Medicinrådet

Bilag til Medicinrådets anbefaling vedrørende pemigatinib til behandling af lokalavanceret eller metastatisk cholangiokarcinom

Vers. 2.0

Bilagsoversigt

1. Medicinrådets sundhedsøkonomiske afrapportering vedr. pemigatinib til lokalavanceret eller metastatisk cholangiokarcinom, version 2.0
2. Forhandlingsnotat fra Amgros vedr. pemigatinib
3. Medicinrådets vurdering vedrørende pemigatinib til behandling af lokalavanceret eller metastatisk cholangiokarcinom, version 1.0
4. Ansøgers endelige ansøgning
5. Ansøgers tekniske dokument til den sundhedsøkonomiske ansøgning
6. Medicinrådets protokol for vurdering vedrørende pemigatinib til behandling af lokalavanceret eller metastatisk cholangiokarcinom, version 1.0

Medicinrådet

Medicinrådets sundheds-økonomiske afrapportering

Pemigatinib

Lokalavanceret eller metastatisk cholangiokarcinom

Version 2.0

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

Den sundhedsøkonomiske analyse indeholder Medicinrådets vurdering af de inkrementelle omkostninger pr. patient og budgetkonsekvenserne ved anbefaling. 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.

Den sundhedsøkonomiske analyse er udarbejdet efter *Metodevejledning for omkostningsanalyse af nye lægemidler og indikationsudvidelser i hospitalssektoren*.

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Indholdsfortegnelse

1. Begreber og forkortelser

AIP	Apotekernes indkøbspris
ASC	*Active supportive care*
BSC	*Best supportive care*
CCA	Cholangiokarcinom
DKK	Danske kroner
DRG	Diagnose Relaterede Grupper
FGFR2	*Fibroblast growth factor receptor 2*
iCCA	Intrahepatisk cholangiokarcinom
NGS	*Next Generation Sequencing*
OS	Samlet overlevelse *(overall survival)*
PFS	Progressionsfri overlevelse (*progression-free survival*)
SAIP	Sygehusapotekernes indkøbspris
TOT	Behandlingslængde *(time on treatment)*

2. Konklusion

Inkrementelle omkostninger og budgetkonsekvenser
I det scenarie, Medicinrådet mener er mest sandsynligt, er de inkrementelle omkostninger for pemigatinib ca. [redacted] DKK pr. patient sammenlignet med *best supportive care* (BSC). Når analysen er udført med apotekernes indkøbspris (AIP), er de inkrementelle omkostninger til sammenligning ca. 984.000 DKK pr. patient. De inkrementelle omkostninger er næsten udelukkende drevet af lægemiddelomkostninger for pemigatinib. Med de anvendte funktioner til ekstrapolering af studiedata medfører behandling med pemigatinib en gennemsnitlig gevinst i PFS og OS på hhv. 7,3 mdr. og 26,5 mdr. sammenlignet med BSC. Estimatet for overlevelsesgevinsten afviger fra estimatet i vurderingsrapporten vedr. pemigatinib, idet overlevelsen opgøres i gennemsnit i den sundhedsøkonomiske afrapportering versus som median i vurderingsrapporten.

Der er usikkerheder forbundet med at estimere omkostningerne for hhv. pemigatinib og BSC, idet det kliniske datagrundlag er baseret på bl.a. et enkeltarms fase II-studie og en indirekte sammenligning, hvor det har været nødvendigt at justere for heterogenitet blandt studiepopulationerne. Medicinrådet anerkender dog, at det kan være svært at generere direkte evidens mellem pemigatinib og den relevante komparator, idet sygdommen er sjælden. På baggrund af dette vurderer Medicinrådet, at datagrundlaget for nuværende er det bedst tilgængelige til at vurdere effekten af pemigatinib.

På trods af at den samlede værdi af pemigatinib sammenlignet med BSC, jf. vurderingsrapporten, ikke kan kategoriseres, accepterer Medicinrådet, at den økonomiske model bygger på en effektforskel mellem pemigatinib og BSC. Det skyldes, at fagudvalget fremhæver, at effekten af pemigatinib for nuværende ser lovende ud, og at der dermed er grund til at skelne mellem effekten for hhv. pemigatinib og BSC. Såfremt der anvendes en økonomisk analyse, hvor der er effektforskel mellem pemigatinib og BSC, er de inkrementelle omkostninger per patient højere, end hvis der anvendes en analyse, hvor der ikke antages at være effektforskel. Såfremt der ikke antages at være effektforskel mellem pemigatinