Ratio; RR: Risk ratio

[a] Der er nedgraderet ét niveau, da kun var ét studie.

[b] Der er nedgraderet ét niveau, da fagudvalget vurderer, at komparator er anderledes end den gængse standardbehandling i dansk klinisk praksis,

[c] Der er nedgraderet ét niveau, da studiet var ublindet,

[d]Der er nedgraderet ét niveau, da data var opgjort anderledes end efterspurgt i protokollen,

Medicinrådet

Application for the assessment of encorafenib (BRAFTOVI®) in combination with cetuximab for the treatment of adult patients with metastatic colorectal cancer (mCRC) with a $BRAF^{V600E}$ mutation, who have received prior systemic therapy

Updated: 23 November 2020

Contains confidential information

Contents

General information

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

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

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

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

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

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

Checklist before submitting the application form:

- Are all relevant fields in the application form filled in?
- Are references indicated for all data?
- Is the application explicit and self-explanatory?
- Does the application meet the general requirements defined in the *Process and Methods Guide (version 2.0)* of the Danish Medicines Council for new medicines and new indications?
- Does the application meet the specific requirements in the protocol?
- Are deviation(s) from the protocol (if any) described?
- Are deviation(s) from the protocol (if any) justified?

1 Basic information

Table 1. Contact information

Name	Erik Arver
Title	Nordic Market Access Head
Area of responsibility	Market Access
Phone	+46 70 750 87 37
E-mail	erik.arver@pierre-fabre.com

Table 2. Overview of the pharmaceutical

Proprietary name	BRAFTOVI®
Generic name	Encorafenib
Marketing authorisation holder in Denmark	Pierre Fabre Pharma Norden AB Karlavägen 108; Plan 9 115 26 Stockholm Sweden
ATC code	L01XE46
Pharmacotherapeutic group	Antineoplastic agents, other antineoplastic agents, protein kinase inhibitors
Active substance(s)	Encorafenib
Pharmaceutical form(s)	Encorafenib is administered orally as hard capsules
Mechanism of action	Encorafenib is a potent and highly selective ATP-competitive small molecule RAF kinase inhibitor that suppresses the RAF/MEK/ERK pathway (MAPK signalling cascade) in CRC cells expressing $BRAF^{V600E}$ mutations. Activation of EGFR has been identified as one of the mechanisms of resistance of BRAF-mutant CRC to RAF inhibitors. Therefore, in the setting of BRAF-mutant CRC, the EGFR-mediated MAPK signalling cascade presents an additional therapeutic opportunity to combine a RAF inhibitor with an EGFR inhibitor, such as cetuximab.
Dosage regimen	The recommended dose is 300 mg encorafenib, administered as 4 × 75 mg capsules taken once daily, used in combination with intravenous cetuximab given once weekly at an initial recommended dose of 400 mg/m^2 body surface area, followed by 250 mg/m^2 for all subsequent doses [1].
Therapeutic indication relevant for assessment (as defined by the EMA)	Encorafenib is indicated, in combination with cetuximab, for the treatment of adult patients with mCRC with a $BRAF^{V600E}$ mutation who have received prior systemic therapy [1].
Other approved therapeutic indications	Encorafenib in combination with binimetinib is indicated for the treatment of adult patients with unresectable or metastatic melanoma with a $BRAF^{V600}$ mutation [1].
Will dispensing be restricted to hospitals?	Encorafenib is prescribed in a hospital or clinic setting under the supervision of an oncology specialist but is an oral drug self-administered by the patient at home. Encorafenib will be dispensed by hospital pharmacists.
Combination therapy and/or co-medication	Encorafenib is indicated for mCRC in combination with intravenous cetuximab.

Packaging – types, sizes/number of units, and concentrations	50-mg encorafenib: 28-tablet pack (or 112-tablet pack, currently not on market) 75-mg encorafenib: 42-tablet pack (or 168-tablet pack, currently not on market)
Orphan drug designation	Not applicable.

ATC, Anatomical Therapeutic Chemical Classification System; ATP, adenosine triphosphate; CRC, colorectal cancer; EGFR, epidermal growth factor receptor; EMA, European Medicines Agency; MAPK = mitogen-activated protein kinase; mCRC, metastatic colorectal cancer.

2 Abbreviations

Abbreviation	Definition
5-FU	5-fluorouracil
AE	adverse event
ASCO	American Society of Clinical Oncology
ATC	Anatomical Therapeutic Chemical Classification System
ATP	adenosine triphosphate
BICR	blinded independent central review
BID	twice daily
BOR	best overall response
CETUX	cetuximab
CI	confidence interval
CR	complete response
CRC	colorectal cancer
CRP	C-reactive protein
CSR	clinical study report
CT	computed tomography
CYP	cytochrome
DMC	Danish Medicines Council
DOR	duration of response
ECOG	Eastern Cooperative Oncology Group
EGFR	epidermal growth factor receptor
EMA	European Medicines Agency
ENCO	encorafenib
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Core Module
EPAR	European Public Assessment Report
ERK	extracellular signal-regulated kinase
EU	European Union
FACT-C	Functional Assessment of Cancer Therapy–Colon Cancer
FAS	full analysis set
FOLFIRI	folinic acid + 5-fluorouracil + irinotecan
FOLFOX	folinic acid + 5-fluorouracil + oxaliplatin
HR	hazard ratio
HRQoL	health-related quality of life
IRI	irinotecan
IV	intravenous
IWRS	interactive web response system
K-M	Kaplan-Meier
MAPK	mitogen-activated protein kinase
mCRC	metastatic colorectal cancer
MEK	MAPK/ERK kinase
MRI	magnetic resonance imaging

Abbreviation	Definition
MT	mutant or mutation
NA	not applicable or not available
NCT	National Clinical Trial Number
NR	not reported
OAT	organic anion transporter
OATP	organic anion transporting polypeptide
ORR	overall response rate
OS	overall survival
PD	progressive disease
PFS	progression-free survival
PGIC	Patient Global Impression of Change
PR	partial response
PS	performance status
Q2W	every 2 weeks
QD	once daily
QoL	quality of life
QW	once a week
RAF	rapidly accelerated fibrosarcoma
RDI	relative dose intensity
RECIST	Response Evaluation Criteria in Solid Tumours
SD	standard deviation
SLI	safety lead-in
SLR	systematic literature review
SmPC	summary of product characteristics
StD	stable disease
TEAE	treatment-emergent adverse event
TTR	time to response
ULN	upper limit of normal
US	United States
VEGF	vascular endothelial growth factor
WT	wild type

3 Summary

Encorafenib (BRAFTOVI®) is an oral, highly selective ATP-competitive small molecule RAF kinase inhibitor. Its mechanism of action is based on the inhibition of the mitogen-activated protein kinase (MAPK) signalling pathway in tumour cells expressing a $BRAF^{V600E}$ mutation (MT), including metastatic colorectal cancer (mCRC) [2]. It is used in combination with cetuximab, an epidermal growth factor receptor (EGFR) inhibitor: the double inhibition of BRAF kinase and EGFR provides synergistic inhibition of the MAPK signalling pathway involved in the aggressive manifestations of $BRAF^{V600E}$-MT mCRC [3].

In Denmark, colorectal cancer (CRC) is the most common incident cancer and was the second most frequent cause of cancer death in 2018 [4]. In Europe, approximately 25% of patients are diagnosed with stage IV mCRC, and a further 50% of those with stage I-III CRC will progress to mCRC [5, 6]. CRC tumours have different molecular subtypes: those with BRAF-MT are the most aggressive and are associated with poor prognosis and an increased risk of metastasis. In Europe, it is estimated that 8% to 12% of patients with mCRC have BRAF-MT tumours [7], with 97% to 100% specifically $BRAF^{V600E}$-MT [8]. Real-world Nordic data show a higher incidence of 21% of patients with $BRAF^{V600E}$-MT [9]. Patients with $BRAF^{V600E}$-MT mCRC have a short life expectancy with a 70% increased risk of mortality compared with patients with BRAF wild-type (WT) mCRC, with the shortest median overall survival (OS) of all CRC mutation subtypes [8].

Currently, there is no agent specifically indicated for patients with $BRAF^{V600E}$-MT mCRC; in Denmark, there are no clear recommendations on the current standard of care for patients with $BRAF^{V600E}$-MT mCRC after prior systemic therapy. The clinician's current choice of treatments is non-standardised; regimens can include various combinations of chemotherapy (e.g., FOLFIRI[1]/FOLFOX[2]), EGFR inhibitors (e.g., cetuximab), and vascular endothelial growth factor (VEGF) inhibitors (bevacizumab). There is a clear and high unmet need in this patient population: patients with $BRAF^{V600E}$-MT mCRC have a poor prognosis with current treatments [9] with no targeted therapy for their BRAF mutation.

The key efficacy data for encorafenib + cetuximab in $BRAF^{V600E}$-MT mCRC after prior systemic therapy are provided by BEACON CRC, the first and only phase 3 randomised controlled trial performed specifically in patients with $BRAF^{V600E}$-MT mCRC. In BEACON CRC, encorafenib + cetuximab consistently showed statistically and clinically significant improvements in OS, progression-free survival (PFS), and overall response rate (ORR), with a favourable and manageable tolerability profile and sustained health-related quality of life (HRQoL) compared with standard chemotherapy + cetuximab (FOLFIRI + cetuximab, or irinotecan [IRI] + cetuximab) [1, 10]:

- A clinically significant 39% reduction in the risk of death, equating to 3.4 additional months of survival: median OS, 9.30 months versus 5.88 months; hazard ratio (HR), 0.61; 95% confidence interval (CI), 0.48-0.77; one-sided $P < 0.0001$.
- A 56% reduction in the risk of disease progression or death: median PFS, 4.27 months versus 1.54 months; HR, 0.44; 95% CI, 0.35-0.55; one-sided $P < 0.0001$.
- A significantly higher rate of complete or partial response (ORR): 19.5% versus 1.8%; one-sided $P < 0.0001$.
- HRQoL findings across several disease-specific and generic patient-reported tools were consistent with the clinical benefit and favourable toxicity and tolerability of encorafenib + cetuximab compared with control.

The use of targeted therapy with encorafenib in combination with cetuximab significantly improved OS, PFS, and ORR while sustaining patient's HRQoL when compared with standard-of-care therapy (FOLFIRI/IRI + cetuximab). The significant OS improvements observed with this new targeted therapy represent a substantial step forward in the treatment options available for $BRAF^{V600E}$-MT mCRC in Denmark, for which prognosis can be extremely poor.

[1] FOLFIRI = folinic acid + 5-fluorouracil + irinotecan.

[2] FOLFOX = folinic acid + 5-fluorouracil + oxaliplatin.

4 Literature search

The Danish Medicines Council (DMC) conducted a literature search for appropriate full-text articles published in scientific, peer-reviewed journals comparing encorafenib in combination with cetuximab with relevant chemotherapy. The literature search identified one full-text article describing the BEACON CRC study: Kopetz et al. [11]. For completeness, Pierre Fabre conducted a clinical systematic literature review (SLR) to identify studies relevant to encorafenib in combination with cetuximab for the treatment of $BRAF^{V600E}$-MT mCRC after prior therapy. The SLR was last updated in May 2020. Once relevant studies were identified, study characteristics, efficacy, HRQoL, and safety data were extracted, and methodologies were critically appraised according to internationally validated methods. See Appendix A for the full search strategy and details of the process and methods used.

The evidence base to support the clinical efficacy of encorafenib in combination with cetuximab reflects the licensed indication and the anticipated use of this treatment in clinical practice in Denmark. No major factors or patient characteristics relating to the evidence have been identified that would likely affect the applicability of the evidence or exert an influence on the clinical response of encorafenib in combination with cetuximab for the treatment of $BRAF^{V600E}$-MT mCRC after prior therapy.

4.1 Databases and search strategy

See Appendix A for the full search strategy and details of the process and methods used by Pierre Fabre to identify and select the clinical evidence relevant to the submission.

4.2 Relevant studies

The only relevant study identified by the DMC was the BEACON CRC study (Kopetz et al. [11]), which is summarised in Table 3. Additional studies that were identified in the SLR performed by Pierre Fabre but that were not identified as relevant for the DMC application are described in Appendix A-3 for completeness.

Table 3. Relevant study included in the assessment

Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)
Kopetz S, Grothey A, Yaeger R, Van Cutsem E, Desai J, Yoshino T, et al. Encorafenib, binimetinib, and cetuximab in BRAF V600E-mutated colorectal cancer. N Engl J Med. 2019 Oct;381(17):1632-43.	BEACON CRC	NCT02928224	July 2009 to October 2019

NCT, National Clinical Trial number.

4.3 Main characteristics of included study: BEACON CRC

One relevant randomised controlled trial was identified by the DMC that evaluated encorafenib + cetuximab in patients with $BRAF^{V600E}$-MT mCRC: the BEACON CRC study. This is the pivotal efficacy trial relevant to this application and is included in the marketing authorisation for encorafenib. BEACON CRC is further described in this section and in Table 4.

Table 4. Clinical efficacy evidence for encorafenib

Study	BEACON CRC (study ARRAY-818-302, NCT02928224) [11, 12]
Study design	A global, multicentre, randomised, open-label, 3-arm, active-controlled phase 3 study
Patient population	Patients with $BRAF^{V600E}$-MT mCRC whose disease had progressed after 1 or 2 prior regimens in the metastatic setting
Intervention(s)	▪ Encorafenib 300 mg QD + cetuximab IV QW (n = 220) ▪ Encorafenib 300 mg QD + binimetinib 45 mg BID + cetuximab IV QW (n = 224)
Comparator(s)	Investigator's choice of either (n = 221): ▪ IRI IV Q2W + cetuximab IV QW ▪ FOLFIRI (folinic acid IV Q2W + 5-fluorouracil Q2W + IRI IV Q2W) + cetuximab IV QW
Outcomes	▪ Overall survival ▪ Progression-free survival ▪ Response rate (overall response rate) ▪ Adverse events ▪ Health-related quality of life (EORTC QLQ-C30, FACT-C, EQ-5D-5L, PGIC)

BID, twice daily; EMA, European Medicines Agency; EORTC QLQ-C3O, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Core Module; FACT-C, Functional Assessment of Cancer Therapy–Colon Cancer; IRI, irinotecan; IV, intravenous; mCRC, metastatic colorectal cancer; PGIC, Patient Global Impression of Change; Q2W, every 2 weeks; QD, once daily; QW, once a week.

4.3.1 BEACON CRC (ARRAY-818-302): trial methodology

4.3.1.1 Location

[redacted] sites in selected countries from the rest of the world. Patients enrolled in Nordic countries included 10 patients at one site in Denmark and 15 patients at one site in Norway [13].

4.3.1.2 Study objective

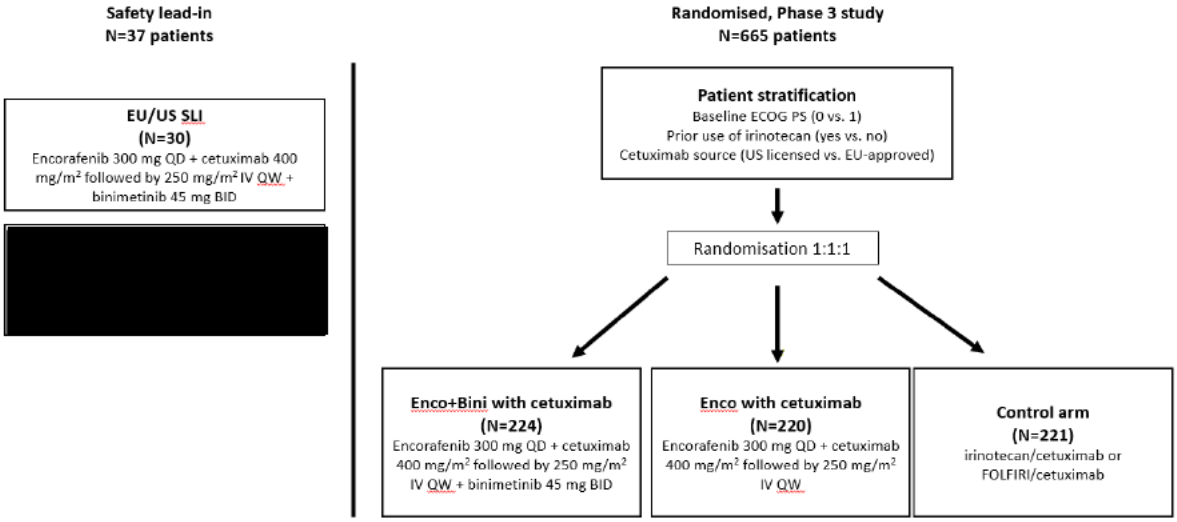
The objective of BEACON CRC was to evaluate whether treatment with encorafenib + cetuximab with or without the MEK inhibitor binimetinib would result in longer OS than standard-of-care therapy in patients with $BRAF^{V600E}$-MT mCRC whose disease had progressed after one or two prior regimens in the metastatic setting.

4.3.1.3 Study design

The BEACON CRC study is a global, multicentre, randomised, open-label, three-arm, active-controlled phase 3 study in patients with $BRAF^{V600E}$-MT mCRC, whose disease had progressed after one or two prior regimens in the metastatic setting. BEACON CRC provides the pivotal evidence supporting the anticipated licensed indication for encorafenib + cetuximab in mCRC.[3]

The study consisted of two main periods: a safety lead-in (SLI) period followed by the phase 3 randomised period (Figure 1).

Figure 1. BEACON CRC: study design



BID, twice daily; Bini, binimetinib; ECOG PS, Eastern Cooperative Oncology Group performance status; Enco, encorafenib; EU, European Union; FOLFIRI, folinic acid + 5-fluorouracil + irinotecan; IV, intravenous; QD, once daily; QW, once a week; SLI, safety lead-in; US, United States.

Safety lead-in period

Before initiation of the randomised phase 3 portion of the study, the study was initiated with an SLI cohort, which evaluated the safety and tolerability of encorafenib + binimetinib + cetuximab in 30 patients at sites in the European Union (EU) and United States (US) [redacted]

The SLI is not discussed further in this submission.

[3] The study also investigated the triple combination of encorafenib + binimetinib + cetuximab. However, these results are not relevant to decision making because this regimen will not be licensed. Key efficacy results for this regimen, which include the primary endpoints of the study (OS and ORR for encorafenib + binimetinib + cetuximab vs. control) and the secondary PFS endpoint are provided in Appendix F for completeness; other secondary efficacy endpoints and safety results for encorafenib + binimetinib + cetuximab are not provided.

Randomised period and follow-up

BEACON CRC was designed to randomise approximately 615 patients (665 patients were actually randomised) at a 1:1:1 ratio to the following arms [14]:

- Encorafenib + cetuximab
- Encorafenib + binimetinib + cetuximab
- Control arm comprising investigator's choice of either:
  - IRI + cetuximab
  - FOLFIRI + cetuximab

Posology details are provided in Section 4.3.1.6. Randomisation was stratified according to the following factors [14]:

- Baseline Eastern Cooperative Oncology Group (ECOG) performance status (PS) (0 vs. 1).
- Prior use of IRI (yes vs. no).
- Cetuximab source (US licensed vs. EU-approved).
- The number of third-line patients (those who had received 2 prior regimens) was limited to 35% of the total randomised phase 3 population (per protocol), after which only patients with one prior regimen were to be randomised. Patients with two prior regimens who had entered screening at the time that the limit had been reached were to be permitted to continue into the study if they were otherwise determined to be eligible.

Method of randomisation

Each patient was assigned a unique patient number via the interactive web response system (IWRS) upon enrolment for molecular prescreening or study screening. Randomisation was used to ensure that treatment assignment was unbiased; before dosing, all patients who fulfilled all inclusion criteria were randomised via IWRS to one of the treatment arms.

Blinding

Because this was an open-label study, investigators and patients knew the study treatment assigned. To minimise bias, the sponsor, their designee trial team, and the independent review committee were blinded to patient treatment assignment. The randomisation schedule was created and managed by a third-party vendor, and treatments were assigned according to a central randomisation list using the IWRS. A limited number of study personnel were not blinded to individual treatment assignments for the purposes of study conduct, but they did not have access to unblinded aggregate summaries of data. These steps were to remain in place until a database lock supporting a clinical study report (CSR) occurred. Sponsor personnel were to remain blinded to aggregate OS results until the encorafenib + binimetinib + cetuximab arm versus control arm OS endpoint exceeded the superiority boundary or until the study was stopped for futility.

4.3.1.4 Study period

- Date of randomisation in phase 3: May 2017 to January 2019
- Date of data cut-off (initial analysis): 11 February 2019
- Date of second data cut-off: 15 August 2019
- Interim OS analysis for DMC (not prespecified): 5 May 2020

4.3.1.5 Eligibility criteria for participants

Patients must have had a $BRAF^{V600E}$ mutation identified to be eligible for the study; as such, patients had to meet eligibility criteria to go through molecular prescreening to determine $BRAF^{V600E}$-MT status before then being assessed for eligibility for study participation. Full eligibility criteria for both molecular prescreening and study participation are provided in Appendix F.

Patients were permitted to undergo molecular tumour prescreening with the central laboratory $BRAF^{V600E}$-MT assay at any time before screening, as long as they met all the molecular prescreening eligibility criteria. Tumour samples that were previously determined to be BRAF-WT by local assessment were permitted to be submitted to the central laboratory.

To participate in the study, patients had to be at least 18 years of age with histologically or cytologically confirmed $BRAF^{V600E}$-MT mCRC as determined by a local or sponsor-designated central laboratory. A patient's disease had to have progressed after one or two prior regimens in the metastatic setting. Patients were eligible to receive cetuximab per locally approved label regarding tumour RAS status.

Patients were also to have evidence of measurable or evaluable non-measurable disease per Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1; an ECOG PS of 0-1 and adequate bone marrow; and organ and cardiac function, including left ventricular ejection fraction ≥ 50% by cardiac imaging and QTcF ≤ 480 msec.

4.3.1.6 Trial drugs

Intervention arms

- Encorafenib once daily (QD) + cetuximab intravenous (IV) once a week (QW) (n = 220)
- Encorafenib QD + binimetinib twice daily (BID) + cetuximab IV QW (n = 224)

Control arm

- Investigator's choice of either (n = 221):
  - IRI IV every 2 weeks (Q2W) + cetuximab IV QW, or
  - FOLFIRI (folinic acid IV once Q2W + 5-fluorouracil [5-FU] Q2W + IRI IV Q2W) + cetuximab IV QW

Encorafenib and binimetinib

Encorafenib and binimetinib were administered at doses of 300 mg QD and 45 mg BID, respectively.

Encorafenib was provided as 75 mg capsules for QD oral administration. Binimetinib was provided as 15 mg film-coated tablets for BID oral administration that were to be taken approximately 12 ± 2 hours apart at home. Patients were instructed to take encorafenib and binimetinib with a large glass of water (approximately 250 mL) daily at approximately the same time each morning. Both encorafenib and binimetinib were to be taken without regard to food. On the days when blood was collected at the clinic, morning doses of encorafenib and binimetinib were to be taken at the clinic. Doses of encorafenib that were missed for any reason were to be taken up to 12 hours before the next dose; missed doses of binimetinib were not to be made up either later in the day or at the end of the dosing period. Patients were instructed to swallow the capsules/tablets whole and not to chew or crush them.

Cetuximab

Cetuximab was administered as a QW IV infusion (days 1, 8, 15, and 22 [± 3 days)] of every 28-day cycle): 400 mg/m^2 initial dose (120-minute infusion on cycle 1 day 1), then 250 mg/m^2 (60-minute infusion) thereafter.

Infusion rate was not to exceed 10 mg/minute. Premedication for routine cetuximab infusions was to be administered as described following institutional standards, 30 minutes before infusion. Oral dosing of encorafenib + binimetinib was to be taken 30 minutes before cetuximab, and cetuximab administration was to be completed 1 hour before the start of FOLFIRI or IRI infusion for control arm patients.

Irinotecan

IRI was administered as a Q2W IV infusion (days 1 and 15 [± 3 days] of every 28-day cycle) at a 180 mg/m^2 dose (90-minute infusion).

Folinic acid

Folinic acid was administered as a Q2W IV infusion (days 1 and 15 [± 3 days] of every 28-day cycle) at a 400 mg/m^2 dose (120-minute infusion).

5-Fluorouracil

5-Fluorouracil was administered as an initial 400 mg/m^2 IV dose followed by 1,200 mg/m^2/day IV infusion for 2 days (total 2,400 mg/m^2 over 46-48 hours) given Q2W (days 1 and 15 [± 3 days] of every 28-day cycle).

All IV drugs were to be administered at the study site.

4.3.1.7 Permitted and disallowed concomitant medications

Permitted therapy

In general, the use of any concomitant medication or therapy deemed necessary for the care of the patient was permitted, unless otherwise specified.

Permitted concomitant therapy requiring caution and/or action

The following therapies were permitted but required caution and/or action:

- Drugs that are sensitive substrates of cytochrome (CYP) 2B6, CYP2C8, CYP2C9, CYP2C19, CYP3A4, and uridine diphosphate-glucuronosyltransferase 1A1 or those substrates that have a narrow therapeutic index.
- Moderate inhibitors of CYP3A4 and strong inhibitors of CYP2C19 when coadministered with encorafenib.
- Strong inhibitors of uridine diphosphate-glucuronosyltransferase 1A1 when coadministered with binimetinib.
- Drugs that are known to inhibit or induce P-glycoprotein or breast cancer-resistance protein.

- Drugs that are known to be sensitive or have narrow therapeutic index substrates of breast cancer-resistance protein, P-glycoprotein, organic anion transporter (OAT) 1, OAT3, organic cation transporter 2, organic anion transporting polypeptide (OATP) 1B1, and OATP1B3.
- Haematopoietic growth factors (e.g., erythropoietin, granulocyte colony-stimulating factor, and granulocyte-macrophage colony-stimulating factor) were not to be administered before first dose of study treatment. After IRI or FOLFIRI treatment, if a dose delay was required owing to any grade of neutropenia, prophylactic use of granulocyte colony-stimulating factor and granulocyte-macrophage colony-stimulating factor before the next administration of FOLFIRI was permitted at the investigator's discretion. Use of these drugs was to be reserved for patients who required this therapy as per the labelling of these agents or as dictated by local practice.
- Drugs with a known, conditional, or possible risk to prolong the QT interval and/or induce Torsades de Pointes.
- Anticholinergics in patients with potential contraindications (e.g., obstructive uropathy, glaucoma, and tachycardia).

Prohibited concomitant therapy

The following therapies were prohibited during the study:

- Other anticancer agents (e.g., cytotoxic chemotherapy, small molecule–targeted agents, biological agents, immune response modifiers, or hormonal therapy)
- Investigational drugs and devices
- Radiation therapy (not including palliative radiotherapy at focal sites that covered ≤ 10% of the bone marrow reserve)
- Herbal preparations/medications
- Concomitant strong systemic CYP3A4 inhibitors
- Combination anticholinergic medications containing barbiturates or other agents in patients receiving IRI

4.3.1.8 Primary outcomes

Overall survival

The original sole primary endpoint was OS in the encorafenib + binimetinib with cetuximab arm as compared with the control group. An interim analysis of OS (initial analysis at data cut-off of 11 February 2019) was added to try to expeditiously assess efficacy.

Definition: OS was defined as the time from randomisation to death due to any cause.

Assessments: After the 30-day safety follow-up visit, all patients were followed for survival status every 3 months, or more frequently as needed, until withdrawal of consent, patient lost to follow-up, death, or end of study.

Overall response rate

The protocol was amended to include an additional primary endpoint of ORR by RECIST version 1.1 in the encorafenib + binimetinib with cetuximab arm as compared with the control group, as assessed by blinded independent central review (BICR).

Definition: ORR was defined as the number of patients achieving a best overall response (BOR) of complete response (CR) or partial response (PR) divided by the total number of patients in that treatment arm (see Appendix F for definitions of BOR, CR, etc.).

Assessments: Tumour response was evaluated locally by the investigator and retrospectively by BICR (blinded to treatment assignment) according to RECIST version 1.1. Any lesion that had been previously treated with loco-regional therapies (e.g., radiotherapy, ablation) was to be considered as a non-target lesion, unless it had shown clear progression since the initiation of study treatment, in which case, it was permitted to be considered as a target lesion.

Tumour assessments were performed every 6 weeks (± 7 days) from the date of randomisation until disease progression for the first 24 weeks of treatment, then every 12 weeks (± 7 days) thereafter until disease progression, withdrawal of consent, initiation of subsequent anticancer therapy, patient lost to follow-up, death, or end of study, regardless of whether trial treatment was discontinued.

Tumour assessments performed at screening/baseline and at postscreening/baseline visits included the following:

- Computed tomography (CT) (preferred) with IV contrast (if not contraindicated) or magnetic resonance imaging (MRI) of the chest, abdomen, and pelvis.
- Brain CT with IV contrast or MRI for patients with history of asymptomatic brain metastases. Postscreening or baseline brain CT or MRI scan only if brain metastases were documented at baseline.
- Whole body bone scan imaging, if clinically indicated (i.e., if bone metastases were suspected or known at baseline), using an imaging method per local standard of care. Postscreening or baseline, whole body bone scans did not need to be repeated unless clinically indicated; however, localised CT, MRI, or X-rays of all skeletal lesions identified on the screening/baseline bone scan, if not visible on the chest, abdomen, and pelvis CT/MRI, were to be performed.

All CRs and PRs were confirmed by a second assessment ≥ 4 weeks later. [redacted]. Patients with an overall response of stable disease (StD) or better per RECIST version 1.1 at ≥ 5 weeks after the first dose who did not satisfy the definition of a BOR of CR or PR were assigned a BOR of StD.

4.3.1.9 Other outcomes

Key secondary efficacy endpoint

- OS: encorafenib + cetuximab versus control

Other secondary endpoints

All remaining analyses of ORR, PFS, duration of response (DOR), and time to response (TTR) (all by BICR and by investigator) and OS were conducted for encorafenib + cetuximab versus control, for encorafenib + binimetinib + cetuximab versus control, and for encorafenib + binimetinib + cetuximab versus encorafenib + cetuximab.

Overall response rate was defined as described in Section 4.3.1.8. Progression-free survival, DOR, and TTR were defined as follows:

- PFS: defined as the time from randomisation to the earliest documented date of disease progression, per RECIST version 1.1 and as determined by the investigator, or death due to any cause.
- DOR: defined as the time from first radiographic evidence of response to the earliest documented progressive disease (PD) or death and calculated for responders only.
- TTR: defined as the time from date of randomisation to date of first radiographic evidence of response (CR or PR).

Health-related quality of life endpoints

Patient-reported outcome measures were assessed at screening/baseline, at day 1 of every treatment cycle, at end of treatment, and at the 30-day safety follow-up visit, and included the following:

- European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Core Module (EORTC QLQ-C30, version 3.0)
- Functional Assessment of Cancer Therapy–Colon Cancer (FACT-C, version 4.0)
- EQ-5D-5L
- Patient Global Impression of Change (PGIC)

4.3.2 BEACON CRC: statistical analysis and definition of study groups

4.3.2.1 Populations analysed

The following populations were considered in the study:

- **Full analysis set (FAS):** included all randomised phase 3 patients. Patients were analysed according to the treatment arm and stratum they were assigned to at randomisation.
- **Per-protocol set:** included all phase 3 patients from the FAS without any major protocol deviations (or other criteria that could largely impact efficacy results) and who received at least one dose of study drug. The deviations that led to patient exclusion included the following:
  - No histologically or cytologically confirmed mCRC
  - Not positive for $BRAF^{V600E}$-MT per central assessment
  - Prior treatment with any serine/threonine-protein kinase (RAF) inhibitor, MEK inhibitor, cetuximab, panitumumab, or other EGFR inhibitor
  - Baseline ECOG PS ≥ 3
  - Study treatment received different from treatment assigned by randomisation
- **Phase 3 response efficacy set:** consisted of the first 330 patients randomised and any additional patients randomised on the same day as the 330th randomised patient (n = 331). Corresponds to initial analysis data cut-off of 11 February 2019.
- **Safety set:** included all patients who received at least one dose of study drug and had at least one posttreatment assessment, which may have included death. Patients who received the wrong study treatment (i.e., different from the one assigned by randomisation) for only a part of the treatment period were analysed according to the randomised treatment. If patients had received a wrong study treatment during the whole treatment period, they were analysed according to the actual treatment received.

The prespecified interim analysis of the primary endpoint of ORR for encorafenib + binimetinib + cetuximab versus control was analysed using the phase 3 response efficacy set. Unless otherwise stated, other efficacy analyses for phase 3 patients were performed using the FAS.

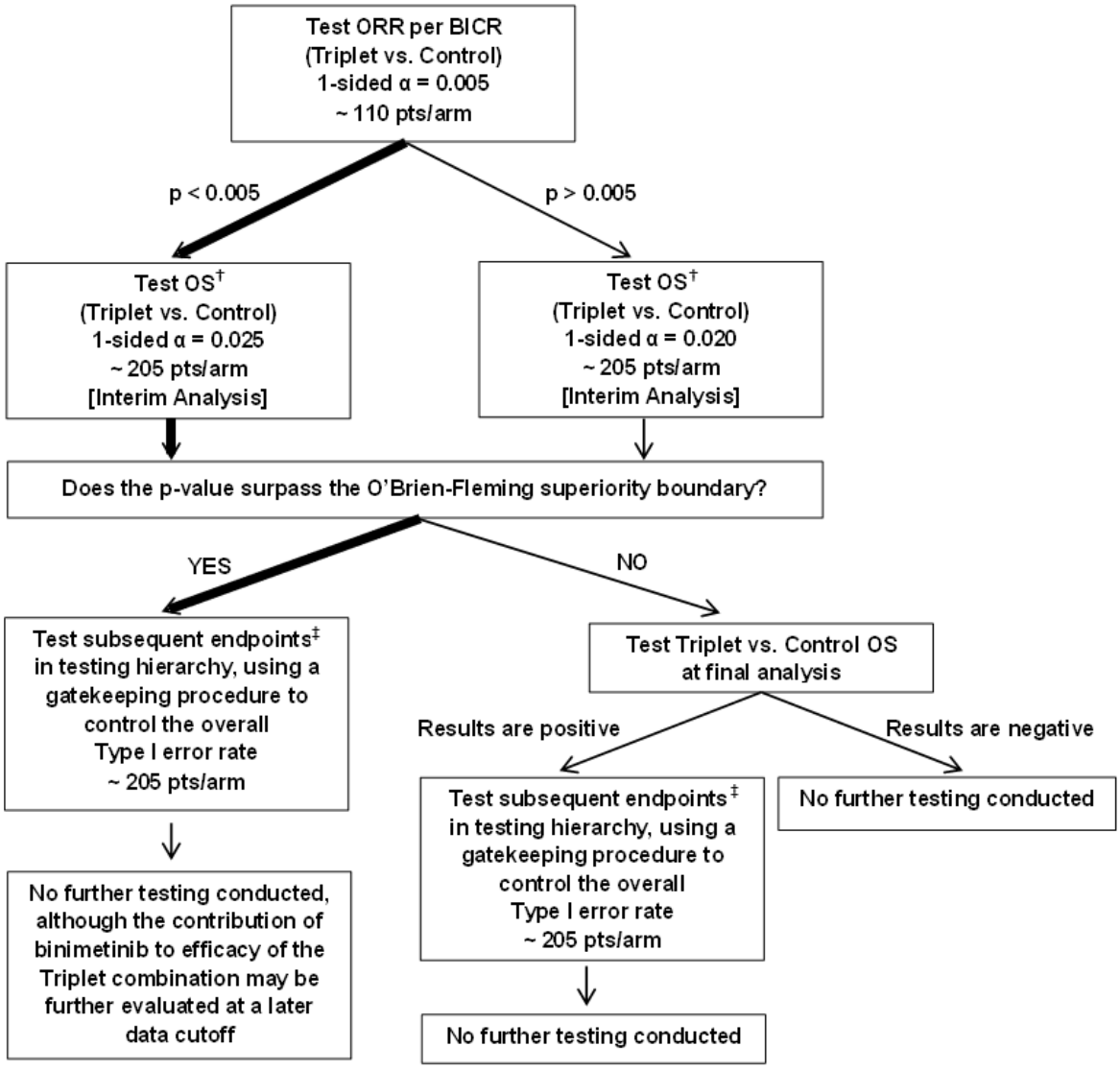
4.3.2.2 Hierarchical statistical testing

The type 1 error rate for the primary endpoints was controlled with the use of a fallback procedure described by Wiens and Dmitrienko [15]. If the *P* value of the encorafenib + binimetinib + cetuximab versus control comparison of ORR at the primary analysis was < 0.005, then the encorafenib + binimetinib + cetuximab versus control OS comparison was to be assigned a total one-sided alpha of 0.025 (Figure 2). Otherwise, it remained at the assigned one-sided 0.020 level.

To incorporate testing of selected secondary endpoints, a gatekeeping procedure with hierarchical testing was used to account for the multiple comparisons (Figure 2). Specifically, if encorafenib + binimetinib + cetuximab versus control OS analysis was positive, the below endpoints were to be tested sequentially until a result that was not statistically significant was found. The endpoints were tested in the following order:

- OS of encorafenib + cetuximab versus control (key secondary endpoint)
- ORR (per BICR) of encorafenib + cetuximab versus control
- PFS (per BICR) of encorafenib + binimetinib + cetuximab versus control
- PFS (per BICR) of encorafenib + cetuximab versus control

Figure 2. Testing strategy for phase 3 primary and secondary endpoints



BICR, blinded independent central review; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; pts, patients.

Note: Bold arrows show the testing sequence performed based on initial analysis.

† A Lan-DeMets spending function that approximates O'Brien-Fleming boundaries was used to account for the multiple (i.e., interim and final) analyses of OS.

‡ Subsequent endpoints were tested in the following order: encorafenib + cetuximab vs. control OS, encorafenib + cetuximab vs. control ORR per BICR, encorafenib + binimetinib + cetuximab vs. control PFS per BICR, and then encorafenib + cetuximab vs. control PFS per BICR.

Planned interim analysis: An interim analysis was prospectively defined, which was planned for when the following three criteria were met:

- Approximately 9 months after randomisation of the 330th patient (i.e., to provide sufficient follow-up for responders)
- At least 188 OS events in the encorafenib + binimetinib + cetuximab and control arms combined
- At least 169 OS events in the encorafenib + cetuximab and control arms combined

ORR analysis by BICR for encorafenib + binimetinib + cetuximab arm versus control: The primary analysis of this outcome was to occur when the criteria for the initial analysis were met.

OS analysis for encorafenib + binimetinib + cetuximab arm versus control: An interim analysis for superiority or (non-binding) futility of the OS endpoint was also performed at the time of the interim analysis based on all available data.

At this initial analysis, the *P* value of the primary ORR analysis of encorafenib + binimetinib + cetuximab versus control comparison was < 0.005; as such, the encorafenib + binimetinib + cetuximab versus control OS comparison was assigned a total one-sided alpha of 0.025 (see Table 5 and bold arrows in Figure 2). Subsequently, as the interim analysis for OS (encorafenib + binimetinib + cetuximab vs. control) was found to exceed the superiority boundary, sequential testing of secondary endpoints was conducted at this point, as described above (see bold arrows in Figure 2).

Table 5. Hierarchical testing summary for efficacy endpoints

	Endpoint		Criterion for	Actual
Primary/secondary	**Assessment**	**Treatment arms**	**significance (*P* value)**	***P* value**
Primary	ORR by BICR	Encorafenib + binimetinib + cetuximab vs. control	0.005	< 0.0001
	OS	Encorafenib + binimetinib + cetuximab vs. control	0.0102	< 0.0001
Key secondary	OS	Encorafenib + cetuximab vs. control	0.0042	0.0002
Secondary	ORR by BICR	Encorafenib + cetuximab vs. control	0.025	< 0.0001
	PFS by BICR	Encorafenib + binimetinib + cetuximab vs. control	0.0112	< 0.0001
	PFS by BICR	Encorafenib + cetuximab vs. control	0.0117	< 0.0001

BICR, blinded independent central review; ORR, overall response rate; OS, overall survival; PFS, progression-free survival.

Continued OS follow-up (as well as other endpoints including ORR and PFS) was prospectively planned for a more mature comparison (15 August 2019 data cut-off).

4.3.2.3 Statistical hypothesis and methods of analyses

Overall survival (primary endpoint)

The following statistical null hypothesis for OS was to be tested:

$$H_0: S_{OS,A}(t) \leq S_{OS,C}(t),$$

where $S_{OS,A}(t)$ is the OS survival distribution function for the encorafenib + binimetinib + cetuximab arm and $S_{OS,C}(t)$ is the OS survival distribution function for the control arm.

The null hypothesis was tested using a stratified log-rank test against the alpha assigned to the endpoint based on the fallback procedure (described in Section 4.3.2.2).

Overall survival was described using the Kaplan-Meier (K-M) method, and the HR and 95% CIs were estimated using Cox proportional hazard models, stratified by randomisation stratification factors.

Futility and superiority boundaries for both the OS interim and final analyses were determined using a Lan-DeMets [16] spending function that approximated O'Brien-Fleming stopping boundaries.

Overall survival (secondary endpoint)

Secondary OS endpoints used the same approach as for the primary OS analysis.

Overall response rate by BICR (primary endpoint)

The ORR by BICR for encorafenib + binimetinib + cetuximab versus control was tested based on the phase 3 response efficacy set and using the Cochran-Mantel-Haenszel test at a one-sided alpha of 0.005. Analysis of the confirmed responses was used for formal testing. The stratification factors used in the test were those used for randomisation and were based on IWRS randomisation information. For the primary analysis, ORR was presented by arm, along with 95% and 99% CIs. A similar analysis for ORR was performed on the FAS.

Secondary overall response rate endpoints

The secondary ORR endpoints were analysed in a similar manner to the primary ORR analyses for the phase 3 response efficacy set and the FAS. The encorafenib + cetuximab versus control comparison of ORR was formally tested using the phase 3 response efficacy set because the preceding endpoints in the testing hierarchy (encorafenib + binimetinib + cetuximab vs. control ORR, encorafenib + binimetinib + cetuximab arm vs. control arm OS, and encorafenib + cetuximab arm vs. control arm OS) were observed to be statistically significant. As all patients in this analysis set were assumed to have sufficient follow-up for response, the full alpha assigned to the OS endpoints (i.e., 1-sided 0.025) was applied to the encorafenib + cetuximab arm versus control arm ORR comparison. Overall response rate by local investigator was also assessed, although this was not part of the hierarchical testing.

Progression-free survival

Progression-free survival was calculated for all patients in the FAS and analysed using the same approach as for OS. [redacted] (see Figure 2). A Lan-DeMets spending function that approximated O'Brien-Fleming stopping boundaries was applied in formal testing.

Progression-free survival by BICR was prioritised in the hierarchical testing. Progression-free survival by local investigator was also analysed, although this was not part of the hierarchical testing.

Other outcomes

Analyses of DOR and TTR were performed using BICR and local investigator assessments and summarised using the K-M method for the FAS and phase 3 Efficacy Response Set. No formal statistical test was performed for TTR.

EORTC QLQ-C30, FACT-C, EQ-5D-5L, and PGIC were assessed in the FAS and summarised with descriptive statistics. Time to definitive deterioration in HRQoL scores was presented as K-M curves.

4.3.2.4 Sample size and power calculation

Sample size (approximately 615) was driven by the secondary endpoint of OS in the encorafenib + cetuximab versus control comparison. For this comparison, it was calculated that 338 deaths would be required to give the trial 90% power to detect a HR for death of 0.70, with the use of a stratified log-rank test at a one-sided significance level of 0.025. This corresponds to a median OS of 7.1 months in the encorafenib + cetuximab arm and 5 months in the control arm.

The final OS analysis was planned to occur when at least 268 and 338 OS events had occurred in the combined encorafenib + binimetinib + cetuximab and control arms and the combined encorafenib + cetuximab and control arms, respectively. With 268 events in the encorafenib + binimetinib + cetuximab and control arms, there would be approximately 90% power to detect an HR of 0.67 at a one-sided significance level of 0.025.

The number of patients needed to be included in the primary analysis of ORR in the encorafenib + binimetinib + cetuximab versus control comparison was based on an assumption that the ORR would be 10% in the control group and 30% in the encorafenib + binimetinib + cetuximab group; it was calculated that 110 patients per group would provide 88% power, at a one-sided significance level of 0.005, to show the higher ORR in the encorafenib + binimetinib + cetuximab group.

4.3.2.5 Sensitivity analyses and other supportive analyses

Several sensitivity analyses were conducted to support the primary analysis of OS and ORR, providing nominal *P* values for descriptive purposes, as described below. Additional sensitivity analyses for key secondary endpoints, including PFS, were also conducted.

Overall survival

- Using the per-protocol set
- Unstratified Cox regression (FAS)
- Using multivariate stratified Cox regression to assess effect of potential prognostic factors; see Section 4.3.2.3 for covariates

Overall response rate

- Using unstratified Chi-squared test
- Using the FAS
- Patients who had measurable disease at baseline (phase 3 response efficacy set)
- Using multivariate stratified Cox regression to assess effect of potential prognostic factors (phase 3 response efficacy set); see Section 4.3.2.3 for covariates

Multivariate stratified Cox regression

Multivariate stratified Cox regression included the following covariates:

- Randomisation stratification factors: ECOG PS status, prior IRI use, cetuximab source.
- Additional baseline factors: sex (male vs. female); age (< 65 vs. ≥ 65 years); removal status of primary tumour (no resection/partial resection, complete resection); C-reactive protein (CRP) baseline level (≤ upper limit of normal [ULN] vs. > ULN); side of tumour (left/right vs. left vs. right); number of organs involved based on target and non-target lesion assessment (≤ 2 vs. 3+); presence of liver metastases at baseline, based on target and non-target lesion assessment (yes vs. no); number of prior regimens (1 vs. 2); and prior oxaliplatin use (yes vs. no). To avoid model instabilities, these covariates were only included if there were ≥ 10 patients in each category; microsatellite instability status (high vs. stable) was excluded from the model for this reason.

4.3.2.6 Data management and withdrawals

Missing data were imputed using rules specified in the statistical analysis plan as described below.

Overall survival

If a death was not observed by the date of analysis cut-off, OS was to be censored at the date of last contact.

Progression-free survival

If death or disease progression was not observed, PFS was censored at the date of last adequate tumour assessment (i.e., at the date of last tumour assessment of CR, PR, StD) before cut-off date or date a subsequent anticancer therapy was started. If a PFS event was observed after more than one missing or inadequate tumour assessment, PFS was censored at the last adequate tumour assessment. If a PFS event was observed after a single missing or non-adequate tumour assessment, the actual date of event was used.

When a patient discontinued treatment for "disease progression" based on clinical deterioration, without documented evidence of progression based on RECIST version 1.1, it was not to be considered as a PFS event.

Table 6 presents censoring rules applied to the PFS endpoint.

Table 6. Censoring rules for progression-free survival

	Situation	Event date	Outcome
A[a]	No baseline assessment	Date of randomisation	Censored
B	Progression or death at or before next scheduled assessment	Date of progression (or death)	Progressed
C1	Progression or death after exactly 1 missing assessment	Date of progression (or death)	Progressed
C2	Progression or death after 2 or more missing assessments	Date of last adequate tumour assessment[b]	Censored
D	No progression	Date of last adequate tumour assessment[b]	Censored
E	Treatment discontinuation due to "disease progression" without documented progression, i.e., clinical progression based on investigator claim	Not applicable (not considered as an event, patient without documented progressive disease should be followed for progression after discontinuation of treatment)	Information ignored
F	New antineoplastic therapy given	Date of last adequate tumour assessment[b]	Censored

[a] Patients with a first tumour assessment postrandomisation but before treatment start were considered as "No baseline assessment." If the patient died no later than the time of the second scheduled assessment as defined in the protocol, then a progression-free survival event at the date of death was counted.

[b] Tumour assessment with non-missing and non-unknown overall lesion response.

When no imaging/measurement was done at all at a particular time point, the patient was classed as "not evaluable" at that time point. If only a subset of lesion measurements was made at an assessment, usually the case was also considered "not evaluable" at that time point, unless a convincing argument could be made that the contribution of the individual missing lesion(s) would not change the assigned time point response. This was most likely to happen in the case of PD.

Duration of response

For DOR, responders who did not have a PD or death date by the data cut-off date were censored at their last adequate radiological assessment (i.e., at the date of last tumour assessment of CR, PR, or StD) before the cut-off date or date when a subsequent anticancer therapy for mCRC was started.

Time to response

For TTR, patients who did not have a CR or PR by the data cut-off date were censored for TTR at their last radiological assessment. Patients who received subsequent anticancer therapy before response were censored at their last radiological assessment before initiation of subsequent anticancer therapy.

4.3.3 BEACON CRC: participant flow

A total of 1,677 patients were screened for eligibility. In total, 665 patients were randomised in a 1:1:1 ratio to receive encorafenib + cetuximab (n = 220), encorafenib + binimetinib + cetuximab (n = 224), or investigator's choice of either IRI + cetuximab or FOLFIRI + cetuximab (control; n = 221). For further details, please refer to Appendix G.

4.3.4 BEACON CRC: baseline characteristics and demographics

Table 7 summarises patient characteristics at phase 3 study baseline. Overall, the treatment arms were mostly balanced with respect to baseline demographic and disease and tumour characteristics.

Most patients were white (82.7%), with a higher proportion of Asian patients in the control arm (17.6%) compared with the encorafenib and encorafenib + binimetinib arms (11.4% and 8.9%, respectively). Overall, slightly more females (52.8%) than males were enrolled. Most patients were younger than 65 years (64.2%), with a median age of 61 years for all patients.

ECOG PS as per the electronic case report form was largely evenly divided between 0 (50.5%) and 1 (48.9%), with 4 patients (0.6%) with an ECOG PS of 2 (all were in the encorafenib + cetuximab arm and were ECOG PS 1 at randomisation).

An inclusion criterion for the study was the presence of a $BRAF^{V600E}$-MT at baseline that was determined either by local or central analysis. [redacted] a central assay outcome that did not confirm the local positive result (i.e., the result was indeterminate, there was no neoplastic cell in tissue, or the result was missing).

Most patients overall (56.8%) had had complete resection of the primary tumour. The mean and median number of organs involved at baseline [redacted] respectively. The liver was the most common sight of metastases, affecting 61.1% of patients, with lung, lymph nodes, and peritoneum/omentum also being affected.

The percentage of patients who had progressed after one or two prior systemic regimens for metastatic disease was similar across the three treatment arms, with more patients overall who received one prior systemic regimen (65.7%) than two prior systemic regimens (34.0%). Approximately [redacted], control arm) [redacted]

Table 7. BEACON CRC: baseline characteristics and demographics—full analysis set

	Encorafenib + binimetinib + cetuximab (n = 224)	Encorafenib + cetuximab (n = 220)	Control (n = 221)
Sex, n (%)			
Male	105 (46.9)	115 (52.3)	94 (42.5)
Female	119 (53.1)	105 (47.7)	127 (57.5)
Age (years)			
Mean (SD)	59.5 (11.65)	60.2 (11.65)	58.4 (12.07)
Median	62	61	60
Min, max	26, 85	30, 91	27, 91

	Encorafenib + binimetinib + cetuximab (n = 224)	Encorafenib + cetuximab (n = 220)	Control (n = 221)
Race, n (%)			
Asian	20 (8.9)	25 (11.4)	39 (17.6)
White	195 (87.1)	183 (83.2)	172 (77.8)
Black/African American	2 (0.9)	0 (0.0)	0 (0.0)
Other[a]	3 (1.3)	3 (1.4)	3 (1.4)
Not reported owing to confidentiality reasons	4 (1.8)	8 (3.6)	7 (3.2)
ECOG PS at baseline, n (%)[b]			
0	116 (51.8)	112 (50.9)	108 (48.9)
1	108 (48.2)	104 (47.3)	113 (51.1)
2	0 (0.0)	4 (1.8)[c]	0 (0.0)
Number of prior systemic regimens for metastatic disease, n (%)			
1	146 (65.2)	146 (66.4)	145 (65.6)
2	77 (34.4)	74 (33.6)	75 (33.9)
> 2	1 (0.4)	0 (0.0)	1 (0.5)
Prior IRI	116 (51.8)	114 (51.8)	117 (52.9)
Prior oxaliplatin	199 (88.8)	210 (95.5)	201 (91.0)
Primary tumour location, n (%)			
Left colon, including rectum	79 (35.3)	83 (37.7)	68 (30.8)
Right colon	126 (56.3)	110 (50.0)	119 (53.8)
Left and right colon	8 (3.6)	11 (5.0)	22 (10.0)
Unknown	11 (4.9)	16 (7.3)	12 (5.4)
Primary tumour removed, n (%)			
Completely resected	133 (59.4)	123 (55.9)	122 (55.2)
Partially resected/unresected	91 (40.6)	97 (44.1)	99 (44.8)
Number of organs involved			
Mean (SD)	3 (1.3)	3 (1.4)	3 (1.3)
Median	2	2	2
Min, max	1, 7	0, 7	1, 8
Number of organs involved, n (%)			
≤ 2	114 (50.9)	117 (53.2)	123 (55.7)
≥ 3	110 (49.1)	103 (46.8)	98 (44.3)
Sites of metastases, n (%)			
Liver	144 (64.3)	134 (60.9)	128 (57.9)
Lung	86 (38.4)	83 (37.7)	86 (38.9)
Lymph node	86 (38.4)	82 (37.3)	88 (39.8)
Peritoneum/omentum	77 (34.4)	97 (44.1)	93 (42.1)

	Encorafenib + binimetinib + cetuximab (n = 224)	Encorafenib + cetuximab (n = 220)	Control (n = 221)
Microsatellite instability status (polymerase chain reaction), n (%)			
Abnormal high	22 (9.8)	19 (8.6)	12 (5.4)
Abnormal low	0 (0.0)	1 (0.5)	1 (0.5)
Normal	153 (68.3)	157 (71.4)	147 (66.5)
Not evaluable	15 (6.7)	16 (7.3)	10 (4.5)
Missing	34 (15.2)	27 (12.3)	51 (23.1)
Carcinoembryonic antigen at baseline, n (%)			
> 5 µg/L	179 (79.9)	153 (69.5)	178 (80.5)
≤ 5 µg/L	45 (20.1)	67 (30.5)	42 (19.0)
Missing	0 (0.0)	0 (0.0)	1 (0.5)
CRP at baseline, n (%)			
> 0.01 g/L	95 (42.4)	79 (35.9)	90 (40.7)
≤ 0.01 g/L	121 (54.0)	139 (63.2)	126 (57.0)
Missing	8 (3.6)	2 (0.9)	5 (2.3)

CRP, C-reactive protein; ECOG PS, Eastern Cooperative Oncology Group performance status; IRI, irinotecan; IWRS, interactive web response system; max, maximum; min, minimum, SD, standard deviation.

Note: No formal comparisons between treatment groups were performed.

[a] Other includes categories of American Indian/Alaska Native and Other.

[b] ECOG PS as per electronic case report form at baseline and not per IWRS at randomisation.

[c] All 4 patients were ECOG PS 1 by the time of randomisation per the IWRS.

Sources: CSR [13]; Kopetz et al. [11].

4.3.5 BEACON CRC: quality assessment

BEACON CRC is a large, global, multinational, multicentre, randomised, open-label, active-controlled, well-conducted, and methodologically robust phase 3 study. The study was approved by the institutional review board or independent ethics committee for each study centre and was conducted according to the requirements of the regulatory authorities of each country and with the provisions of the Declaration of Helsinki and the Good Clinical Practice guidelines of the International Council on Harmonisation.

All patients provided written informed consent. The steering committee and one of the sponsors (Array BioPharma) jointly designed the trial and reviewed the data. An independent Data Monitoring Committee was established to monitor data to ensure the continuing safety of the study participants.

BEACON CRC was conducted in an open-label manner; however, several steps were taken to minimise bias, as described in Section 4.3.1.3. The randomisation schedule was created and managed by a third-party vendor, and treatments were assigned according to a computerised central randomisation list using an IWRS.

Table 8 presents a summary of the quality assessment for BEACON CRC, which was performed according to the York Centre for Reviews and Dissemination quality assessment tool [17].

Table 8. Quality assessment for BEACON CRC

Trial name	BEACON CRC
Was randomisation carried out appropriately?	Yes. The randomisation schedule was created and managed by a third-party vendor, and treatments were assigned according to a computerised central randomisation list using an IWRS.
Was the concealment of treatment allocation adequate?	Yes. See above.
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes. Baseline characteristics were balanced between the groups.
Were the care providers, participants, and outcome assessors blind to treatment allocation?	No. This was an open-label trial. To minimise bias, the sponsor, their designee trial team, and the independent review committee were blinded to patient treatment assignment. The randomisation schedule was created and managed by a third-party vendor, and treatments were assigned according to a central randomisation list using the IWRS.
Were there any unexpected imbalances in dropouts between groups?	No. Discontinuation rates for any reason were similar across study arms. Most discontinuations across all arms were due to disease progression.
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No.
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes. Analyses were conducted on the full analysis set, consisting of all randomised phase 3 patients. Following the intention-to-treat principle, patients were analysed according to the treatment arm and stratum they were assigned to at randomisation.

IWRS, interactive web response system.

5 Clinical question

5.1 What is the value of encorafenib + cetuximab compared with FOLFIRI (± bevacizumab or EGFR inhibitor) or FOLFOX (± bevacizumab or EGFR inhibitor) in patients with metastatic colorectal cancer and BRAF^{V600E} mutation?

5.1.1 Presentation of relevant studies

This submission is based primarily on the BEACON CRC study. The DMC requests published clinical evidence for consideration by the committee. For BEACON CRC, the following clinical data from three cut-off dates are available as published and unpublished data and are presented in this application:

- 11 February 2019 data cut-off
  - [redacted] [13]
  - BRAFTOVI summary of product characteristics (SmPC) [1] and European Public Assessment Report (EPAR) [14]
  - Kopetz et al. *New England Journal of Medicine,* 2019, supplementary appendix and protocol (phase 3) [11]
  - Kopetz et al. Gastrointestinal Cancers Symposium, 2020 [18]
  - Van Cutsem et al. *Journal of Clinical Oncology*, 2019 (SLI) [12]
  - Kopetz et al. American Society of Clinical Oncology (ASCO) Symposium, 2020 (HRQoL data) [19]
- 15 August 2019 data cut-off
  - [redacted] [20]
  - [redacted] [21]
  - [redacted] [22]
  - BRAFTOVI SmPC [1] and EPAR [14]
  - Kopetz et al. Gastrointestinal Cancers Symposium, 2020 [18]
  - Kopetz et al. ASCO Symposium, 2020 [23]
- 5 May 2020 data cut-off
  - [redacted]

BEACON CRC included three study arms:

- Encorafenib + cetuximab
- Encorafenib + binimetinib + cetuximab
- Control arm comprising investigator's choice of either:
  - IRI + cetuximab, or
  - FOLFIRI + cetuximab

The key efficacy and safety results presented here that will inform decision making and are of direct relevance to future clinical practice in Denmark are those that compare the double regimen of encorafenib + cetuximab versus control. These include the key secondary (OS) and other secondary

(ORR, PFS, DOR, TTR) endpoints for the study. Patient-reported outcome endpoints, including the EQ-5D, are also provided.

Results for the triple combination of encorafenib + binimetinib + cetuximab are not relevant to decision making because marketing authorisation for the triple combination is not being sought at this time. Key efficacy results for this regimen, which include the primary endpoints of the study (OS and ORR for encorafenib + binimetinib + cetuximab versus control) and the secondary PFS endpoint, are provided in Appendix F for completeness. Other secondary efficacy endpoints and safety results for the encorafenib + binimetinib + cetuximab regimen are not provided.

Data are available from three data cut-offs: the prespecified interim analysis, as of 11 February 2019; the prespecified analysis as of 15 August 2019; and the long-term post hoc survival analyses as requested by the DMC as of 5 May 2020. Because the 15 August 2019 and 5 May 2020 data sets are the most mature, results from these cut-offs are presented as the key results in the main application, with the earlier February data set presented in Appendix F. Table 9 presents a full description of the location of all results in this application.

Table 9. BEACON CRC: summary of results presented in application

	Encorafenib + cetuximab vs. control			Encorafenib + binimetinib + cetuximab vs. control	
Outcomes[a]	**5 May 2020**	**15 August 2019**	**11 February 2019**	**15 August 2019**	**11 February 2019**
OS	Table 10, Section 5.1.1	Table 10, Section 5.1.1	Appendix F, Section F.2.2	Appendix F, Section F.2.3	Appendix F, Section F.2.3
ORR	Not presented	Appendix F, Section F.2.1			
PFS					
DOR				Not presented	Not presented
TTR					
Quality of life		Table 10, Section 5.1.1	Table 10, Appendix F.2.2.6		
Safety and side effects		Table 10, Section 5.1.1	Appendix F, Section F.3.1	Not presented	Not presented

DOR, duration of response; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; TTR, time to response.

[a] Outcomes identified as critical or important by the DMC are highlighted in bold.

In the protocol, the DMC requested data on OS (critical outcome), quality of life (QoL; important outcome), and side effects (important outcome). Table 10 provides a summary of the BEACON CRC results for the outcome measures specified in the protocol.

Table 10. Summary of the value of encorafenib + cetuximab compared with FOLFIRI (± bevacizumab or EGFR inhibitor) or FOLFOX (± bevacizumab or EGFR inhibitor) in patients with metastatic colorectal cancer and BRAF^{V600E} mutation

Results per outcome (minimum clinically relevant difference identified in protocol)	Study arm	N	Result	BEACON CRC data set included in the analysis	Absolute difference in effect vs. control			Relative difference in effect vs. control			Description of methods used for estimation	Methods used for quantitative synthesis
					Difference	CI	*P* value	Hazard/ odds/ risk ratio	CI	*P* value		
Median OS, months (3 months)	Enco + cetux	220	9.3 months (95% CI, 8.05-11.30)	August 2019 cut-off [18, 23]	3.4 months	NA	NA	HR = 0.61	0.48-0.77	< 0.0001	Stratified Cox proportional hazard ratios, log-rank 1-sided *P* value; stratified by ECOG PS, source of cetuximab, and prior IRI use at randomisation.	NA
	Control	221	5.9 months (95% CI, 5.09–7.10)									
	Enco + cetux	220	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		NA
	Control	221	[redacted]									
12-month survival	Enco + cetux	220	41.5% (95% CI, 34.2-48.7)	August 2019 cut-off [18, 20, 23]	16.7%	NA	NA	NA	NA	NA	Event-free probability estimates were obtained from K-M survival estimates. The Greenwood formula was used for CIs of K-M estimates.	NA
	Control	221	24.8% (95% CI, 18.5-31.5)									
	Enco + cetux	220	[redacted]	[redacted]	[redacted]	NA	NA	NA	NA	NA		NA
	Control	221	[redacted]									

Results per outcome (minimum clinically relevant difference identified in protocol)	Study arm	N	Result	BEACON CRC data set included in the analysis	Absolute difference in effect vs. control			Relative difference in effect vs. control			Description of methods used for estimation	Methods used for quantitative synthesis
					Difference	CI	*P* value	Hazard/ odds/ risk ratio	CI	*P* value		
Quality of life												
EORTC QLQ-C30 Global Health Status (10 points): time to definitive 10% deterioration, months	Enco + cetux	[redacted]									Stratified Cox proportional hazard ratios; stratified by ECOG PS, source of cetuximab, and prior IRI use at randomisation.	NA
	Control											
	Enco + cetux											NA
	Control											
EORTC QLQ-C30 Global Health Status (10 points): mean (SD) change from baseline at end of treatment, points	Enco + cetux										Descriptive statistics only	NA
	Control											NA
	Enco + cetux											NA
	Control											NA
FACT-C Colorectal Cancer subscale (not specified):	Enco + cetux										Stratified Cox proportional hazard ratios; stratified by ECOG PS, source of cetuximab, and	NA
	Control											
	Enco + cetux											NA

Results per outcome (minimum clinically relevant difference identified in protocol)	Study arm	N	Result	BEACON CRC data set included in the analysis	Absolute difference in effect vs. control			Relative difference in effect vs. control			Description of methods used for estimation	Methods used for quantitative synthesis
					Difference	CI	*P* value	Hazard/ odds/ risk ratio	CI	*P* value		
time to definitive 10% deterioration	Control	221	[redacted]								prior IRI use at randomisation.	
EQ-5D-5L Visual Analogue Scale (not specified): time to definitive 10% deterioration	Enco + cetux	220									Stratified Cox proportional hazard ratios; stratified by ECOG PS, source of cetuximab, and prior IRI use at randomisation.	NA
	Control	221										
	Enco + cetux	220										NA
	Control	221										
EQ-5D-5L Utility Index score (not specified): time to definitive 10% deterioration	Enco + cetux	220									Stratified Cox proportional hazard ratios; stratified by ECOG PS, source of cetuximab, and prior IRI use at randomisation.	NA
	Control	221										
	Enco + cetux	220										NA
	Control	221										
PGIC (not specified): proportion with "much improved" or "very	Enco + cetux	220									Descriptive statistics only	NA
	Control	221										
	Enco + cetux	220										NA

Results per outcome (minimum clinically relevant difference identified in protocol)	Study arm	N	Result	BEACON CRC data set included in the analysis	Absolute difference in effect vs. control			Relative difference in effect vs. control			Description of methods used for estimation	Methods used for quantitative synthesis
					Difference	CI	*P* value	Hazard/ odds/ risk ratio	CI	*P* value		
much improved" at cycle 2	Control	221	[redacted]									

Results per outcome (minimum clinically relevant difference identified in protocol)	Study arm	N	Result	BEACON CRC data set included in the analysis	Absolute difference in effect vs. control			Relative difference in effect vs. control			Description of methods used for estimation	Methods used for quantitative synthesis
					Difference	CI	*P* value	Hazard/ odds/ risk ratio	CI	*P* value		
Side effects												
Any AE (n [%], not specified)	Enco + cetux	216	212 (98%)	February 2019 cut-off [10, 11]	1%	NA	NA	RR = 1.01	0.98-1.04	0.6146	Descriptive statistics only	NA
	Control	193	188 (97%)									
Grade 3 or 4 AE (n [%], 5% points)	Enco + cetux	216	108 (50%)	February 2019 cut-off [10, 11]	-11%	-21% to -1%	NA	RR = 0.82	0.69-0.98	0.0312		NA
	Control	193	117 (61%)									
Any TEAE (n [%], not specified)	Enco + cetux	216	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Descriptive statistics only	NA
	Control	193	[redacted]									
Grade 3 or 4 TEAE (n [%], 5% points)	Enco + cetux	216	46 (21.3%)	August 2019 cut-off [14]	−21.2%	-30.1% to -12.3%	NA	RR = 0.50	0.37-0.68	<0.0001		NA
	Control	193	82 (42.5%)									
On-treatment deaths[a] (n [%], not specified)	Enco + cetux	216	38 (17.6%)	August 2019 cut-off [14]	2.6%	NA	NA	RR = 1.17	0.75-1.82	0.4849		NA
	Control	193	29 (15.0%)									

AE = adverse event; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group Performance Status; EGFR, epidermal growth factor receptor; Enco + cetux, encorafenib + cetuximab; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer QLQ-C30; FACT-C, Functional Assessment of Cancer Therapy–Colorectal Cancer; FOLFIRI, folinic acid + 5-fluorouracil + irinotecan; FOLFOX, folinic acid + 5-fluorouracil + oxaliplatin; HR = hazard ratio; IRI, irinotecan; K-M, Kaplan-Meier; NA, not available; OS, overall survival; PGIC, Patient Global Impression of Change; RR, relative risk; SD, standard deviation; TEAE, treatment-related adverse event.

Note: The control arm in BEACON CRC was FOLFIRI or IRI + cetuximab. Data highlighted and underlined in yellow are unpublished and confidential.

[a] Most on-treatment deaths were due to progression of metastatic colorectal cancer.

5.1.2 Results per study

5.1.2.1 Overall survival

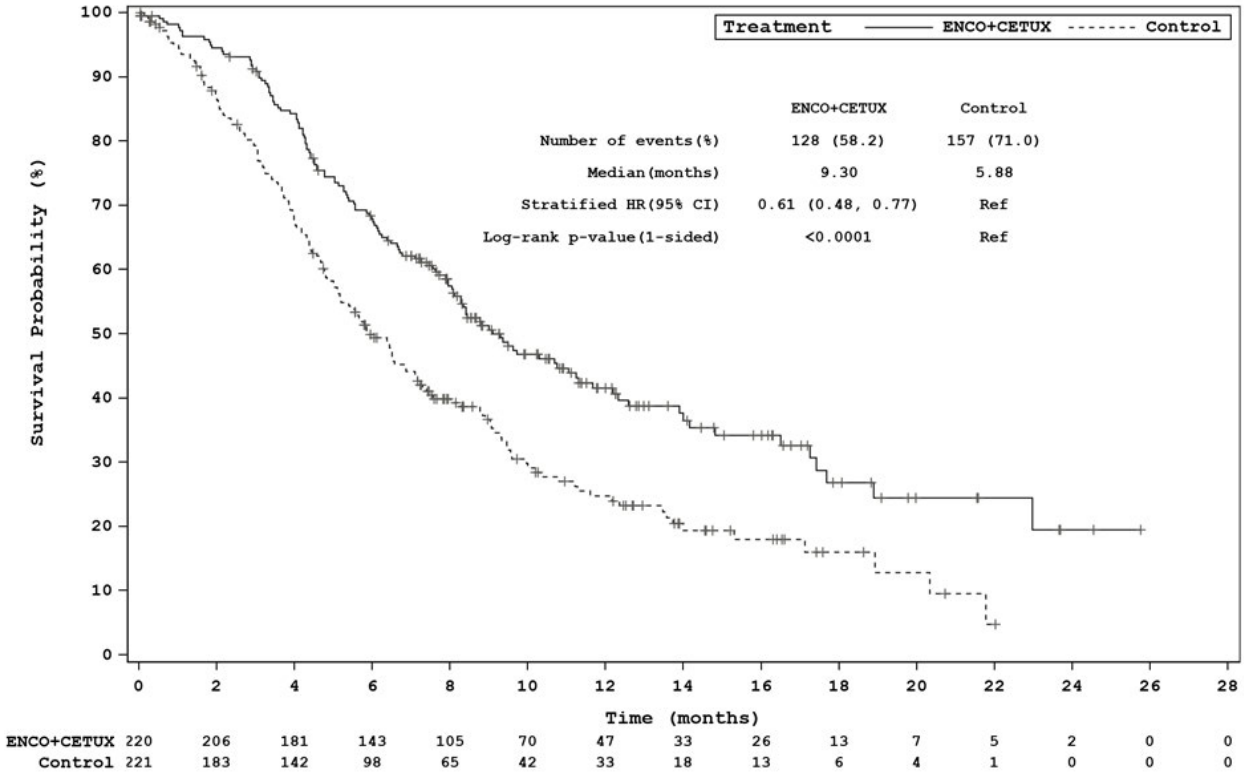
Overall survival data are available from three data cut-offs: the prespecified interim analysis (11 February 2019), the prespecified analysis (15 August 2019), and the long-term post hoc survival analyses as requested by the DMC (5 May 2020). Because the 15 August 2019 and 5 May 2020 data sets are the most mature, results from these cut-offs are presented as the key results in the main application below, with the earlier February data set presented in Appendix F, Section F.2.2.

Overall survival: encorafenib + cetuximab versus control (prespecified analyses, data cut-off 15 August 2019) [23]

- As of the cut-off date for the prespecified analysis (15 August 2019), the median duration of follow-up for survival was 12.8 months (using a reverse K-M analysis). A total of 128 (58.2%) and 157 (71.0%) patients in the encorafenib + cetuximab and control arms, respectively, died on or before the data cut-off date.
- Median OS was 9.30 months (95% CI, 8.05-11.30 months) in the encorafenib + cetuximab group and 5.88 months (95% CI, 5.09-7.10 months) in the control group, representing a clinically meaningful[iv] improvement of 3.4 months (Figure 3 and Table 11). The OS curves separate early (by 2 months after randomisation) and remain evenly separated over time (Figure 3) [23].
- The risk of death was significantly lower (by 39%) in the encorafenib + cetuximab group than in the control group (HR, 0.61; 95% CI, 0.48-0.77; 1-sided $P < 0.0001$).
- Estimated 12-month survival was 41.5% with encorafenib + cetuximab and 24.8% with control; 6-month survival was 67.9% with encorafenib + cetuximab and 49.9% with control.

[iv] In CRC, ASCO recommends that an increase in OS between 3 and 5 months and an HR of 0.67 translate to a clinically meaningful benefit [25].

Figure 3. Overall survival: encorafenib + cetuximab versus control—full analysis set, data cut-off 15 August 2019



CI, confidence interval; CETUX, cetuximab; ENCO, encorafenib; HR, hazard ratio.

Sources: Kopetz Gastrointestinal Cancers Symposium 2020 [18]; CSR Addendum Figure 5 [20]; Kopetz [23]; Pierre Fabre [1].

Table 11. Overall survival: encorafenib + cetuximab versus control—full analysis set, data cut-off 15 August 2019

	Encorafenib + cetuximab (n = 220)	Control (n = 221)
Patients with events/patients included in analysis, n/N (%)	128/220 (58.2)	157/221 (71.0)
Median (95% CI), months	9.30 (8.05-11.30)	5.88 (5.09-7.10)
Stratified hazard ratio (95% CI)[a,b]	0.61 (0.48-0.77)	—
Stratified log-rank (1-sided) *P* value[a,b]	< 0.0001	—
Survival probability estimates, % (95% CI)[c]		
2 months	94.5 (90.5-96.8)	86.9 (81.6-90.8)
4 months	84.3 (78.7-88.5)	67.8 (61.1-73.7)
6 months	67.9 (61.2-73.7)	49.9 (42.9-56.4)
8 months	57.5 (50.5-63.9)	39.9 (33.1-46.6)
10 months	46.8 (39.6-53.7)	29.2 (22.7-35.9)
12 months	41.5 (34.2-48.7)	24.8 (18.5-31.5)
14 months	36.5 (29.0-44.1)	19.4 (13.4-26.1)
16 months	34.2 (26.5-42.0)	18.0 (12.0-24.9)
18 months	26.9 (18.5-36.0)	16.0 (9.9-23.4)

CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; IRI, irinotecan; K-M, Kaplan-Meier; OS, overall survival.

[a] Reference group for comparisons is control.

[b] Stratified by ECOG PS, source of cetuximab, and prior IRI use at randomisation.

[c] Probability estimate is the estimated probability that a patient will remain event-free up to the specified time point. Event-free probability estimates were obtained from K-M survival estimates. The Greenwood formula was used for CIs of K-M estimates.

Sources: CSR Addendum Table 9 and Table 14.2-2.1.1 [20]; Kopetz [23]; Pierre Fabre [1].

Censoring and potential follow-up of overall survival

A total of 41.8% and 29.0% of patients in the encorafenib + cetuximab and control arms, respectively, were censored for the OS analysis; 38.6% and 22.2% of patients, respectively, were alive and ongoing in OS follow-up. Fewer patients in the encorafenib + cetuximab arm than in the control arm were censored because they withdrew consent (censored patients: 5 of 92 vs. 14 of 64, respectively). Most censored patients were last contacted ≤ 3 months before the data cut-off date.

Overall survival supportive analyses

A supportive multivariate Cox regression model stratified by study strata (ECOG PS, prior IRI use, and cetuximab source) and adjusted for prespecified baseline covariates was used to explore the consistency of treatment effect on OS.

- The analysis demonstrated that, after adjusting for the prespecified baseline covariates, the OS comparison of encorafenib + cetuximab arm versus control was consistent with the primary OS analysis (HR, 0.54; 95% CI, 0.42-0.69; 2-sided $P < 0.0001$).
- The following four prespecified covariates also reached statistical significance: the presence of liver metastases at baseline, baseline CRP, patient age, and number of organs involved at baseline. Baseline CRP > ULN had the largest effect on OS and increased the risk of death 2.56-fold (expressed as inverse of HR, 0.39; 95% CI, 0.30-0.51; 2-sided $P < 0.0001$).

Overall survival: encorafenib + cetuximab versus control (data cut-off 5 May 2020)

- Pierre Fabre performed an exploratory analysis of BEACON CRC assessing OS using the most recent data set, dated 5 May 2020 (cut-off not predefined). At the cut-off date, the median [redacted] patients in the encorafenib + cetuximab and control arms, respectively, died on or before the data cut-off date.
- Figure 4 presents the K-M curves from BEACON CRC for encorafenib + cetuximab and for the control arm, FOLFIRI or IRI + cetuximab.
- This exploratory analysis demonstrated a proportion of patients alive with encorafenib + cetuximab at 34 months of [redacted]

[redacted]

[redacted]

Survival probability estimates, % (95% CI)[a]	Encorafenib + cetuximab (n = 220)	Control (n = 221)
2 months	[redacted]	
4 months		
6 months		
8 months		
10 months		
12 months		
14 months		
16 months		
18 months		
20 months		
22 months		
24 months		
26 months		
28 months		
30 months		
32 months		
34 months		
36 months		

CI, confidence interval; K-M, Kapla

[a] Probability estimate is the estimated probability that a patient will remain event-free up to the specified time. Event-free probability estimates were obtained from K-M survival estimates. The Greenwood formula was used for CIs of K-M estimates.

Source: [redacted]

- The OS HRs comparing the treatment arms and their medians were similar to the predefined BEACON CRC analysis from the 15 August 2019 data cut-off (Table 13).

Table 13. Overall Survival: encorafenib + cetuximab versus control—full analysis set, data cut-offs 15 August 2019 and 5 May 2020

	15 August 2019		5 May 2020	
	Stratified HR (95% CI)	Median OS	Stratified HR (95% CI)	Median OS
Encorafenib + cetuximab (n = 220)	0.61 (0.48-0.77)	9.3 months	[redacted]	[redacted]
Control (n = 221)	-	5.88 months	[redacted]	[redacted]

CI, confidence interval; HR, hazard ratio; OS, overall survival.

Sources: [redacted] Kopetz [23].

5.1.2.2 Health-related quality of life

In BEACON CRC, HRQoL measures were assessed at screening/baseline, day 1 of every treatment cycle, end of treatment, and the 30-day safety follow-up visit; measures included the EORTC QLQ-C30, FACT-C, EQ-5D-5L, and PGIC. Results reported in the main application are from the latest August 2019 data cut (unpublished); published results from the February 2019 data cut

[18, 19] are included in Appendix F, Section F.2.2.6. Results showed encorafenib + cetuximab demonstrated longer maintenance of QoL in patient-reported assessments when compared with standard chemotherapy in patients with $BRAF^{V600E}$-MT mCRC whose disease had progressed after prior regimens, and similar results were observed across all QoL assessments [22].

EORTC QLQ-C30: encorafenib + cetuximab versus control (data cut-off 15 August 2019)

Median EORTC QLQ-C30 Global Health Status and Physical, Emotional, and Social Functioning scores were similar in the encorafenib + cetuximab and control arms at baseline [22].

The estimated median time to definitive 10% deterioration in the EORTC QLQ-C30 Global Health Status score was longer in the encorafenib + cetuximab arm [redacted] months) compared with the control arm [redacted] Similar results were observed for the remaining EORTC QLQ-C30 scores [22].

FACT-C: encorafenib + cetuximab versus control (data cut-off 15 August 2019)

Median FACT-C Functional Well-being, Physical Well-being, Social/Family Well-being, Emotional Well-being, and CRC subscale scores were similar in the encorafenib + cetuximab and control arms at baseline [22].

The estimated median time to definitive 10% deterioration in the FACT-C Functional Well-being score was longer in the encorafenib + cetuximab arm [redacted] months) versus the control arm [redacted] Similar results were observed for the remaining FACT-C subscales [22].

EQ-5D-5L: encorafenib + cetuximab versus control (data cut-off 15 August 2019)

Median EQ-5D-5L Visual Analogue Scale and Utility Index scores were similar in the encorafenib + cetuximab and control arms at baseline [22].

The estimated median time to definitive 10% deterioration in the EQ-5D-5L (Visual Analogue Scale and Utility Index scores) was [redacted] 48-[redacted] respectively [22].

PGIC: encorafenib + cetuximab versus control (data cut-off 15 August 2019)

The proportion of patients who responded to the PGIC questionnaire with "much improved" or "very much improved" at cycles 2, 3, and 4 [redacted]. This proportion remained in favour of encorafenib + cetuximab through later cycles; measurements from cycle 11 onwards became uncertain with < 10 patients available in the control arm [22].

5.1.2.3 Other efficacy endpoints and subgroup analyses

Other outcomes reported in BEACON CRC that were not specified in the DMC protocol, including PFS, ORR, DOR, and TTR, are presented in Appendix F. Prespecified subgroup analyses performed in BEACON CRC are presented in Appendix H.

5.1.2.4 Safety and side effects

BEACON CRC was the only phase 3 study reporting adverse reactions and other safety outcomes with encorafenib + cetuximab in patients with $BRAF^{V600E}$-MT mCRC. Safety data were recorded in the phase 3 randomised part of the BEACON CRC study. The safety analysis set (n = 409 patients: encorafenib + cetuximab, n = 216; control, n = 193) included patients who received at least one dose of study drug and had at least one posttreatment assessment.

The safety analysis presented here represents the latest data available from the 15 August 2019 data cut-off for the encorafenib + cetuximab and control arms of the study; these data were submitted to the European Medicines Agency (EMA) as part of the marketing authorisation application for encorafenib + cetuximab [14]. Safety data from the 11 February 2019 data cut are presented in Appendix F. Safety data for the triplet combination of encorafenib + binimetinib + cetuximab arm (n = 222) are not presented.

Duration of exposure

Median duration of exposure to study treatment [redacted]

[redacted]

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ol (cetuximab,

Table 14. BEACON CRC: duration of exposure to study treatment—safety set, data cut-off 15 August 2019

	Encorafenib + cetuximab			Control				
	Encorafenib (n = 216)	Cetuximab (n = 216)	Encorafenib + cetuximab (n = 216)	Cetuximab (n = 193)	IRI (n = 193)	5-FU (n = 107)	Folinic acid (n = 107)	Control (n = 193)
Duration of exposure (we	[redacted]							
N								
Mean (SD)								
Median								
Min, max								
Exposure ≥ 16 weeks, n (%)								
RDI categories, n (%)								
< 50%								
50 to < 80%								
80 to < 100%								
100%								
> 100%								
RDI (%)								
N								
Mean (SD)								
Median								
Min, max								

5-FU, 5-fluorouracil; IRI,

Note: RDI = 100*[dose intensity/planned dose intensity]. Only control arm patients receiving FOLFIRI + cetuximab were eligible to receive 5-FU and folinic acid.

Source: CSR Addendum Table 3 and Table 4 [20].

Adverse events

An overview of adverse event (AE) data from BEACON CRC is provided for the safety set by treatment arm (Table 15).

Table 15. BEACON CRC: summary of deaths and adverse events—safety set, data cut-off 15 August 2019

Category	Encorafenib + cetuximab (n = 216)		Control (n = 193)	
	All grades n (%)	Grade 3+ n (%)	All grades n (%)	Grade 3+ n (%)
On-treatment deaths[a]	[redacted]			
On-treatment AEs leading to death				
AEs				
AE, treatment-related (suspected)				
Serious AEs				
Serious AEs, treatment-related (suspected)				
AEs requiring additional therapy				
AEs requiring dose interruption of any study drug				
AEs requiring dose reduction of any study drug				
AEs leading to discontinuation of any study drug				
AEs leading to discontinuation of all study treatments				

AE, adverse event.

[a] [redacted]

Sources: EMA CHMP [14]; August update Tables 14.3-1.1.1, 14.3.1-1.1.1, and 14.3.1-1.40 [21].

Table 16 presents a summary of AEs, regardless of relationship to study drug, by preferred term, treatment, and severity (all grades and maximum grade 3+).

The most frequently reported AEs (> 30% of patients) by preferred term were mostly similar across the treatment arms [14]:

- Encorafenib + cetuximab: diarrhoea (38.4%), nausea (38.0%), fatigue (33.3%), decreased appetite (31.0%), and dermatitis acneiform (30.1%)
- Control: diarrhoea (48.7%), nausea (43.5%), dermatitis acneiform (39.9%), and vomiting (31.6%)

The most frequently reported grade 3+ AEs (> 5.0% of patients) by preferred term were:

- Encorafenib + cetuximab: anaemia (5.6%)
- Control: diarrhoea (10.4%), neutropenia (10.4%), neutrophil count decreased (8.3%), anaemia (6.7%), abdominal pain (5.2%), and asthenia (5.2%)

Table 16. Overall adverse events, regardless of relationship to study drug, by preferred term—overall (≥ 10% in any treatment arm) or grade 3+ (≥ 2% in any treatment arm)—safety set, data cut-off 15 August 2019

	Encorafenib + cetuximab (n = 216)		Control (n = 193)	
Preferred term	**All grades n (%)**	**Grade 3+ n (%)**	**All grades n (%)**	**Grade 3+ n (%)**
Any AE[a]	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhoea[a]	83 (38.4)	6 (2.8)	94 (48.7)	20 (10.4)
Nausea	82 (38.0)	1 (0.5)	84 (43.5)	3 (1.6)
Fatigue[a]	72 (33.3)	9 (4.2)	54 (28.0)	9 (4.7)
Decreased appetite[a]	67 (31.0)	3 (1.4)	56 (29.0)	6 (3.1)
Dermatitis acneiform[a]	65 (30.1)	1 (0.5)	77 (39.9)	5 (2.6)
Abdominal pain[a]	60 (27.8)	7 (3.2)	54 (28)	10 (5.2)
Vomiting[a]	59 (27.3)	3 (1.4)	61 (31.6)	6 (3.1)
Asthenia[a]	52 (24.1)	8 (3.7)	53 (27.5)	10 (5.2)
Arthralgia	49 (22.7)	3 (1.4)	3 (1.6)	0 (0)
Headache	43 (19.9)	0 (0)	5 (2.6)	0 (0)
Anaemia[a]	42 (19.4)	12 (5.6)	36 (18.7)	13 (6.7)
Pyrexia	40 (18.5)	3 (1.4)	28 (14.5)	1 (0.5)
Constipation	39 (18.1)	0 (0)	39 (20.2)	2 (1)
Melanocytic naevus	34 (15.7)	0 (0)	0 (0)	0 (0)
Myalgia	33 (15.3)	1 (0.5)	4 (2.1)	0 (0)
Rash	32 (14.8)	0 (0)	28 (14.5)	3 (1.6)
Musculoskeletal pain	29 (13.4)	0 (0)	5 (2.6)	0 (0)
Dry skin	28 (13.0)	0 (0)	16 (8.3)	1 (0.5)
Back pain	28 (13.0)	3 (1.4)	27 (14)	2 (1.0)
Dyspnoea[a]	28 (13.0)	2 (0.9)	20 (10.4)	6 (3.1)
Hypomagnesaemia	25 (11.6)	1 (0.5)	19 (9.8)	3 (1.6)
Pain in extremity	25 (11.6)	0 (0)	2 (1)	0 (0)
Pruritus	24 (11.1)	0 (0)	10 (5.2)	0 (0)
Weight decreased	24 (11.1)	1 (0.5)	12 (6.2)	0 (0)
Insomnia	24 (11.1)	0 (0)	13 (6.7)	0 (0)
Oedema peripheral	23 (10.6)	0 (0)	14 (7.3)	1 (0.5)
Abdominal pain upper	22 (10.2)	2 (0.9)	15 (7.8)	1 (0.5)
Urinary tract infection[a]	17 (7.9)	5 (2.3)	6 (3.1)	2 (1)
Alanine aminotransferase increased[a]	14 (6.5)	1 (0.5)	14 (7.3)	4 (2.1)
Intestinal obstruction[a]	14 (6.5)	10 (4.6)	8 (4.1)	5 (2.6)
Stomatitis[a]	13 (6.0)	0 (0)	45 (23.3)	4 (2.1)
Hypokalaemia[a]	13 (6.0)	2 (0.9)	27 (14.0)	6 (3.1)
Alopecia	9 (4.2)	0 (0)	21 (10.9)	0 (0)
Hypertension[a]	8 (3.7)	3 (1.4)	6 (3.1)	5 (2.6)
Blood alkaline phosphatase increased[a]	7 (3.2)	4 (1.9)	10 (5.2)	4 (2.1)
Cancer pain[a]	6 (2.8)	5 (2.3)	2 (1.0)	1 (0.5)

Preferred term	Encorafenib + cetuximab (n = 216)		Control (n = 193)	
	All grades n (%)	Grade 3+ n (%)	All grades n (%)	Grade 3+ n (%)
Hypocalcaemia[a]	4 (1.9)	0 (0)	9 (4.7)	5 (2.6)
Pulmonary embolism[a]	3 (1.4)	3 (1.4)	10 (5.2)	9 (4.7)
Small intestinal obstruction[a]	3 (1.4)	3 (1.4)	6 (3.1)	5 (2.6)
Neutropenia[a]	3 (1.4)	2 (0.9)	36 (18.7)	20 (10.4)
Subileus[a]	2 (0.9)	0 (0)	4 (2.1)	4 (2.1)
General physical health deterioration[a]	1 (0.5)	1 (0.5)	4 (2.1)	4 (2.1)
Neutrophil count decreased[a]	1 (0.5)	1 (0.5)	21 (10.9)	16 (8.3)
White blood cell count decreased[a]	1 (0.5)	0 (0)	14 (7.3)	8 (4.1)
Febrile neutropenia[a]	0 (0)	0 (0)	5 (2.6)	5 (2.6)

AE, adverse event.

Note: Preferred terms are presented by descending order of frequency in the encorafenib + cetuximab all grades column down to 10% incidence. For all additional AEs, their presentation is determined by AEs (any grade) that occurred in the control arm at ≥ 10% or any grade 3+ AE that occurred in either arm at ≥ 2%.

[a] Denotes AEs that occur at a rate of ≥ 2% in any treatment arm for grade 3+ but at < 10% in any treatment arm for all grades.

Sources: EMA CHMP [14]; August update Table 14.3.1-1.3.1 [21].

Table 17 presents a summary of serious AEs, regardless of relationship to study drug, by preferred term, treatment, and severity (all grades and maximum grade 3+).

The most frequently reported serious AEs (> 2.0% of patients) by preferred term were as follows:

- Encorafenib + cetuximab: [redacted]
- [redacted]

Table 17. Serious adverse events, regardless of relationship to study drug, by preferred term—overall and grades 3+ (> 1% in any treatment arm)—safety set, data cut-off 15 August 2019

	Encorafenib + cetuximab (n = 216)		Control (n = 193)	
Preferred term	**All grades n (%)**	**Grade 3/4 n (%)**	**All grades n (%)**	**Grade 3/4 n (%)**
Any serious AE	[redacted]			
Intestinal obstruction				
Abdominal pain				
Urinary tract infection				
Cancer pain				
Acute kidney injury				
Ileus				
Large intestinal obstruction				
Pulmonary embolism				
Nausea				
Small intestinal obstruction				
Sepsis				
Bile duct obstruction				
Pneumonia				
Atrial fibrillation				
Infusion related reaction				
Malignant melanoma				
Diarrhoea				
Febrile neutropenia				
Vomiting				
Subileus				
Pain				
Respiratory failure				
Large intestine perforation				
Septic shock				
General physical health deterioration				
Hypokalaemia				

AE, adverse event.

Note: Preferred terms are presented by descending order of frequency in the encorafenib + cetuximab all grades column, followed by any additional AEs (all grades) that occurred in the control arm ≥ 1%.

Source: August update Table 14.3.1-1.8.1 [21].

5.1.3 Comparative analyses

In the DMC protocol, the clinical head-to-head evidence provided by the BEACON CRC study was deemed to provide sufficient evidence to answer the clinical question. For completeness, Pierre Fabre have also conducted an indirect treatment comparison and narrative comparisons that provide additional evidence against other comparators, which is provided in Appendix B.

5.1.4 Other considerations

The protocol requested further information from the BEACON CRC study on the distribution of the two interventions used in the control arm (IRI + cetuximab, or FOLFIRI + cetuximab) and the proportion of patients who had already received an IRI-based regimen as a first- or second-line therapy.

As presented in Section 4.3.1 (see Table 7), the baseline demographics of participants in BEACON CRC show the percentage of patients who had progressed after one or two prior systemic regimens for mCRC, and the use of prior chemotherapy regimens was balanced across the three treatment arms [11]. Most patients had received one prior systemic regimen (65.7%) versus two prior systemic regimens (34.0%). Approximately [redacted] use of IRI was also one of the three stratification factors during randomisation. Subgroup analyses for OS (Appendix H, Figure H-1) show there was no statistically significant interaction between OS and prior IRI use or the number of prior regimens for metastatic disease.

In BEACON CRC, the choice of whether to treat with either IRI + cetuximab or FOLFIRI + cetuximab in the control arm was at the discretion of the treating investigator and had to be declared before randomisation. In one of the few head-to-head comparisons of IRI and FOLFIRI in patients with mCRC without specific molecular characterisation of their disease, the treatment groups did not differ significantly in ORR, PFS, or OS; the authors reported these findings to be consistent with a meta-analysis of 29 phase 2 trials [26]. Safety data from BEACON CRC show that of all patients in the control arm (n = 193), approximately 55% (n = 107) received the FOLFIRI regimen. Dose intensity data (see Section 5.1.2) show that, in the control arm, the median relative dose intensity was [redacted] median relative dose intensity [redacted] [21].

6 References

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Application for the assessment of encorafenib (BRAFTOVI®) in combination with cetuximab for the treatment of adult patients with metastatic colorectal cancer (mCRC) with a $BRAF^{V600E}$ mutation, who have received prior systemic therapy

DMC Dokumentnummer: 80887

DMC ECONOMIC ANALYSIS

Contains confidential information

Updated in response to questions: 9 October 2020

Contents

Abbreviations

Abbreviation/term	Definition
AE	adverse event
AIC	Akaike information criterion
ATC	Anatomical Therapeutic Chemical Classification System
BIC	Bayesian information criterion
BRAF	B-Raf proto-oncogene, serine/threonine-protein kinase B-Raf
BSA	body surface area
CRC	colorectal cancer
CT	computed tomography
DKK	Danish krone
DMC	Danish Medicines Council
DRG	diagnosis-related group
DSU	Decision Support Unit
EGFR	epidermal growth factor receptor
FOLFIRI	folinic acid + 5-fluorouracil + irinotecan
FOLFOX	folinic acid + 5-fluorouracil + oxaliplatin
GP	general practitioner
HR	hazard ratio
IPD	individual patient-level data
IRI	irinotecan
ITC	indirect treatment comparison
KM	Kaplan-Meier
KOL	key opinion leader
mCRC	metastatic colorectal cancer
MT	mutation/mutant
NA	not applicable
NICE	National Institute for Health and Care Excellence
OS	overall survival
PFS	progression-free survival
PICC	peripherally inserted central catheter
PICO	population, intervention, comparator, and outcomes
PPS	postprogression state
RAS	rat sarcoma viral oncogene homologue
RCT	randomised controlled trial
RDI	relative dose intensity
SD	standard deviation
SmPC	summary of product characteristics
trt	treatment
TSD	Technical Support Document
TTD	time to treatment discontinuation
VEGF	vascular endothelial growth factor
WT	wild-type

1 Executive summary

In Denmark, colorectal cancer (CRC) is the most common incident cancer and the second most frequent cause of cancer death [1]. In Europe, approximately 25% of patients are diagnosed with stage IV metastatic CRC (mCRC), and a further 50% of patients with stage I-III CRC will progress to mCRC during the course of their disease [2, 3]. Colorectal cancer tumours have different molecular subtypes with distinct characteristics: tumours with a BRAF mutation (MT) are the most aggressive form of CRC and are associated with poor prognosis and increased risk of metastasis. In Europe, it is estimated that approximately 8% to 12% of patients with mCRC have BRAF-MT tumours [4], with 97% to 100% specifically $BRAF^{V600E}$-MT [5]. Real-world Nordic data show a higher incidence of BRAF mutations, with 21% of patients with a $BRAF^{V600E}$ mutation [6]. Patients with $BRAF^{V600E}$-MT mCRC have a short life expectancy with a 70% increased risk of mortality compared with patients with BRAF wild-type (WT) mCRC, with the shortest median overall survival (OS) of all CRC mutation subtypes [5].

Currently, there is no agent specifically indicated for patients with $BRAF^{V600E}$-MT mCRC; in Denmark, there are no clear recommendations on the current standard of care for patients with $BRAF^{V600E}$-MT mCRC after prior systemic therapy. The clinician's current choice of treatments is non-standardised; regimens can include various combinations of chemotherapy (e.g., FOLFIRI[i]/FOLFOX[ii]), epidermal growth factor receptor (EGFR) inhibitors (e.g., cetuximab), and vascular endothelial growth factor (VEGF) inhibitors (bevacizumab). There is a clear and high unmet need in this patient population: patients with $BRAF^{V600E}$-MT mCRC have a poor prognosis with current treatments [6] with no targeted therapy for their BRAF mutation.

The key efficacy data for encorafenib + cetuximab in $BRAF^{V600E}$-MT mCRC after prior systemic therapy are provided by BEACON CRC, the first and only phase 3 randomised controlled trial (RCT) performed specifically in patients with $BRAF^{V600E}$-MT mCRC. In BEACON CRC, the double combination of encorafenib + cetuximab consistently showed statistically and clinically significant improvements in OS, progression-free survival (PFS), and overall response rate, with a favourable and manageable tolerability profile and sustained health-related quality of life compared with standard chemotherapy + cetuximab (FOLFIRI + cetuximab, or irinotecan [IRI] + cetuximab) [7, 8]:

- A clinically significant 39% reduction in the risk of death equating to 3.4 additional months of survival: median OS, 9.30 months versus 5.88 months; hazard ratio (HR), 0.61; 95% confidence interval, 0.48-0.77; one-sided $P < 0.0001$.
- A 56% reduction in the risk of disease progression or death: median PFS, 4.27 months versus 1.54 months; HR, 0.44; 95% confidence interval, 0.35-0.55; one-sided $P < 0.0001$.

A cost and budget-impact analysis was undertaken to assess the economic effects of encorafenib + cetuximab in patients with $BRAF^{V600E}$-MT mCRC after prior systemic therapy based on the clinical data from BEACON CRC. The analysis was based on a partitioned survival model. The comparator was clinician's choice in BEACON CRC (chemotherapy + cetuximab) based on the Danish Medicines Council (DMC) protocol.

[i] FOLFIRI = folinic acid + 5-fluorouracil + irinotecan.

[ii] FOLFOX = folinic acid + 5-fluorouracil + oxaliplatin.

The primary evidence used in the model was the BEACON CRC trial, for both encorafenib + cetuximab and chemotherapy + cetuximab. Resource use and costs were estimated based on previous technology appraisals in Denmark, published sources, and clinical experts. The economic analysis predicted that patients treated with encorafenib + cetuximab would incur an additional cost of DKK [redacted] versus clinician's choice of therapy (FOLFIRI/IRI + cetuximab).

2 Formalities pertaining to this application

Table 1 summarises the Danish submission for encorafenib in $BRAF^{V600E}$-MT CRC and the economic analysis, respectively.

Table 1. Overview of submission to Denmark

Company Name	Pierre Fabre Pharma Norden AB Karlavägen 108; Plan 9 115 26 Stockholm Sweden
Contact person for this assessment	Erik Arver, Market Access Nordics Phone: +46 70 750 87 37 E-mail: erik.arver@pierre-fabre.com
Consulting firm commissioned	RTI Health Solutions
Brand/trade name	BRAFTOVI®
Active substance	Encorafenib
ATC code	L01XE46
Indications	New indication covered in this submission: ▪ Encorafenib, in combination with cetuximab, for the treatment of adult patients with mCRC with a $BRAF^{V600E}$ mutation, who have received prior systemic therapy. Existing indication previously assessed by DMC: ▪ Encorafenib in combination with binimetinib for the treatment of adult patients with unresectable or metastatic melanoma with a $BRAF^{V600}$ mutation
Pharmaceutical form/method of administration and posology	Encorafenib is administered orally as hard capsules.
Required additional tests/medication	No. According to clinical experts, relevant patients are already tested for $BRAF^{V600E}$ mutation.
Patient population in Denmark the indication applies to (5-year prevalence)	According to Pierre Fabre estimates, based on available Danish population projections, Danish cancer registry statistics, and clinical expert opinion, the population over the next 5 years is expected to be approximately as follows:

Year	Year 1	Year 2	Year 3	Year 4	Year 5
Patients	7	14	21	29	36

Clinical experts who have been contacted	Per Pfeiffer, Department of Oncology, Odense University Hospital, Denmark

ATC, Anatomical Therapeutic Chemical Classification System; mCRC, metastatic colorectal cancer.

3 Scope

This submission follows the DMC protocol (Dokumentnummer 80887) and covers encorafenib's full marketing authorisation for the following indication: in combination with cetuximab for the treatment of adult patients with mCRC with a $BRAF^{V600E}$ mutation, who have received prior systemic therapy. Table 2 presents an overview of the scope of the submission in terms of the population, intervention, comparator, and outcomes (PICO).

Table 2. Scope for the encorafenib submission for Denmark

Population	Adult patients with $BRAF^{V600E}$-MT mCRC
Intervention	Encorafenib 300 mg given orally once daily, in combination with cetuximab given intravenously
Comparator(s)	The main comparator in this submission is chemotherapy (FOLFIRI or IRI) + cetuximab after prior systemic therapy, which is per the investigators' choice in the pivotal phase 3 BEACON CRC study. Key opinion leaders in Denmark validated this main comparator (see Section 4.1.3 for further details supporting the choice of the main comparator). Other comparators, such as FOLFIRI ± bevacizumab or trifluridine + tipiracil (Lonsurf), are included in the model as scenario analyses or narratively discussed.
Outcomes	▪ Overall survival ▪ Progression-free survival ▪ Overall response rate ▪ Duration of response ▪ Health-related quality of life ▪ Adverse effects of treatment
Subgroups considered	Subgroups were considered, but none were identified as having an effect on efficacy. See final clinical application.
Health economic analysis	Cost and budget-impact analyses over a lifetime horizon, with costs in Danish krone from a Danish healthcare perspective.

FOLFIRI, folinic acid + 5-fluorouracil + irinotecan; IRI, irinotecan; mCRC, metastatic colorectal cancer; MT, mutant.

4 Health economic analysis and model

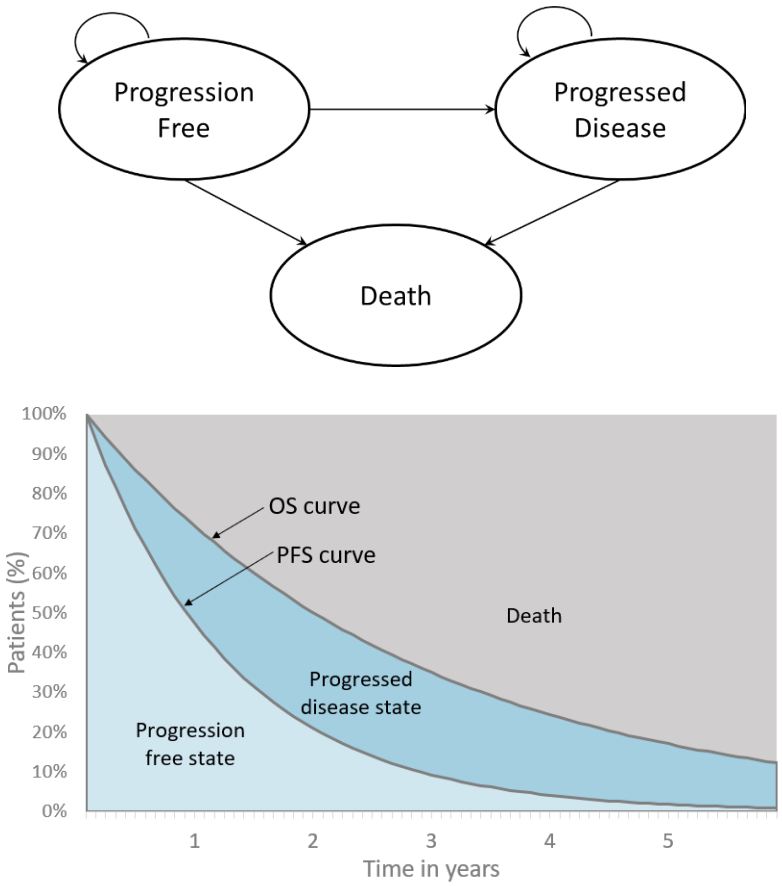
4.1 Health economic analysis

4.1.1 Model structure

Several different modelling approaches were considered during the development of the model structure. Partitioned survival models are used routinely in economic evaluations in oncology and have been the most commonly used in DMC and Amgros I/S (Amgros) appraisals [9]. Therefore, a partitioned survival model with a lifetime horizon was developed to analyse the costs and budget impact of encorafenib + cetuximab versus relevant comparators as defined in the decision problem for the treatment of patients with $BRAF^{V600E}$-MT mCRC who have received prior systemic therapy.

The current model was developed in Microsoft Excel 2016 and includes three mutually exclusive health states (Figure 1): preprogression (or progression free), postprogression (or progressed disease), and death.

Figure 1. Model structure



OS, overall survival; PFS, progression-free survival.

Note: The bottom panel of this figure is purely illustrative and is not based on any efficacy data reported elsewhere in this document.

State membership is determined from a set of non-mutually exclusive survival curves. The cohort enters the model in the preprogression health state, and any transitions to postprogression and

death are defined by the PFS and OS curves. The proportion of the cohort remaining in the preprogression health state over time is derived directly from the PFS curve (see Figure 1). State membership for the death state is calculated as 1 minus the OS curve, and state membership for the postprogression health state is derived as the difference between the OS and the PFS curve (the proportion of patients who are alive but not preprogression).Treatment costs included costs of drug acquisition, administration, and monitoring. Costs associated with adverse events (AEs) were estimated per episode and were applied once at the beginning of the simulation, based on the proportion of patients in each treatment arm experiencing each AE. Costs were discounted at 4% per annum according to DMC guidelines.

4.1.2 Patient population

The economic evaluation includes patients with $BRAF^{V600E}$-MT mCRC who have received prior systemic therapy. This is consistent with the population included in the BEACON CRC study and the European marketing authorisation for encorafenib + cetuximab in mCRC [8].

The base-case cohort characteristics (Table 1) reflect the baseline patient characteristics across the entire study population in BEACON CRC, the pivotal phase 3 RCT for encorafenib, and were confirmed to be reflective of the expected Danish patient population (expert opinion; see Appendix I).

Table 1. Base-case cohort characteristics at baseline

Characteristic	BEACON CRC	Source
Age, years (SD)	59.30 (11.80)	BEACON CRC clinical study report Table 14.1-3.1.1 [10]
Body surface area, m^2 (SD)	1.79 (0.23)	
Percentage males	47.2%	

SD, standard deviation.

Body surface area (BSA) is used to determine the doses required for drugs that are dosed based on BSA, as described in Section 4.3.1.1.

4.1.3 Relevant comparators included

4.1.3.1 Comparator included in the base case analysis

To answer the decision problem in current Danish practice, clinician's choice (chemotherapy + cetuximab) in the BEACON CRC study is the main comparator assessed in this submission. This selection aligns with the DMC protocol and is based on the following:

- Clinical evidence for other comparators is limited in this patient population.
- No specific recommendations exist for patients with $BRAF^{V600E}$-MT mCRC in Denmark after first-line therapy. Therefore, the treatment used in these patients varies widely as confirmed by clinical experts (see Appendix I).
- The BEACON CRC control arm (chemotherapy + cetuximab) represents an appropriate therapeutic option in global clinical practice [2, 11] among second- and third-line therapies in patients with $BRAF^{V600E}$-MT mCRC. It is recommended by national and supranational guidelines for the treatment of mCRC, especially for patients with RAS-WT, of which BRAF-MT is a subcategory [2, 11, 12].

- Danish clinical experts indicated that currently used treatments have a lower or similar clinical effectiveness as the treatment used in the trial.

4.1.3.2 Relevant comparators included in scenario analyses

The following comparators were included in the model as scenario analyses:

- FOLFIRI (based on an indirect treatment comparison [ITC], see Appendix B)
- Trifluridine + tipiracil (based on a naive comparison, see Appendix B)

Further, for completeness, the model included bevacizumab as a possible comparator as an add-on to FOLFIRI as well as a naïve comparison to FOLFOX.

In order to facilitate comparison with FOLFOX, assumptions needed to be made to due to a lack of data availability. The assumption that clinical equivalence exists between FOLFOX and the Clinician's Choice arm is made and costs associated with FOLFOX regimen are added to the model when this analysis is programmed.

4.2 Time horizon and analysis perspective

The base-case time horizon is 15 years, which is deemed sufficiently long to represent a lifetime horizon and account for all incurred costs and effects (expert opinion; see Appendix I). The model has a cycle length of 1 month (365 days ÷ 12 months = 30.42 days per month), which corresponds to a sufficient length of time to account for changes in PFS, OS, and time to treatment discontinuation (TTD) and is not too short to impair computational efficiency. The monthly cycle length also aligns with chemotherapy treatment cycle durations, which are usually given in cycles numbered in weeks (e.g., 2 weeks for a cycle of treatment with cetuximab; expert opinion; see Appendix I).

A Danish healthcare perspective was used to capture all relevant costs. The model allows the user to change the time horizon in the scenario analyses.Clinical data used in the model

4.2.1 Extrapolation of time-to-event data

Kaplan-Meier data are limited to the data reported from the BEACON CRC study for PFS, OS, and TTD (approximately 22 months for PFS and TTD and 34 months for OS) at which point patients are still at risk for an event for all outcomes. Therefore, to estimate the long-term effect associated with encorafenib +cetuximab and clinician's choice of therapy (chemotherapy + cetuximab), it was necessary to extrapolate beyond trial follow-up. Long-term extrapolations are sensitive to the parametric distributions applied, and goodness of fit during the trial period may not always be informative with respect to the accuracy of curve projections beyond the follow-up period. To mitigate such concern, several extrapolation approaches were explored, and the extrapolated curves were validated by a clinical expert (see Appendix I) and by external data.

4.2.1.1 Encorafenib + cetuximab and clinician's choice (chemotherapy + cetuximab)

Base-case efficacy was estimated by using data from BEACON CRC to generate OS, PFS, and TTD curves. Kaplan-Meier curves were generated using the individual patient-level data (IPD) from BEACON CRC for the following treatment arms:

- Encorafenib + cetuximab (intervention arm in the model)
- Clinician's choice (chemotherapy + cetuximab, control arm in the model)

4.2.1.2 Scenario analysis: FOLFIRI

To enable a scenario analysis of encorafenib + cetuximab versus FOLFIRI the relative treatment effect of FOLFIRI was estimated by applying HRs derived from the ITC described in Appendix B to encorafenib + cetuximab OS and PFS curves.

4.2.1.3 Scenario analysis: Trifluridine + tipiracil (Lonsurf)

Absence of relevant evidence for trifluridine + tipiracil in the $BRAF^{V600E}$-MT mCRC population meant that an ITC was not feasible to compare trifluridine + tipiracil with encorafenib + cetuximab. Therefore, based on evidence identified in the clinical systematic literature review (described in Appendix A), a naive comparison was made against the BEACON CRC data. Mayer et al. [13] (RECOURSE) was identified as the most appropriate trifluridine + tipiracil trial conducted to be used for comparison. The IPD used for this publication was not available, so the Kaplan-Meier plots presented in the trial publication were digitised, and the methods described in Guyot et al. [14] were applied to reconstruct an estimate of the IPD using the OS and PFS curves along with their censoring information and number of patients at risk. The RECOURSE population included predominantly patients with BRAF-WT. To adjust for this, the generated parametric models fit to the OS and PFS curves were further adjusted by applying HRs for the presence of $BRAF^{V600E}$-MT.

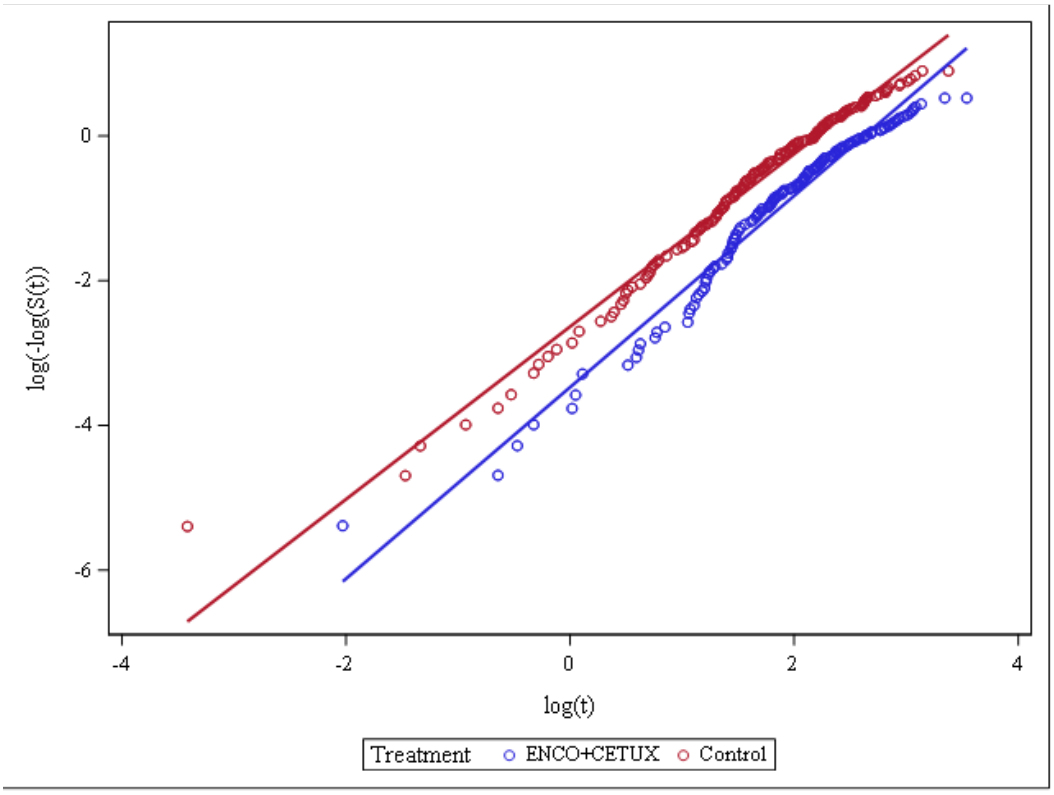
4.2.2 Model selection for overall survival and progression-free survival for encorafenib + cetuximab and clinician's choice (chemotherapy + cetuximab)

The DMC guidelines were followed for the model selection process. The following criteria were used to determine the parametric model to use for extrapolations of OS, PFS, and TTD curves:

- Complementary log-log plots
- Statistical methods, i.e., use of the Akaike information criterion (AIC) and Bayesian information criterion (BIC)
- Expert feedback (visual inspection and clinical validity)

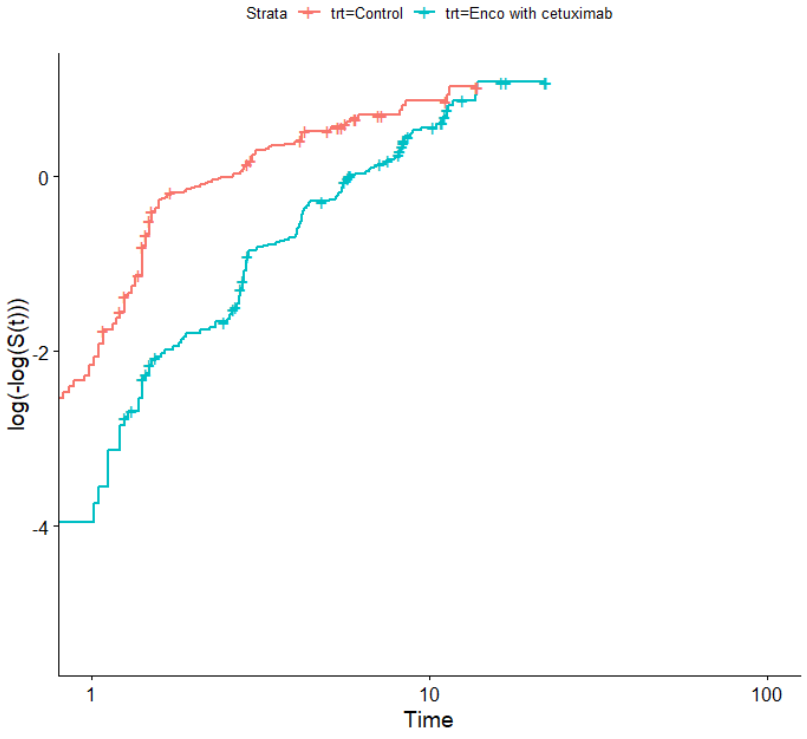
Figure 2 and Figure 3 present complementary log-log plots for encorafenib + cetuximab versus the BEACON CRC control arm for OS and PFS, respectively. The proportional hazards assumption appeared to be reasonable for OS as shown by the approximately parallel lines for encorafenib + cetuximab and the control arm but did not appear to be appropriate for PFS, as the lines for each arm have different gradients. Based on these analyses, to ensure that the modelling approaches were consistent for both OS and PFS, it was determined that the proportional hazards assumption was not appropriate, and individual parametric models needed to be fit to the Kaplan-Meier data.

Figure 2. Complementary log-log plot for encorafenib + cetuximab versus clinician's choice (chemotherapy + cetuximab) arm: overall survival



CETUX, cetuximab; ENCO, encorafenib.

Figure 3. Complementary log-log plot for encorafenib + cetuximab versus clinician's choice (chemotherapy + cetuximab) arm: progression-free survival



Enco, encorafenib; trt, treatment.X

To determine the parametric models to be used for extrapolation of survival estimates, AIC and BIC were considered. Table 2 presents a summary of the AIC and BIC statistics for each parametric model across each intervention and comparator.

Table 2. AIC and BIC for parametric models fit to individual patient-level data

		OS		PFS	
Arm	**Model**	**AIC**	**BIC**	**AIC**	**BIC**
Encorafenib + cetuximab (based on BEACON CRC)	Exponential	1,195.8	1,199.2	960.9	964.3
	Generalised gamma	1,183.5	1,193.7	924.4	934.6
	Gompertz	1,197.8	1,204.6	956.8	963.6
	Log-logistic (base case)	**1,178.1**	**1,184.9**	**920.5**	**927.3**
	Lognormal	1,182.6	1,189.4	924.2	931.0
	Weibull	1,193.2	1,200.0	936.6	943.3
FOLFIRI + cetuximab or IRI + cetuximab (clinician's choice based on BEACON CRC)	Exponential	1,185.1	1,188.5	642.6	646.0
	Generalised gamma	1,178.5	1,188.7	604.1	614.3
	Gompertz	1,187.1	1,193.9	640.2	**647.0**
	Log-logistic (base case)	**1,172.7**	**1,179.5**	**588.6**	595.4
	Lognormal	1,185.5	1,192.3	602.2	609.0
	Weibull	1,183.7	1,190.5	641.1	647.9

AIC, Akaike information criterion; BIC, Bayesian information criterion; FOLFIRI, folinic acid + 5-fluorouracil + irinotecan; IRI, irinotecan; OS, overall survival; PFS, progression-free survival.

The National Institute for Health and Care Excellence (NICE) Decision Support Unit (DSU) Technical Support Document (TSD) 14 states that the same type of parametric model should be used across treatment arms—that is, if a log-logistic model is used to model OS in one arm of a trial, then a log-logistic model should be fit to the other arms in the trial as well [15]. To determine the optimal models to use, the parametric model with the lowest AIC and BIC across all treatment arms was identified. In this context, the optimal average (across all treatments, for OS and PFS) parametric model identified was the log-logistic model.

Model fits were validated by visual inspection by oncology experts (see Appendix I) who stated that the log-logistic model provided feasible estimates of long-term survival. As the log-logistic parametric model also had the lowest AIC and BIC across all BEACON CRC treatment arms, the log-logistic model was selected for the base-case analysis. The log-logistic model predicted approximately 4% of patients in the encorafenib + cetuximab arm and 2.4% of patients in the control arm of BEACON CRC were still alive at 60 months. The Danish CRC registry suggests that a much higher percentage of all patients with mCRC would be alive after 60 months [16]. Even after adjusting this survival rate for the poorer prognosis observed with $BRAF^{V600E}$-MT (published HRs for OS for $BRAF^{V600E}$-MT vs. BRAF-WT: 2.24 from Safaee Ardekani meta-analysis of RCTs and cohort studies [17]; 4.0 from Peeters et al. [18]), it could be expected that a small proportion of patients on current treatments would still be alive at the 60-month point. Hence, the log-logistic models provide feasible estimates whereas some other parametric models would be too pessimistic.

Figure 4 to Figure 7 show the parametric models and the Kaplan-Meier data.

Figure 4. Model fits for encorafenib + cetuximab OS

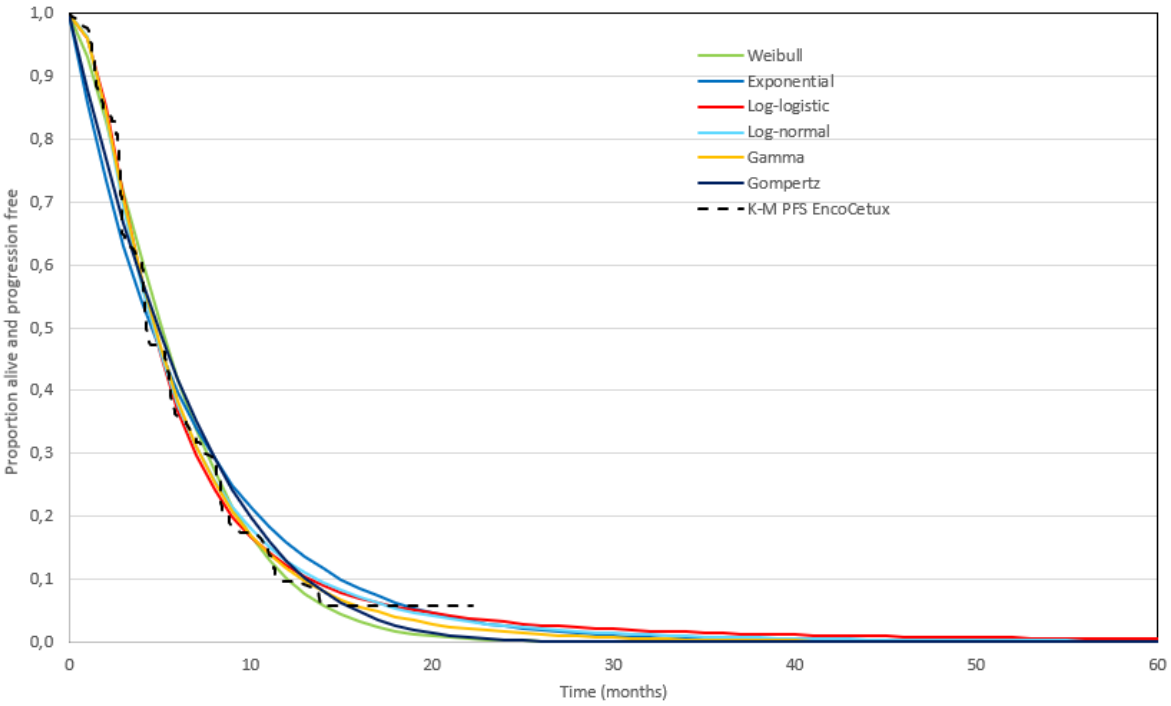
K-M, Kaplan-Meier; OS, overall survival; PFS, progression-free survival.

Figure 5. Model fits for the clinician's choice (chemotherapy + cetuximab) arm OS

IRI, irinotecan; K-M, Kaplan-Meier; OS, overall survival; PFS, progression-free survival.

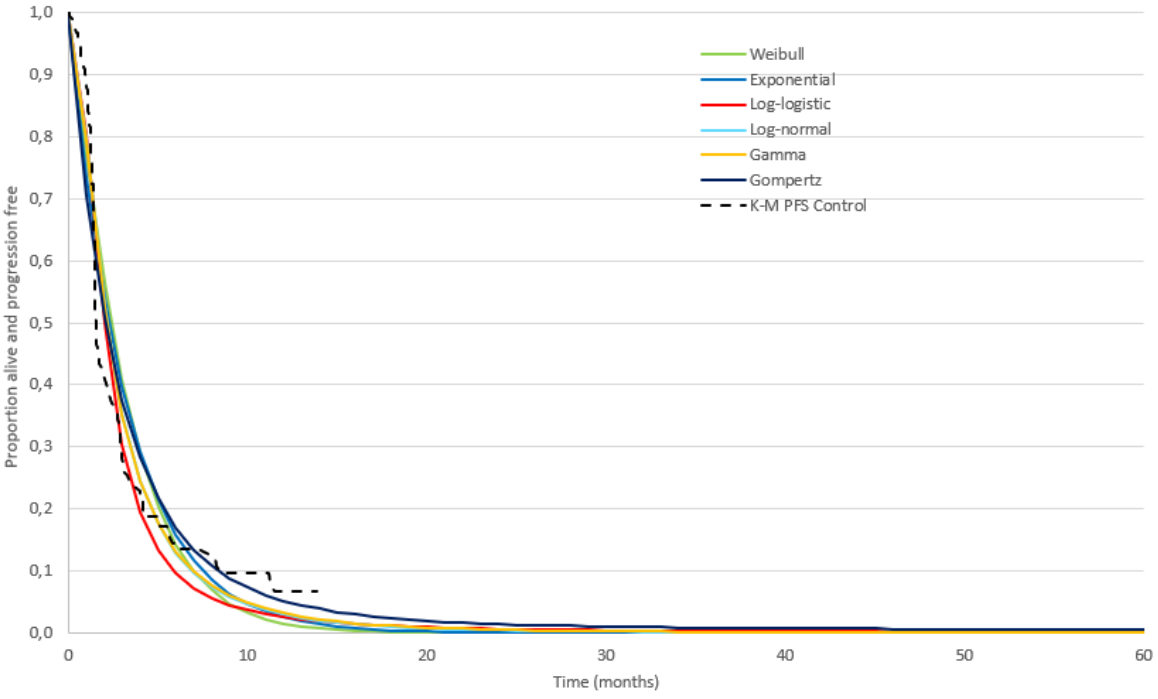
Similar to OS, the log-logistic distribution also provided the best statistical and visual fit to the PFS data for both arms (Figure 18 and Figure 19) as well as a reasonable hazard function compared with the smooth hazard function (see Appendix K) and was therefore selected as the base-case distribution for PFS.

Figure 6. Model fits for encorafenib + cetuximab: PFS



EncoCetux, Encorafenib with cetuximab; K-M, Kaplan-Meier; PFS, progression-free survival.

Figure 7. Model fits for the clinician's choice (chemotherapy + cetuximab) arm: PFS



K-M, Kaplan-Meier; PFS, progression-free survival.

Figure 8 and Figure 9 present the base-case log-logistic parametric models.

Figure 8. Final model fits for the encorafenib + cetuximab arm

K-M, Kaplan-Meier; OS, overall survival; PFS, progression-free survival; P(S), probability of survival.

Figure 9. Final model fits for the clinician's choice (chemotherapy + cetuximab) arm

K-M, Kaplan-Meier; OS, overall survival; PFS, progression-free survival; P(S), probability of survival.

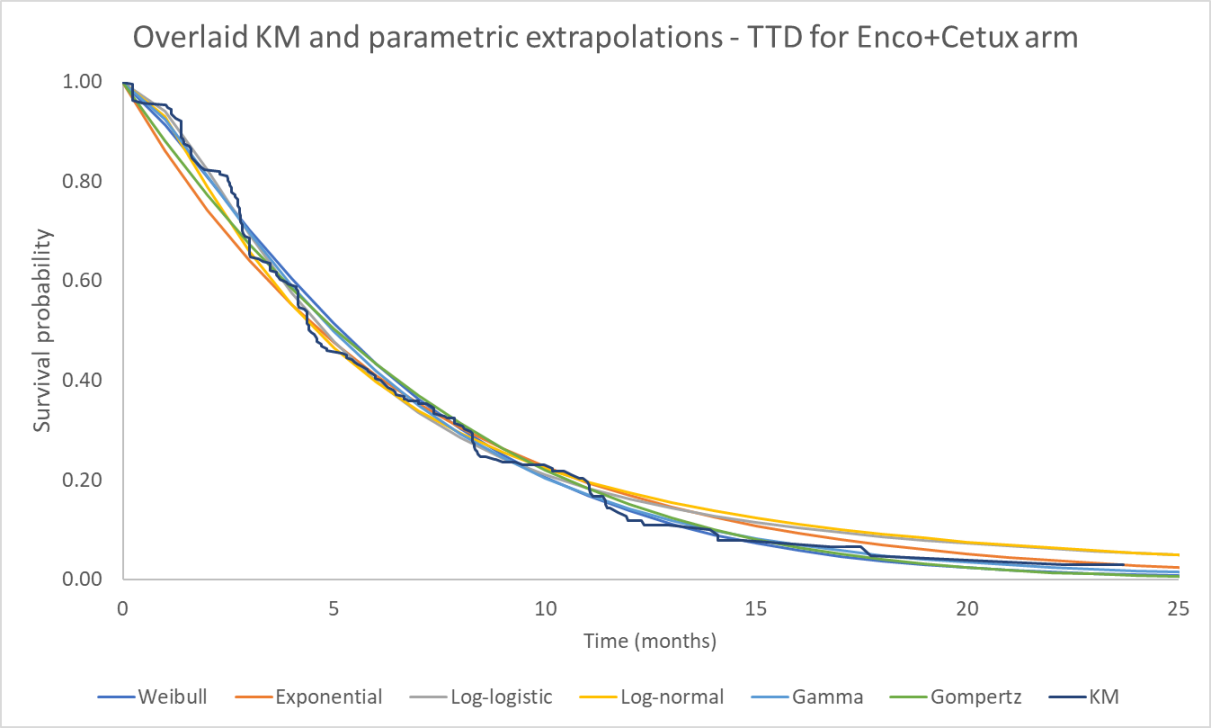
4.2.3 Model selection for time to treatment discontinuation for encorafenib + cetuximab and clinician's choice (chemotherapy + cetuximab)

4.2.3.1 Modelling time on treatment from BEACON CRC

Patients in the BEACON CRC study could discontinue treatment at any time owing to different causes such as AEs, disease progression, or investigator or patient preference. After disease

progression, patients could also continue encorafenib + cetuximab if there was an expected benefit for them based on investigator opinion. Thus, instead of assuming that treatment terminated with disease progression, TTD was analysed to better estimate treatment duration in order to capture the most accurate costs associated with the primary and subsequent treatments. Figure 6 presents the different parametric function fittings for TTD in the encorafenib + cetuximab arm.

Figure 10. Time to treatment discontinuation parametric function fitting in the encorafenib + cetuximab arm



Enco + Cetux, encorafenib + cetuximab; KM, Kaplan-Meier; TTD, time to treatment discontinuation.

Table 3 presents AIC and BIC statistics for different parametric distributions for modelling TTD for the encorafenib + cetuximab arm.

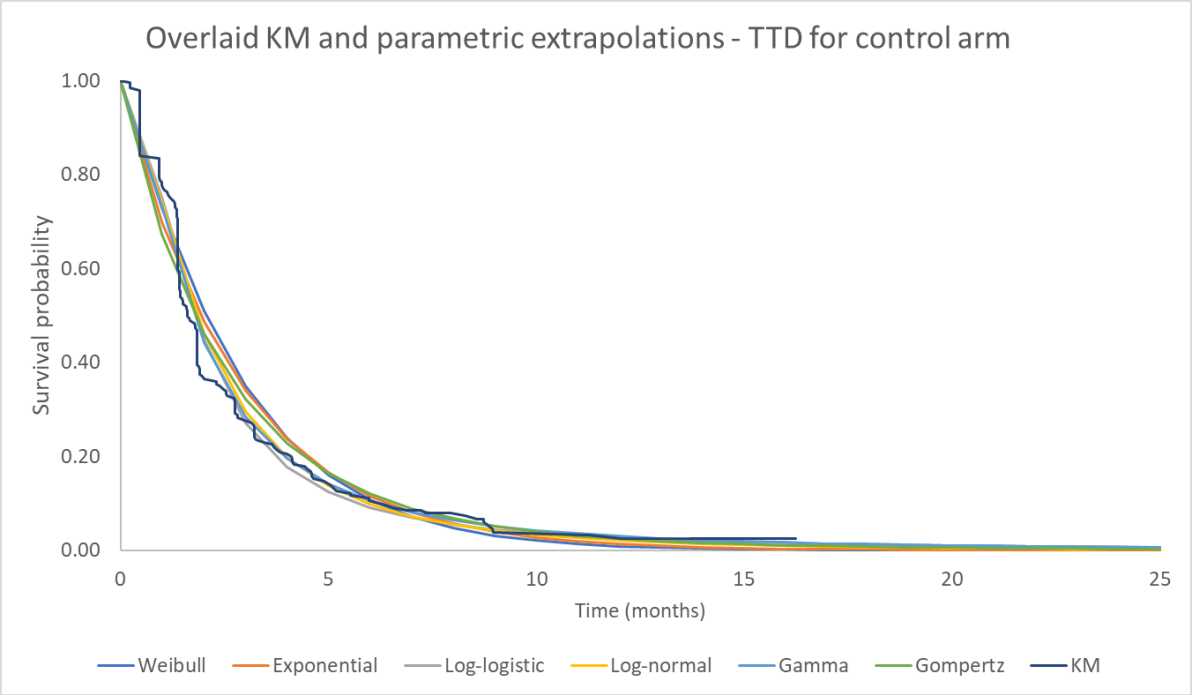
Table 3. Time to treatment discontinuation modelling AIC and BIC statistics for alternate parametric distributions for the encorafenib + cetuximab arm

	Unadjusted model	
Parametric model	**AIC**	**BIC**
Exponential	1,082.86	1,086.24
Weibull	1,072.11	1,078.86
Gompertz	1,080.41	1,087.17
Log-logistic	1,072.46	1,079.21
Lognormal	1,083.23	1,089.98
Gamma (base case)	**1,071.53**	**1,081.65**

AIC, Akaike information criterion; BIC, Bayesian information criterion.

Figure 7 presents the different parametric function fittings for TTD in the control arm.

Figure 11. Parametric function fittings for time to treatment discontinuation in the clinician's choice (chemotherapy + cetuximab) arm



KM, Kaplan-Meier; TTD, time to treatment discontinuation.

Table 4 presents AIC and BIC statistics for different parametric distributions for modelling TTD for the control arm.

Table 4. Time to treatment discontinuation modelling AIC and BIC statistics for alternate parametric distributions for the clinician's choice (chemotherapy + cetuximab) arm

	Unadjusted model	
Parametric model	**AIC**	**BIC**
Exponential	754.67	757.93
Weibull	754.20	760.73
Gompertz	753.75	760.27
Log-logistic	715.71	722.23
Lognormal	715.32	721.84
Gamma (base case)	**714.86**	**724.65**

AIC, Akaike information criterion; BIC, Bayesian information criterion.

In conclusion, based on model selection criteria (AIC and BIC values) and the visual inspection of the fit, gamma models were recommended for encorafenib + cetuximab.

4.3 Resource use and costs

4.3.1 Intervention and comparators' costs and resource use

The current analysis was developed with the aim of including costs that would represent the actual costs of treatment in Denmark.

The following costs are included in the model:

- Primary treatment (intervention and comparators in the model), including drug costs, and administration costs
- Subsequent treatments, including drug costs, and administration costs
- Resource use
- Treating AEs
- Terminal care at the end of life
- Transportation and patient time

4.3.1.1 Primary treatments

Intervention costs

The dose of encorafenib implemented in the model aligned with the dosing recommendation in the marketing authorisation and as used in the BEACON CRC study. For cetuximab, dosing was in line with key opinion leader (KOL) guidance and as used in clinical practice (see Appendix I) but differed from summary of product characteristics (SmPC) recommendations on the frequency of dosing (see below). Cetuximab was dosed according to BSA. Body surface area was assumed to be the mean BSA from BEACON CRC: 1.79 m^2.

Encorafenib + cetuximab was priced based on the listed price approved by medicinpriser.dk [19].

Relative dose intensity (RDI) multipliers were used to account for the proportion of patients who remained on primary treatment but with a dose reduction and temporary interruptions based on data from BEACON CRC. Relative dose intensity is an estimate of the ratio between the actual cumulative dose (in milligrams) and the planned cumulative doses and is seen to better reflect actual dosing of treateatment in clinical practise. The total dose per drug cycle of 28 days was calculated by multiplying the total daily dose (corrected for mean RDI) by the number of days in the drug cycle and then rounding up to the nearest whole tablet (or vial for intravenous drugs).

Encorafenib

The recommended dose of encorafenib is 300 mg (four 75 mg capsules) daily when used in combination with cetuximab.

Cetuximab

Before the first infusion, patients must receive premedication with an antihistamine and a corticosteroid at least 1 hour before administration of cetuximab. This premedication is recommended before all subsequent infusions [20]. Table 6 presents the premedication costs for encorafenib + cetuximab. No RDI assumptions were made for premedication drugs.

Table 5. Cost components of the encorafenib + cetuximab treatment regimen

	mg per tablet or vial	Tablets or vials per pack	List price per pack (DKK)	Dose mg/m²	Dose per administration (mg)	Mean RDI (E + C)	Frequency per drug cycle	Length of drug cycle (days)
Encorafenib	75	42	11,960.00	—	300	[redacted]	28	28
Cetuximab	500	1	7,884.68	500	900	[redacted]	1	14

E + C, encorafenib + cetuximab; RDI, relative dose intensity.

Table 6. Premedication costs for encorafenib + cetuximab

	mg per tablet or vial	Tablets or vials per pack	List price per pack (DKK)	Cost per tablet or vial (DKK)	Cost/mg (DKK)	Frequency/ drug cycle	Length of drug cycle (days)	Cost per model cycle (DKK)
Tetrasyklin	1	100	19.32	0.19	0.00	1	7	1.68
Hydrokortisonkrem	1	150	95.84	0.64	1.28	1	7	44.42

Table 7. Cost components of the FOLFIRI / FOLFOX treatment regimen

	mg per tablet or vial	Tablets or vials per pack	List price per pack (DKK)	Cost per tablet or vial (DKK)	Cost/mg (DKK)	Frequency/ drug cycle	Length of drug cycle (days)	Cost per model cycle (DKK)
Calciumfolinate	100	1	111.00	111.00	1.11	1	14	1208.19
Calciumfolinate	350	1	220.00	220.00	0.63	1	14	684.18
Calciumfolinate	1000	1	340.00	340.00	0.34	1	14	370.08
Oxaliplatin	50	1	41.18	41.18	0.82	1	14	194.85
Oxaliplatin	100	1	68.80	68.80	0.69	1	14	162.77
Oxaliplatin	200	1	127.82	127.82	0.64	1	14	151.20
Fluorouracil	2500	1	200.00	200.00	0.08	1	14	584.78
Fluorouracil	5000	1	400.00	400.00	0.08	1	14	584.78
Irinotecan	100	1	80.00	80.00	0.80	1	14	403.24
Irinotecan	500	1	200.00	200.00	0.40	1	14	201.62

The SmPC recommendation on cetuximab dosing is an initial dose of 400 mg/m^2 BSA, followed by 250 mg/m^2 for all subsequent doses given once a week [20]. In contrast, according to the KOLs interviewed during the development of this submission, a maintenance dosing schedule of 500 mg/m^2 every 2 weeks is used in Denmark. This assumption is used in the base case because it reflects current Danish clinical practice.

Table 7 presents the total monthly costs for encorafenib + cetuximab.

Table 8. Primary treatment costs per model cycle for encorafenib + cetuximab

Intervention	Drug cost per model cycle, excluding RDI (DKK)	Drug cost per model cycle based on RDI (DKK)
Encorafenib	34,646.07	[redacted]
Cetuximab	30,834.76	[redacted]
Encorafenib + cetuximab	65,480.83	[redacted]

RDI, relative dose intensity.
Note: Model cycle = 30.42 days.

Comparator costs

FOLFIRI and trifluridine + tipiracil are dosed according to BSA, so the mean BSA from BEACON CRC is assumed. The SmPCs for folinic acid, 5-fluorouracil, and IRI [21-23] are used to calculate the doses for the components of FOLFIRI, and the dosing table in the SmPC is used for trifluridine + tipiracil [24].

The costs of the components of FOLFIRI are sourced from Danish Medicines Agency (DMA) [19]. As several different medicinal forms (e.g., tablet or vials per pack, concentration of treatments) were available, the treatment costs were calculated for each medicinal form, and then the average cost per cycle for each of the forms was taken.

The cost of trifluridine + tipiracil is based on the list price provided in DMA for the only formulation available (trifluridine + tipiracil [Lonsurf]) [19].

Table 8 presents the costs per pack for each of the comparators.

Table 9. Unit costs used for comparators

Regimen	Drug	mg per tablet or vial	Tablets or vials per pack	Cost per pack (DKK)
FOLFIRI/FOLFOX	Folinic acid	100	1	111.00
FOLFIRI/FOLFOX	Folinic acid	350	1	220.00
FOLFIRI/FOLFOX	Folinic acid	1000	1	340.00
FOLFIRI/FOLFOX	5-Fluorouracil	2,500	1	200.00
FOLFIRI/FOLFOX	5-Fluorouracil	5,000	1	400.00
FOLFIRI	IRI	100	1	80.00
FOLFIRI	IRI	500	1	200.00
FOLFOX	Oxaliplatin	50	1	41.18
FOLFOX	Oxaliplatin	100	1	68.80
FOLFOX	Oxaliplatin	200	1	127.82
Lonsurf	Trifluridine + tipiracil	20	60	24,534.17
Lonsurf	Trifluridine + tipiracil	15	60	18,398.64
Bevacizumab	Bevacizumab	100	1	2,144.43
Bevacizumab	Bevacizumab	400	1	7,905.39
Regorafenib	Regorafenib	40	84	21,744.64

FOLFIRI, folinic acid + 5-fluorouracil + irinotecan; IRI, irinotecan.

The cost per tablet or vial for each drug was taken from the cost per pack. This was then used to calculate a cost per milligram. The dose in milligrams per metre squared was then used in conjunction with National Dosing Tables to determine the total dose of each treatment received per administration.

Table 9 presents the RDIs and calculated vials or tablets per administration along with the duration of the drug cycles.

Table 10. Relative dose intensities, vials or tablets per administration, and length of treatment cycles used for comparators

Regimen	Drug	RDI	Vials or tablets per administration	Length of drug cycle (days)
FOLFIRI/FOLFOX	Folinic acid	[redacted]	5.01	14
FOLFIRI/FOLFOX	Folinic acid	[redacted]	1.43	14
FOLFIRI/FOLFOX	Folinic acid	[redacted]	0.50	14
FOLFIRI/FOLFOX	5-Fluorouracil	[redacted]	1.35	14
FOLFIRI/FOLFOX	5-Fluorouracil	[redacted]	0.67	14
FOLFIRI	IRI	[redacted]	2.32	14
FOLFIRI	IRI	[redacted]	0.46	14
FOLFOX	Oxaliplatin	[redacted]	2.18	14
FOLFOX	Oxaliplatin	[redacted]	1.09	14
FOLFOX	Oxaliplatin	[redacted]	0.54	14
Lonsurf	Trifluridine + tipiracil	1.000	6.00	28
Lonsurf	Trifluridine + tipiracil	1.000	8.00	28
Bevacizumab	Bevacizumab	1.000	5.00	21
Bevacizumab	Bevacizumab	1.000	1.25	21
Regorafenib	Regorafenib	1.000	4.00	28

FOLFIRI, folinic acid + 5-fluorouracil + irinotecan; IRI, irinotecan; RDI, relative dose intensity.

Table 10 presents the calculated costs used for the comparators, taking into consideration Table 8 and Table 9.

Table 11. Cost per regimen per model cycle

Regimen	Drug	Total cost per model cycle (DKK)[a]
FOLFIRI	Folinic acid	[redacted]
FOLFIRI	Folinic acid	[redacted]
FOLFIRI	Folinic acid	[redacted]
FOLFIRI	5-Fluorouracil	[redacted]
FOLFIRI	5-Fluorouracil	[redacted]
FOLFIRI	IRI	[redacted]
FOLFIRI	IRI	[redacted]
FOLFOX	Oxaliplatin	[redacted]
FOLFOX	Oxaliplatin	[redacted]
FOLFOX	Oxaliplatin	[redacted]
Lonsurf	Trifluridine + tipiracil	26,651.73
Lonsurf	Trifluridine + tipiracil	26,648.85
Bevacizumab	Bevacizumab	15,530.12
Bevacizumab	Bevacizumab	14,312.85
Regorafenib	Regorafenib	23,621.44

FOLFIRI, folinic acid + 5-fluorouracil + irinotecan; IRI, irinotecan.

[a] Model cycle = 30.42 days.

For FOLFIRI, the vial administration cost was applied every 14 days; for trifluridine + tipiracil, the tablet administration cost was applied every 28 days—that is, at the start of each new treatment cycle. Table 11 presents the total monthly costs for FOLFIRI and trifluridine + tipiracil.

Table 12. Primary treatment costs per model cycle for comparators

Regimen	Drug	Number of options	Average cost across options per model cycle with RDI (DKK)
Cetuximab	Cetuximab	1	[redacted]
FOLFIRI / FOLFOX	Folinic acid	3	[redacted]
	5-Fluorouracil	2	[redacted]
	IRI	2	[redacted]
	Oxaliplatin	3	[redacted]
Lonsurf	Trifluridine + tipiracil	2	[redacted]

FOLFIRI, folinic acid + 5-fluorouracil + irinotecan; IRI, irinotecan; RDI, relative dose intensity.

Note: Model cycle = 30.42 days. Number of options = number of treatment formulations available.

Administration costs

Administration costs were included in the model in the form of vial administration costs (Table 12). The vial administration cost was assumed to be DKK 835 based on a unit cost that had been frequently used for infusions in previous submissions to the DMC. [25]

Table 13. Treatment administration unit costs

Administration type	Unit cost (DKK)	Source
Vial administration	835.00	Administration (Infusion) [25]

For encorafenib + cetuximab, only the vial administration cost was applied, as only one payment will be issued, and it was assumed that the patient will receive their cetuximab intravenous treatment and their encorafenib tablets at the same time. In the base case, cetuximab was assumed to be administered every 2 weeks in line with guidance from KOLs. An administration cost of DKK 835 was incurred every 14 days (Table 13) based on Olsen et al. [25].

Table 14. Encorafenib + cetuximab administration cost calculations

Vial administration unit cost (DKK)	Frequency per model cycle	Subtotal for 28 days (DKK)	Adjustment for 30.42-day cycle length (DKK)
852	2	1,704	1,851

For all other treatment-related costs in the model, the treatment cycle lengths were adjusted to fit the model cycle length of 30.42 days (Table 14).

Table 15. Total treatment administration costs

	Encorafenib + cetuximab (DKK)	Clinician's choice (chemotherapy + cetuximab) (DKK)	FOLFIRI / FOLFOX
Cost per model cycle	1,816	1,816	1,816

4.3.2 Health state unit costs and resource use

The published literature that details the resource use associated with adults with $BRAF^{V600E}$-MT CRC is limited. Resource use data were validated and, in some cases, updated by input from the two Danish clinical experts (Appendix I). Costs per resource were sourced from Danish sources where available or converted to Danish krone where costs from other countries were applied.

4.3.2.1 Health state resource use

Table 15 presents the resource costs used for each health state and their associated frequency per cycle. The resource use was validated by clinical expert feedback (Appendix I). Patients treated with FOLFIRI incurred additional costs relating to peripherally inserted central catheter line clearance, which was estimated to be performed once per week to prevent infections and deleterious effects associated with peripherally inserted central catheter line presence (clinical expert feedback, Appendix I).

Table 16. Health states and associated costs in the economic model

Health states	Items	Value (DKK)	Frequency per model cycle	Source
Preprogression	CT scan	1,862.00	0.50	DRG: 30PR07 CT-scanning, ukompliceret, el. Osteodensitometri
	Medical oncologist outpatient consultation	451.95	1.00	DMC DMC [26]
	Nurse visit (peripherally inserted central catheter line care—only for FOLFIRI regimens)	544.00	4.00	DMC [26]
	Total of above (including frequency weights)	Non-FOLFIRI: 1,382.95 FOLFIRI: 3,558.95	NA	Calculation
Postprogression	Nurse specialist visit	544.00	2.00	Sygeplejersker. DMC [26]
	GP consultation	1,176.00	0.25	Kommunallæger. DMC [26]
	Nurse visit (PICC line care)	544.00	2.00	Sygeplejersker. DMC [26]
	Total of above (including frequency weights)	2,470.00	NA	Calculation

CT, computed tomography; FOLFIRI = folinic acid + 5-fluorouracil + irinotecan; GP, general practitioner; NA, not applicable; PICC, peripherally inserted central catheter.

4.3.3 Adverse reaction unit costs and resource use

The rates of adverse events were sources from the Beacon CRC trial and are presented in Table 16. The economic model incorporates AEs likely to have a notable impact on costs, namely those of severity grade 3+ with an incidence of at least 2% in either the encorafenib + cetuximab arm of BEACON CRC, the FOLFIRI arm of RAISE,[27] or the trifluridine + tipiracil arm of RECOURSE.[13]

Table 17. Adverse event rates used in the model

Event type	E+C	Clinician's choice (chemo+cetuximab)
Abdominal pain	3.2%	5.2%
Anaemia	5.6%	6.7%
Asthenia	3.7%	5.2%
Cancer pain	2.3%	0.5%
Decreased appetite	1.4%	3.1%
Diarrhoea	2.8%	10.4%
Fatigue	4.2%	4.7%
Febrile neutropenia	0.0%	2.6%
Hypertension	1.4%	2.6%
Intestinal obstruction	4.6%	2.6%

Event type	E+C	Clinician's choice (chemo+cetuximab)
Leukopenia	0.0%	4.1%
Liver injury/failure	0.0%	0.0%
Nausea	0.0%	1.6%
Neutropenia	0.9%	10.4%
Stomatitis	0.0%	2.1%
Thrombocytopenia	0.0%	0.0%
Urinary tract infection	2.3%	0.0%
Venous thrombosis	0.0%	0.0%
Vomiting	1.4%	3.1%

E+C, encorafenib + cetuximab.

The costs of AEs were sourced from previous Danish DRG cost database (Table 17).

Table 18. Adverse events and summary of costs in the economic model

A	Value (DKK)	Source
Abdominal pain	2,343.00	DRG06MA98
Anaemia	4,732.00	DRG16PR02
Asthenia	2,343.00	DRG06MA98
Cancer pain	2,343.00	DRG06MA98
Decreased appetite	—	Advised to not include AE cost per key opinion leader feedback
Diarrhoea	5,297.00	DRG06MA11
Fatigue	2,343.00	DRG06MA98
Febrile neutropenia	3,149.00	DRG16MA98
Hypertension	14,514.00	DRG05MA11
Intestinal obstruction	5,297.00	DRG06MA11
Leukopenia	3,149.00	DRG16MA98
Liver injury/failure	2,343.00	DRG06MA98
Nausea	2,343.00	DRG06MA98
Neutropenia	3,149.00	DRG16MA98
Stomatitis	2,343.00	DRG06MA98
Thrombocytopenia	37,603.00	DRG16MA03
Urinary tract infection	2,343.00	DRG06MA98
Venous thrombosis	1,162.00	DRG05MA98
Vomiting	2,343.00	DRG06MA98

AE, adverse event; DRG, diagnosis-related group.

Note: AE rates are provided in the final application.

4.3.4 Subsequent treatment costs after recurrence

After discontinuation of the primary treatment, patients switched to a subsequent therapy. The subsequent therapy that patients switched to was determined by their prior treatment and confirmed by expert feedback. According to the expert feedback, no differences in subsequent treatment is expected between the treatment arms.

Table 18 shows the allocation of subsequent treatments for each arm in the economic model.

Table 19. Subsequent treatments administered in the model based on prior treatment received

	Prior treatment	
Subsequent treatment	**Encorafenib + cetuximab**	**Clinician's choice (chemotherapy + cetuximab)**
Trifluridine + tipiracil	20%	20%
Regorafenib	0%	0%
Best supportive care	80%	80%

It was assumed that best supportive care would be those associated with normal health state resource use for preprogression and postprogression; the patients who moved to best supportive care after treatment discontinuation did not incur any additional treatment costs as a result.

For patients who moved to trifluridine + tipiracil after treatment discontinuation, it was assumed that they would receive, on average, two full cycles of treatment before coming off treatment altogether. This value was sourced from clinical expert opinion owing to the lack of data of subsequent treatments in patients with $BRAF^{V600E}$-MT mCRC (Table 19).

Table 20. Subsequent treatment costs for patients who progressed to trifluridine + tipiracil and bevacizumab

Parameter	**Trifluridine + tipiracil after progression**	**Source**
Mean subsequent treatment cycles	2.00	Clinical expert feedback
Conversion from treatment cycles (28 days) to model cycles (30.42 days)	2.17	Calculation
Mean cost per model cycle (DKK)	26,650.29	Table 11
Mean administration cost per cycle (DKK)	0	Table 14
Subtotal per cycle (DKK)	26,650.29	Calculation
Total cost of subsequent treatment (DKK)	57,901.00	Calculation

As the costs of subsequent treatments were applied as a one-off cost at the point of discontinuation, only patients who were estimated to have stopped the treatment in that specific model cycle incurred the costs. The proportion of patients who would receive treatment with trifluridine + tipiracil was used as a weight for the total cost of subsequent treatment with trifluridine + tipiracil.

4.3.5 End of life cost

The last months of all patients' lives are expected to involve additional costs. Therefore, a cost of DKK 118,782.45 per patient is expected, based on the calculations by French et al. [28] of the last 3 months' cost for Danish patients. The cost from 2014 was converted to Danish krone and 2020 prices using a consumer price index.

4.3.6 Transportation and time costs

Pierre Fabre could not identify a reliable source for the patient time spent on healthcare visits and therefore used a conservative estimate of 0.5 hours per visit. Cost will likely vary between the

different types of visits but overall, this parameter has a minimal impact on the results and a conservative assumption is therefore used.

Some differences in terms of time in the hospitals for drug administration can be expected between the treatment arms. However, given that cetuximab is expected to be provided in both treatment arms there are probably no relevant differences that would have an impact on the decision problem. The FOLFIRI components is expected to take between 5 to 90 minutes to administer while encorafenib is an oral drug. Hence, we prefer to keep our base-case conservative and not overestimate the patient time in the comparator arm compared to the encorafenib arm.

Table 21. Transportation and time cost

Unit	Unit cost (DKK)	Source
Time per visit	0.5	Assumption
Transport cost per visit	98.56	DMC [26]
Cost for patient time	179.00	

4.4 Summary table of model inputs

Table 22. Summary table of model inputs

Parameter	Parameter value
Cost discount rate	0.04
Mean age at baseline	59.30
Proportion male	0.47
Mean BSA	1.79
OS hazard ratio for mortality; FOLFIRI	2.56
PFS hazard ratio for mortality; FOLFIRI	3.33
OS hazard ratio for mortality; trifluridine/tipiracil	4.00
PFS hazard ratio for mortality; trifluridine/tipiracil	3.57
E+C OS Exponential	1.00
E+C OS Gompertz Rate	0.00
E+C OS Weibull Scale	2.72
E+C OS Gen Gamma Mu	2.41
E+C OS Log-logistic Scale	2.31
E+C OS Weibull Shape	0.86
E+C OS Gompertz Shape	-2.72
E+C OS Gen Gamma Sigma	1.05
E+C OS Log-logistic Shape	0.62
E+C OS Gen Gamma Q	0.22
E+C OS Lognormal Mean	2.31
E+C OS Lognormal SD	1.10
E+C PFS Exponential	-1.87
E+C PFS Gompertz Rate	-2.08
E+C PFS Weibull Scale	1.89
E+C PFS Gen Gamma Mu	1.62
E+C PFS Log-logistic Scale	1.53

Parameter	Parameter value
E+C PFS Weibull Shape	0.33
E+C PFS Gompertz Shape	0.05
E+C PFS Gen Gamma Sigma	-0.21
E+C PFS Log-logistic Shape	0.73
E+C PFS Gen Gamma Q	0.25
E+C PFS Lognormal Mean	1.53
E+C PFS Lognormal SD	-0.17
Clinicians choice OS Exponential	1.00
Clinicians choice OS Gompertz Rate	0.00
Clinicians choice OS Weibull Scale	2.25
Clinicians choice OS Gen Gamma Mu	2.03
Clinicians choice OS Log-logistic Scale	1.82
Clinicians choice OS Weibull Shape	0.89
Clinicians choice OS Gompertz Shape	-2.22
Clinicians choice OS Gen Gamma Sigma	0.99
Clinicians choice OS Log-logistic Shape	0.61
Clinicians choice OS Gen Gamma Q	0.50
Clinicians choice OS Lognormal Mean	1.79
Clinicians choice OS Lognormal SD	1.11
Clinicians choice PFS Exponential	-1.18
Clinicians choice PFS Gompertz Rate	-1.02
Clinicians choice PFS Weibull Scale	1.20
Clinicians choice PFS Gen Gamma Mu	0.74
Clinicians choice PFS Log-logistic Scale	0.69
Clinicians choice PFS Weibull Shape	0.11
Clinicians choice PFS Gompertz Shape	-0.07
Clinicians choice PFS Gen Gamma Sigma	-0.08
Clinicians choice PFS Log-logistic Shape	0.71
Clinicians choice PFS Gen Gamma Q	-0.05
Clinicians choice PFS Lognormal Mean	0.76
Clinicians choice PFS Lognormal SD	-0.09
Lonsurf OS Exponential	-2.34
Lonsurf OS Gompertz Rate	-2.72
Lonsurf OS Weibull Scale	2.29
Lonsurf OS Gen Gamma Mu	2.13
Lonsurf OS Log-logistic Scale	1.98
Lonsurf OS Weibull Shape	0.39
Lonsurf OS Gompertz Shape	0.07
Lonsurf OS Gen Gamma Sigma	-0.24
Lonsurf OS Log-logistic Shape	0.70
Lonsurf OS Gen Gamma Q	0.50
Lonsurf OS Lognormal Mean	1.97
Lonsurf OS Lognormal SD	-0.11
Lonsurf PFS Exponential	-1.23
Lonsurf PFS Gompertz Rate	-1.33

Parameter	Parameter value
Lonsurf PFS Weibull Scale	1.30
Lonsurf PFS Gen Gamma Mu	0.77
Lonsurf PFS Log-logistic Scale	0.88
Lonsurf PFS Weibull Shape	0.29
Lonsurf PFS Gompertz Shape	0.04
Lonsurf PFS Gen Gamma Sigma	-0.33
Lonsurf PFS Log-logistic Shape	0.86
Lonsurf PFS Gen Gamma Q	-0.44
Lonsurf PFS Lognormal Mean	0.93
Lonsurf PFS Lognormal SD	-0.30
Clinician's choice	0.68
Price Folinic acid Pack 1	DKK 111.00
Price Folinic acid Pack 2	DKK -
Price Folinic acid Pack 3	DKK -
Price Folinic acid Pack 4	DKK 220.00
Price Folinic acid Pack 5	DKK -
Price Folinic acid Pack 6	DKK 340.00
Price Fluorouracil Pack 1	DKK 200.00
Price Fluorouracil Pack 2	DKK 400.00
Price Irinotecan Pack 1	DKK 80.00
Price Irinotecan Pack 2	DKK -
Price Irinotecan Pack 3	DKK -
Price Irinotecan Pack 4	DKK 200.00
Lonsurf 20 mg/Pack size 60	DKK 24,534.17
Lonsurf 15 mg/Pack size 60	DKK 18,398.64
Encorafenib RDI	0.88
Cetuximab RDI	0.87
Cetuximab RDI	0.87
Folinic acid RDI 1	0.72
Folinic acid RDI 2	0.00
Folinic acid RDI 3	0.00
Folinic acid RDI 4	0.00
Folinic acid RDI 6	0.72
Folinic acid RDI 7	0.00
Fluorouracil RDI 1	0.67
Fluorouracil RDI 7	0.67
Irinotecan RDI 1	0.73
Irinotecan RDI 2	0.73
Irinotecan RDI 3	0.73
Irinotecan RDI 4	0.73
Trifluridine/tipiracil RDI 1	1.00
Trifluridine/tipiracil RDI 2	1.00
Hydrocortisone cost	19.32
Paracetamol cost	95.84
Vial administration costs	835.94

Parameter	Parameter value
Encorafenib list price	11,960.00
Cetuximab list price	7,884.68
Cetuximab list price	7,884.68
Oral chemotherapy day case attendance cost	1,862.00
OC FOLFIRI PF frequency	0.50
OC non-FOLFIRI PF frequency	0.50
Medical oncologist outpatient consultation cost	451.95
MO FOLFIRI PF frequency	1.00
MO non-FOLFIRI PF frequency	1.00
GP home consultation cost	451.95
GP FOLFIRI PD frequency	0.00
GP non-FOLFIRI PD frequency	0.00
Community nurse specialist cost	544.00
CN FOLFIRI PD frequency	2.00
CN non-FOLFIRI PD frequency	2.00
Health home visitor cost	1,176.00
HHV FOLFIRI PF frequency	0.00
HHV FOLFIRI PD frequency	0.25
HHV non-FOLFIRI PF frequency	0.00
HHV non-FOLFIRI PD frequency	0.25
District nurse cost	544.00
DN FOLFIRI PF frequency	4.00
DN FOLFIRI PD frequency	2.00
DN non-FOLFIRI PD frequency	2.00
GP visit cost	0.00
GP FOLFIRI PD frequency	0.00
GP non-FOLFIRI PD frequency	0.00
Terminal care costs	118,782.45
E+C trifluridine/tipiracil on progression users	20.00%
FOLFIRI trifluridine/tipiracil on progression users	20.00%
Mean subsequent treatment cycles of trifluridine/tipiracil	2.00
Abdominal pain	2,343.00
Anaemia	4,732.00
Asthenia	2,343.00
Cancer pain	2,343.00
Decreased appetite	-
Diarrhoea	5,297.00
Fatigue	2,343.00
Febrile neutropenia	3,149.00
Hypertension	14,514.00
Intestinal obstruction	5,297.00
Leukopenia	3,149.00
Liver injury/failure	2,343.00
Nausea	2,343.00
Neutropenia	3,149.00

Parameter	Parameter value
Stomatitis	2,343.00
Thrombocytopenia	37,603.00
Urinary tract infection	2,343.00
Venous thrombosis	1,162.00
Vomiting	2,343.00
Abdominal pain rate, Enco with cetuximab	3.24%
Anaemia rate, Enco with cetuximab	5.56%
Asthenia rate, Enco with cetuximab	3.70%
Cancer pain rate, Enco with cetuximab	2.31%
Decreased appetite rate, Enco with cetuximab	1.39%
Diarrhoea rate, Enco with cetuximab	2.78%
Fatigue rate, Enco with cetuximab	4.17%
Febrile neutropenia rate, Enco with cetuximab	0.00%
Hypertension rate, Enco with cetuximab	1.39%
Intestinal obstruction rate, Enco with cetuximab	4.63%
Leukopenia rate, Enco with cetuximab	0.00%
Liver injury/failure rate, Enco with cetuximab	0.00%
Nausea rate, Enco with cetuximab	0.00%
Neutropenia rate, Enco with cetuximab	0.93%
Stomatitis rate, Enco with cetuximab	0.00%
Thrombocytopenia rate, Enco with cetuximab	0.00%
Urinary tract infection rate, Enco with cetuximab	2.31%
Venous thrombosis rate, Enco with cetuximab	0.00%
Vomiting rate, Enco with cetuximab	1.39%
Abdominal pain rate, FOLFIRI	3.60%
Anaemia rate, FOLFIRI	3.60%
Asthenia rate, FOLFIRI	0.00%
Cancer pain rate, FOLFIRI	0.00%
Decreased appetite rate, FOLFIRI	1.89%
Diarrhoea rate, FOLFIRI	9.66%
Fatigue rate, FOLFIRI	7.77%
Febrile neutropenia rate, FOLFIRI	2.46%
Hypertension rate, FOLFIRI	2.84%
Intestinal obstruction rate, FOLFIRI	0.00%
Leukopenia rate, FOLFIRI	2.65%
Liver injury/failure rate, FOLFIRI	3.98%
Nausea rate, FOLFIRI	2.65%
Neutropenia rate, FOLFIRI	23.30%
Stomatitis rate, FOLFIRI	2.27%
Thrombocytopenia rate, FOLFIRI	0.76%
Urinary tract infection rate, FOLFIRI	0.00%
Venous thrombosis rate, FOLFIRI	2.08%
Vomiting rate, FOLFIRI	2.46%
Abdominal pain rate, Trifluridine-tipiracil	2.44%
Anaemia rate, Trifluridine-tipiracil	18.18%

Parameter	Parameter value
Asthenia rate, Trifluridine-tipiracil	3.38%
Cancer pain rate, Trifluridine-tipiracil	0.00%
Decreased appetite rate, Trifluridine-tipiracil	3.56%
Diarrhoea rate, Trifluridine-tipiracil	3.00%
Fatigue rate, Trifluridine-tipiracil	3.94%
Febrile neutropenia rate, Trifluridine-tipiracil	3.75%
Hypertension rate, Trifluridine-tipiracil	0.00%
Intestinal obstruction rate, Trifluridine-tipiracil	0.00%
Leukopenia rate, Trifluridine-tipiracil	21.40%
Liver injury / failure rate, Trifluridine-tipiracil	0.00%
Nausea rate, Trifluridine-tipiracil	0.00%
Neutropenia rate, Trifluridine-tipiracil	37.88%
Stomatitis rate, Trifluridine-tipiracil	0.00%
Thrombocytopenia rate, Trifluridine-tipiracil	5.11%
Urinary tract infection rate, Trifluridine-tipiracil	0.00%
Venous thrombosis rate, Trifluridine-tipiracil	0.00%
Vomiting rate, Trifluridine-tipiracil	2.06%

BSA, body surface area; E + C, encorafenib + cetuximab; FOLFIRI, folinic acid + 5-fluorouracil + irinotecan; GP, general practitioner; MO, medical oncologist; OS, overall survival; PD, Progressed disease; PF, progression free; PFS, progression-free survival; RDI, relative dose intensity; SD, standard deviation.

Note: See model for more details.

5 Economic results

5.1 Cost analysis results

The results of the cost analyses show that treatment with encorafenib + cetuximab compared with chemotherapy + cetuximab would result in an incremental cost of DKK [redacted] (Table 22).

Table 23. Cost analysis results

Mean total expected lifetime costs, per patient (DKK, discounted)	Encorafenib + cetuximab	Chemotherapy + cetuximab	Incremental
Treatment cost	[redacted]	[redacted]	[redacted]
Administration cost	12,669	6,238	6,432
Adverse event cost	1,287	2,441	-1,154
Subsequent treatment cost	4,000	5,431	-1,431
Health state costs	35,483	33,242	2,242
Terminal cost	112,206	114,471	2,265
Total direct costs	[redacted]	[redacted]	[redacted]
Patient costs	10,267	10,401	134
Total cost	[redacted]	[redacted]	[redacted]

Scenario analyses are provided in Table 23.

Table 24. Scenario analyses

Scenario	Base-case assumption	Scenario assumption	Incremental cost (DKK)
Base case			[redacted]
Patient time per visit	0.5 hours per visit	2 hours per visit	[redacted]
Administration cost	Based on Olsen et al. [27]	According to DRG code 04MA98 (1799)	[redacted]
Dose intensity	According to BEACON CRC	100%	[redacted]
FOLFIRI as comparator	No	Yes	[redacted]
Lonsurf as comparator	No	Yes	[redacted]
FOLFIRI + bevacizumab as comparator (only cost)	No	Yes	[redacted]
FOLFOX as comparator	No	Yes	[redacted]
FOLFOX + bevacizumab as comparator	No	Yes	[redacted]
Wastage	No	Yes	[redacted]

5.2 Budget-impact results

The results of the budget-impact analysis (Table 24) show that approximately 143 patients could be eligible for encorafenib treatment per year and that 7 patients will be treated with encorafenib the first

year, increasing to 36 patients by year 5 (Table 25). Based on these numbers, the total budget impact of encorafenib in year 1 would be DKK [redacted], increasing to DKK [redacted] by year 5 (Table 26).

Table 25. Patient numbers

Population	No. of patients	Calculation	Source
Number of patients with CRC in Denmark	4,433		Reported cases in DCCG [29]
Number of patients with mCRC	2,217	50%	Van Cutsem et al. [2], Benitez Majano et al. [30]
Number of patients with $BRAF^{V600E}$-MT mCRC	465	21%	Sorbye et al. [6]
Number of patients treated with first-line therapy	265	57%	Sorbye et al. [6]
Number of patients treated with second-line therapy	143	54%	Sorbye et al. [6]
Number of patients eligible for encorafenib treatment	143	100%	Assumption; confirmed by key opinion leader (Appendix I)

CRC, colorectal cancer; mCRC, metastatic colorectal cancer.

Table 26. Market share and expected patient numbers: encorafenib

Pharmaceutical	Year 1	Year 2	Year 3	Year 4	Year 5
Encorafenib market share	5%	10%	15%	20%	25%
Encorafenib patient numbers	7	14	21	29	36

Table 27. Budget impact: encorafenib, years 1-5

	Year 1	Year 2	Year 3	Year 4	Year 5
If encorafenib is adopted					
Treatment cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Administration cost	865,990	960,988	1,021,852	1,074,793	1,124,852
AE cost	341,503	333,237	324,970	316,704	308,437
Subsequent treatment cost	767,935	757,796	747,658	737,520	727,381
Health state costs	3,183,775	3,897,745	4,207,871	4,389,894	4,515,622
Terminal cost	11,851,717	14,961,501	15,767,671	16,084,162	16,238,618
Total cost (DKK)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
If encorafenib is not adopted					
Treatment cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Administration cost	826,662	874,827	888,334	894,044	896,998
AE cost	349,770	349,770	349,770	349,770	349,770
Subsequent treatment cost	778,073	778,073	778,073	778,073	778,073
Health state costs	3,235,143	3,978,018	4,302,090	4,488,170	4,610,941
Terminal cost	12,011,662	15,213,530	16,075,064	16,428,525	16,609,609
Total cost (DKK)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Budget impact					
Treatment cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Administration cost	39,327	86,161	133,519	180,749	227,854
AE cost	-8,267	-16,533	-24,800	-33,066	-41,333
Subsequent treatment cost	-10,138	-20,277	-30,415	-40,553	-50,692
Health state costs	-51,368	-80,273	-94,219	-98,277	-95,319
Terminal cost	-159,944	-252,028	-307,392	-344,363	-370,991
Total cost (DKK)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

AE, adverse event.

6 Discussion on the submitted documentation

6.1 Interpretation and conclusions of economic evidence

A cost analysis has been developed to estimate the economic impact of encorafenib + cetuximab for patients with previously treated $BRAF^{V600E}$-MT mCRC in line with its marketing authorisation and with the decision problem of this submission. The base-case analysis compares encorafenib + cetuximab versus clinician's choice (chemotherapy + cetuximab) from BEACON CRC (investigator's choice), as it was deemed to be the most suitable comparator based on the DMC protocol. Key strength of the analysis are that;

- In the BRAF-MT population for which clinical evidence for comparators is extremely limited, the analysis has made use of the best available evidence identified by systematic means. For both encorafenib + cetuximab and the clinician's choice (chemotherapy + cetuximab), effectiveness and safety data were derived from the phase 3 RCT BEACON CRC, which was specifically designed to investigate the effectiveness and safety of the encorafenib regimen in the BRAF-MT population and thus represents the most robust evidence available.
- All costs are taken from Danish cost sources, including unit and drug costs from DMA's databases.

If adopted in Denmark, encorafenib + cetuximab would provide, to a reasonable cost, a first-in-class, chemotherapy-free treatment that is specifically indicated for patients with $BRAF^{V600E}$-MT mCRC and improves survival and maintain health-related quality of life longer. Given the very poor prognosis of BRAFV600E-MT mCRC and the lack of specific treatment, there is a strong unmet need for an effective and tolerated treatment option that would increase survival and maintain quality of life (QOL) for patients with BRAFV600E-MT mCRC.

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Medicinrådet

Medicinrådets protokol for vurdering af encorafenib i kombination med cetuximab til patienter med metastatisk kolorektalkræft, der har $BRAF^{V600E-}$mutation

Versionsnr.: 1.0

Om Medicinrådet

Medicinrådet er et uafhængigt råd etableret af Danske Regioner.

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

Om protokollen

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

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

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

Godkendt af Medicinrådet 10. juli 2020
Dokumentnummer 80887
Versionsnummer: 1.0

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

Indhold

1 Begreber og forkortelser

BRAF	*Proto-oncogene B-Raf*
CI	Konfidensinterval
DCCG	Dansk Colorektal Cancer Gruppe
dMMR	Defekter i *mismatch repair*-systemet
EGFRi	*Epidermal Growth Factor Receptor inhibitor*
EMA	Det Europæiske Lægemiddelagentur (*European Medicines Agency)*
EPAR	*European Public Assessment Report*
GRADE	System til at vurdere evidens (*Grading of Recommendations, Assessment, Development and Evaluation*)
HR	*Hazard ratio*
ITT	*Intention to treat*
IV	Intravenøs
K-RAS	Kirsten Rat Sarcoma Viral Oncogene Homologue
KRC	Kolorektalcancer
MAPK	*Mitogen-activated protein kinases*
mKRC	Metastaseret kolorektalcancer
OR	*Odds ratio*
PICO	Population, intervention, komparator og effektmål (*Population, Intervention, Comparator and Outcome)*
PP	*Per-protocol*
RADS	Rådet for Anvendelse af Dyr Sygehusmedicin
RCT	Randomiseret kontrolleret studie *(Randomised Controlled Trial)*
RR	Relativ risiko
SMD	*Standardized Mean Difference*

2 Introduktion

Protokollen er udarbejdet, fordi Medicinrådet har modtaget en foreløbig ansøgning fra Pierre-Fabre, som ønsker, at Medicinrådet vurderer encorafenib i kombination med cetuximab til behandling af patienter med metastatisk $BRAF^{V600E}$-positiv kolorektalkræft, som tidligere har modtaget behandling for deres sygdom. Vi modtog den foreløbige ansøgning den 14. april 2020.

2.1 Kolorektalcancer

Kræft i tyk- og endetarm (kolorektalcancer herefter forkortet KRC) er en af de hyppigste kræftsygdomme i Danmark. I 2018 blev i alt 4433 diagnosticeret med KRC, størstedelen med tyktarmskræft. Hyppigheden stiger med alderen, og ses sjældent før 40-års alderen, og de fleste tilfælde ses først efter 60 års-alderen [1]. Siden 2014 er alle i aldersgruppen 50-74 år i Danmark blevet tilbudt screening for KRC [2]. Femårsoverlevelsen for endetarmskræft er hhv. 66 og 69 % for mænd og kvinder, mens den for tyktarmskræft er hhv. 63 og 65 % [3,4]. Årsagen til sygdommen er ofte ukendt.

Symptomerne ved KRC manifesterer sig hyppigt ved ændringer i afføringsmønsteret, herunder slim og blod i afføringen, anæmi samt uforklarlige almene symptomer heriblandt vægttab, mavesmerter og svækkelse. De uspecifikke og sene symptomer medfører, at patienter først sent i sygdomsudviklingen opsøger læge. Konsekvensen heraf er, at omkring 20-30 % af patienterne allerede har metastatisk KRC (mKRC) ved diagnosetidspunktet, og yderligere 20 % udvikler mKRC inden for fem år [5]. Overlevelsen for patienter med mKRC er forbedret i takt med introduktionen af nye målrettede behandlingsformer og mere aggressiv metastasekirurgi [6].

For at tilrettelægge den rette behandling undersøges tumorvævet for mutationer i *epidermal growth factor receptor* (EGFR)-signaleringsvejen (K-RAS, BRAF og N-RAS-mutationer) og for defekter i *mismatch repair*-systemet (dMMR). Identifikation af mutationer anvendes med henblik på at planlægge og målrette behandlingen. Patienter med BRAF-mutationer har den dårligste prognose, da standardbehandlingen ofte har begrænset effekt med en median overlevelse på 4-6 måneder efter førstelinjebehandling [6–10]. BRAF-mutationer findes i ca. 10 % af patienter med mKRC [7]. BRAF er en proteinkinase, som er involveret i MAPK-signaleringskaskaden (*mitogen-activated protein kinase*), som driver celledeling. Næsten alle BRAF-mutationer er af typen $BRAF^{V600E}$, som overaktiverer BRAF, hvilket resulterer i, at maligne celler med denne mutation deler sig hastigt, og tumor vokser sig større med mulig spredning [11].

2.2 Nuværende behandling

Behandlingen følger retningslinjer fra Dansk Colorektal Cancer Gruppe (DCCG) [12]. Formålet med behandlingen af mKRC afhænger af udbredelsen af primær tumor og metastaser, og dermed hvorvidt det vurderes muligt at opnå kirurgisk fjernelse ved diagnose.

For alle patienter, hvor kirurgisk fjernelse ikke er mulig initielt, består førstelinjebehandlingen af kemoterapi, eventuelt i kombination med targeteret antistofbehandling (bevacizumab, samt EGFRinhibitor (EGFRi); som enten kan være panitunumab eller cetuximab), hvor hovedformålet er livsforlængelse og evt. symptomlindring.

Ved progression under eller efter endt førstelinjebehandling tilbydes patienterne videre behandlingsforløb i form af anden- og sjældent tredjelinjebehandling, hvis performancestatus og almentilstand tillader det.

Førstelinjebehandling af BRAF-muteret mKRC er:

- To-stof kemoterapi i form af FOLFIRI (folinsyre, fluorouracil (5-FU), irinotecan) eller FOLFOX (folinsyre, fluorouracil, oxaliplatin), eventuelt, men sjældent, i kombination med targeteret antistofbehandling (bevacizumab og evt. EGFRi (cetuximab eller panitumumab)).
- Triple kemoterapi i form af FOLFOXIRI (folinsyre, 5-FU, oxaliplatin og ironotecan), eventuelt, men sjældent, i kombination med targeteret antistofbehandling.
- Capecitabine i kombination med bevacizumab.

Valg af førstelinjebehandling er en individuel vurdering, hvilket blandt andet skyldes, at behandling mod BRAF muteret tumorer er forbundet med dårlig evidens. FOLFIRI samt FOLFOX anses som ligeværdige behandlingsalternativer, hvad angår deres effekt, men der er i Danmark praksis for at tilbyde størstedelen af patienterne FOLFIRI i førstelinje, da oxaliplatin i FOLFOX er kendetegnet ved neurologiske bivirkninger, der kan blive persisterende. Patienten vil ofte progrediere på behandlingen, hvorfor der ikke er en fast behandlingslængde.

Særlig aggressiv behandling med FOLFOXIRI, evt. med tillæg af targeteret antistofbehandling med bevacizumab eller EGFRi, tilbydes kun få patienter, der har særlig god helbredsstatus og ofte stor tumorbyrde med behov for tumorreduktion – enten grundet potentiel mulighed for kirurgi eller med henblik på symptomlindring.

Der foretages individuelt en vurdering af, hvorvidt der skal tillægges targeteret antistofbehandling, og det er for BRAF-muterede patienter kun en mindre andel, hvor targeteret behandling anvendes i førstelinje. F.eks. Får patienter med potentiel mulighed for kirurgi tilbudt targeteret behandling. Et hensyn for denne behandling er også lokalisation af tumor, hvor EGFRi evt. anvendes ved venstresidige tumorer og bevacizumab i højere grad ved højresidige, da der ses differentieret respons.

Ved progression tilbydes andenlinje kemoterapi kun til ca. 50 % af patienterne, da patienternes almentilstand ofte ikke er forenelig med yderligere behandling. Andenlinje kemoterapi afhænger af, hvad patienten fik som førstelinjebehandling. Er der givet irinotecan-baseret kemoterapi i førstelinje, tilbydes der efterfølgende oxaliplatin-baseret kemoterapi i andenlinje og omvendt.

Som andenlinjebehandling tilbydes patienter med BRAF-muteret mKRC kemoterapi i kombination med enten EGFRi eller bevacizumab, hvis dette ikke blev givet ved førstelinjebehandling. Der er tvivl om, hvilken plads EGFRi-behandling har hos BRAF-muterede mKRC-patienter, da data er inkonklusive [13,14]. Der foreligger derfor ikke konsensus om dette i dansk klinisk praksis, og EGFRi-behandling kan derfor tilbydes til patienter, der ikke har mutation i K- eller N-RAS (K-RAS og N-RAS-wildtype), da mutation i K-RAS eller N-RAS giver behandlingsresistens mod EGFRi.

Der er ikke nogen veletableret tredjelinjebehandling af BRAF-muterede mKRC-patienter. Eneste mulighed vil, som udgangspunkt, være eksperimentel behandling. Hvis der ikke har været manifest progression under et tidligere pågående behandlingsregime, kan dette også i få tilfælde reinduceres, hvis bivirkningerne tillader det.

2.3 Encorafenib

Encorafenib er en potent RAF kinasehæmmer, som hæmmer MAPK-signaleringsvejen i tumorceller, der udtrykker $BRAF^{v600E}$-mutationer. Lægemidlet er på den måde i stand til at inhibere tumorens vækst. Encorafenib er godkendt i kombination med cetuximab (én af de to EGFRi, som anvendes i KRC). Behandlingen har indikation til voksne patienter med mKRC, der udtrykker $BRAF^{V600E}$-mutation.
Der tillægges cetuximab eftersom, at der ved BRAF-inhibering sker en feedback mekanisme, der aktiverer EGFR, dette resulterer i resistens over for behandling mod BRAF-mutationer, såsom behandling med

encorafenib. Kombinationsbehandling er derfor nødvendig, i og med det ene stof inhiberer tumorens vækst, mens det andet modvirker resistensproblemer, der opstår ved behandlingen.

Encorafenib er godkendt til patienter, der tidligere har modtaget første- eller andenlinjebehandling jf. afsnit 2.2, hvorfor encorafenib kombinationsbehandlingen både kan anvendes i anden- og tredjelinjebehandling.

Encorafenib findes i tabletform. Den anbefalede dosis af encorafenib er fire kapsler af 75 mg (300 mg) én gang dagligt. Kapslerne indtages oralt med vand. Encorafenib skal administreres i kombination med cetuximab, som gives i forhold til gældende produktresumé (intravenøst (IV) én gang ugentlig, initialdosis 400 mg/m2, efterfølgende doser er 250 mg/m2).

Behandling bør fortsættes, indtil patienten ikke længere oplever forbedring, eller patienten udvikler uacceptable bivirkninger/toksicitet.

Encorafenib er af Det Europæiske Lægemiddelagentur (*European Medicines Agency* (EMA)) allerede godkendt til behandling af metastatisk modermærkekræft, som ikke kan fjernes ved kirurgi.

Fagudvalget skønner, at ca. 110 patienter med $BRAF^{V600E}$-positiv mKRC årligt vil være kandidater til encorafenib i kombination med cetuximab efter førstelinjebehandling. Dette er baseret på følgende estimater; 4433 diagnosticeret med KRC om året, 50 % af dem vil udvikle mKRC (ca. 2217 patienter), 10 % med $BRAF^{v600E}$ (ca. 221 patienter). Heraf forventes 50 % at tilbydes andenlinjebehandling (ca. 110 patienter).

3 Kliniske spørgsmål

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

3.1 Klinisk spørgsmål

Hvilken værdi har encorafenib i kombination med cetuximab sammenlignet med FOLFIRI ± bevacizumab eller EGFRi eller FOLFOX ± bevacizumab eller EGFRi for patienter med metastatisk kolorektalkræft, som har $BRAF^{V600E}$-mutation?

Population
Patienter med metastatisk kolorektalkræft, der har $BRAF^{V600E}$-mutation, og som tidligere har modtaget systemisk terapi i form af kemoterapi i første- og/eller andenlinje, jf. afsnit 2.2.

Intervention
300 mg oral administreret encorafenib én gang dagligt i kombination med intravenøst cetuximab én gang ugentligt, initialdosis 400 mg/m2, efterfølgende doser er 250 mg/m2.

Komparator
FOLFIRI (folinsyre, fluorouracil, irinotecan) ± bevacizumab eller EGFRi.

FOLFOX (folinsyre, fluorouracil, oxaliplatin) ± bevacizumab eller EGFRi.

Andenlinje kemoterapi afhænger af, hvad patienten fik som førstelinjebehandling. Er der givet irinotecan-baseret kemoterapi i førstelinje, tilbydes der efterfølgende oxaliplatin-baseret kemoterapi i andenlinje og omvendt. Det er derfor tilstrækkeligt, at ansøger belyser én af de to komparatorer, eftersom de er ligestillede.

Dosering af lægemidlerne er, som følger:

Fluorouracil: individuelt i henhold til produktresumeet (2400–3000 mg/m^2).

Irinotecan: 180 mg/ m^2 hver anden uge givet iv.

Oxaliplatin: 85 mg/ m^2 hver anden uge givet iv.

Folinsyre: 400 mg/m^2 hver anden uge givet iv.

Bevacizumab: gives ved 5 mg/kg iv. en gang hver 2. uge eller 7,5 mg/kg en gang hver 3. uge.

Cetuximab: gives iv. hver anden uge, initialdosis 400 mg/m2, efterfølgende doser er 250 mg/m2.

Effektmål
De valgte effektmål står i tabel 1.

3.2 Effektmål

Medicinrådet mener, at vurderingen af lægemidlets værdi bliver bedst understøttet af de effektmål, vi har nævnt i Tabel 1. For hver effektmål har Medicinrådet fastsat en mindste klinisk relevant forskel (MKRF). I det følgende afsnit argumenterer vi for valget af effektmål og de mindste klinisk relevante forskelle.

Tabel 1. Effektmål.

Effektmål	Vigtighed	Effektmålsgruppe	Måleenhed	Mindste klinisk relevante forskel
Overlevelse (OS)	Kritisk	Dødelighed/ overlevelse	Median OS	3 måneder
			Andel, som er i live efter 12 måneder	5 %-point
Livskvalitet	Vigtig	Livskvalitet, alvorlige symptomer og bivirkninger	Forskel i gennemsnitlig ændring fra baseline i EORTC-QLQ-C30	10 point
Bivirkninger	Vigtig	Livskvalitet, alvorlige symptomer og bivirkninger	Andel af patienter, der får én eller flere grad 3-4 uønskede hændelser	5 %-point
			Kvalitativ gennemgang af uønskede hændelser	-

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

3.2.1 Kritiske effektmål

Overlevelse

Forbedret samlet overlevelse (OS) med mindst mulig toksicitet er målet for behandling af uhelbredelig mKRC. Derfor vurderer fagudvalget, at OS er et kritisk effektmål. I denne sammenhæng vurderer fagudvalget, at det er relevant at se på både median OS samt overlevelsesraten ved 12 måneder.

Fagudvalget mener, at median OS afspejler overlevelsen for den samlede population. Medicinrådet vurderer i lighed med lignende sager, at 3 måneder er den mindste klinisk relevante forskel i anden- og tredjelinjebehandling.

Derudover ønsker fagudvalget data på andelen af patienter, der overlever i ≥ 12 måneder. Raten ved 12 måneder belyser, om en gruppe af patienter opnår længerevarende effekt af behandlingen, der ligger væsentlig ud over den mediane overlevelse for patientgruppen. For patienter, der starter andenlinjebehandling med gældende standardbehandling, forventer fagudvalget, at 10 % af patienterne fortsat er i live efter 12 måneder. På baggrund af dette vurderer fagudvalget, at 5 % er den mindste klinisk relevante forskel.

Fagudvalget vil som udgangspunkt lægge hovedvægt på median overlevelse, men ønsker også at se på andelen af patienter, der overlever i ≥ 12 måneder. De mindste klinisk relevante forskelle er fastsat ud fra en betragtning om, at der er tale om en sygdom med særdeles dårlig prognose med nuværende standardbehandling og ingen effektive efterfølgende behandlingslinjer andet end eksperimentel behandling.

3.2.2 Vigtige effektmål

Livskvalitet

Bevarelse af livskvalitet, trods alvorlig kræftsygdom, er et væsentligt helbredsrelateret mål for den enkelte patient, hvorfor fagudvalget anser effektmålet som vigtigt. Livskvalitet kan for kræftpatienter måles med flere forskellige instrumenter. I denne vurdering ønsker fagudvalget at vurdere livskvalitet baseret på følgende instrument: European Organisation for Research and Treatment of Cancer Quality-of-life Questionnaire-Core 30 (EORTC QLQ-C30). EORTC QLQ-C30 består af fem funktionsskalaer, tre symptomskalaer og en global helbredsstatus. Der anvendes en scoringsskala fra 0-100. En høj score på de fem funktionsskalaer repræsenterer et højt funktionsniveau. En høj score for global helbredsstatus repræsenterer høj livskvalitet, mens en høj score på de tre symptomskalaer repræsenterer høj forekomst af symptomer/problemer. En lille ændring i livskvaliteten er defineret som 5-10 point på den globale skala, mens en moderat ændring er 10-20 point, og en stor ændring er > 20 point [15]. Fagudvalget har defineret den mindste klinisk relevante forskel som en gennemsnitlig ændring på 10 point fra baseline, da dette vil overstige grænsen for en lille ændring.

Hvis der ikke foreligger data på EORTC QLQ-C30 opgjort på ovenstående måde, vil fagudvalget være interesseret i at se andre data for livskvalitet. Fagudvalget vil i det tilfælde vurdere data for livskvalitet narrativt og beder ansøger indsende argumentation for mindste klinisk relevante forskelle i denne sammenhæng.

Bivirkninger

Forskellen i forekomsten af uønskede hændelser grad 3-4 forventes at være et udtryk for forskellen i alvorlig toksicitet mellem lægemidlerne. Fagudvalget vurderer, at der for denne patientgruppe er nogen grad af tolerance for alvorlige bivirkninger, da alternative behandlingsmuligheder er begrænsede, og prognosen er meget ringe, patienternes almen tilstand kan dog være svækket, både som følge af sygdommen og tidligere førstelinje (og eventuelt andenlinje) behandling. Fagudvalget anser derfor andelen af patienter, som oplever grad 3-4 uønskede hændelser, som et vigtigt effektmål, og vurderer, at den mindste klinisk relevante forskel er på 5 %-point.

Derudover ønsker fagudvalget en kvalitativ gennemgang af bivirkningsprofilerne forbundet med intervention og komparator med henblik på at vurdere bivirkningernes type, håndterbarhed og reversibilitet. Fagudvalget

vil specielt fokusere på de bivirkninger, som adskiller sig mellem intervention og komparator, inklusive eventuelle bivirkninger, der resulterede i dødsfald.

4 Litteratursøgning

Medicinrådet har på baggrund af den foreløbige ansøgning undersøgt, om der findes en eller flere fuldtekstartikler publiceret i videnskabelige, fagfællebedømte tidsskrifter, hvor encorafenib i kombination med cetuximab er sammenlignet med relevant kemoterapi jf. afsnit 3.1.

Medicinrådet har fundet følgende fuldtekstartikel/fuldtekstartikler, som indeholder en direkte sammenligning mellem encorafenib i kombination med cetuximab og FOLFIRI eller irinotecan i kombination med cetuximab:

- BEACON studiet: Encorafenib, Binimetinib, and Cetuximab in BRAF V600E–Mutated Colorectal Cancer, 2019 (NCT02928224) [10]

Det er tilstrækkeligt datagrundlag til at besvare det kliniske spørgsmål. Dog indeholder publikationen ikke data for effektmålet livskvalitet, så hvis ansøger har data for livskvalitet fra BEACON-studiet, skal dette ligeledes indgå i den endelige ansøgning. Samtidig er fagudvalget også interesseret i at se opfølgende data på overlevelse, hvis ansøger har dette. Disse data vil indgår i vurderingen også selvom de ikke er publicerede, jf. Medicinrådets kriteriepapir vedrørende upublicerede data.

Ansøger skal derfor ikke søge efter yderligere fuldtekstartikler, men skal konsultere Det Europæiske Lægemiddelagenturs (EMA) European public assessment reports (EPAR) for både det aktuelle lægemiddel og dets komparator(er).

5 Databehandling og -analyse

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

Studier og resultater

- Beskriv de inkluderede studier og baselinekarakteristikken af studiepopulationerne.
- Angiv, hvilke studier/referencer der er benyttet til at besvare hvilke kliniske spørgsmål.
- Brug som udgangspunkt ansøgningsskemaet til ekstraktion af al relevant data.
- Krydstjek de ekstraherede data med de resultater, der fremgår af de relevante EPARs.
- Angiv årsager, hvis der er uoverensstemmelser mellem resultaterne fra artikler og EPARs.
- Angiv årsager, hvis der er uoverensstemmelser i forhold til PICO mellem protokollen og studierne.
- Vurdér, hvordan uoverensstemmelserne påvirker estimaterne.

Statistiske analyser

- Begrund valget af syntesemetode (metaanalyse eller narrativ beskrivelse), og lad specifikke analysevalg fremgå tydeligt.
- Udfør en komparativ analyse for hvert enkelt effektmål på baggrund af de ekstraherede data.
- Hvis data for et effektmål ikke er baseret på alle deltagere i et studie, skal ansøger ikke gøre forsøg på at erstatte manglende data med en meningsfuld værdi.

- Angiv for hvert effektmål og studie, hvilken analysepopulation (f.eks. intention-to-treat (ITT), per-protocol) der er anvendt.
- Angiv en sensitivitetsanalyse baseret på ITT-populationen, hvis den komparative analyse ikke er baseret herpå.
- Angiv for hvert effektmål og studie, hvilken statistisk analysemetode der er anvendt.
- Basér de statistiske analyser for dikotome effektmål på den relative forskel.
- Beregn den absolutte forskel med udgangspunkt i den estimerede relative forskel for et antaget niveau på hændelsesraten i komparatorgruppen (jævnfør Appendiks 5 i Håndbog for Medicinrådets proces og metode vedr. nye lægemidler og indikationsudvidelser).
- Foretag eventuelt en indirekte analyse, hvis der ikke foreligger direkte sammenlignende studier, og hvis intervention og komparator er sammenlignet med samme alternative komparator i separate studier. Anvend eventuelt Buchers metode for indirekte justeret sammenligning.

Metaanalyser

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

Narrative analyser

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

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

6 Evidensens kvalitet

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

7 Andre overvejelser

Fagudvalget bemærker, at for komparatorarmen i BEACON-studiet gives enten irinotecan + cetuximab eller FOLFIRI + cetuximab. Fagudvalget ønsker oplyst fordeling mellem de to komparatorer, samt hvor stor en andel af patienter, der forud for BEACON-studiet, allerede havde fået et irinotecan-baseret paradigme i første- eller andenlinje.

Ligeledes skal den økonomiske ansøgning afspejle eventuelle forskelle i efterfølgende behandlinger.

8 Relation til behandlingsvejledning

Der findes ikke en relevant behandlingsvejledning fra Medicinrådet, men der findes en behandlingsvejledning fra Rådet for Anvendelse af Dyr Sygehusmedicin (RADS), lægemidlet vil ikke blive indplaceret i behandlingsvejledningen fra RADS.

9 Referencer

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10 Sammensætning af fagudvalg og kontaktinformation til Medicinrådet

Medicinrådets fagudvalg vedrørende tyk- og endetarmskræft

Formand	**Indstillet af**
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11 Versionslog

Version	Dato	Ændring
1.0	10. juli 2020	Godkendt af Medicinrådet.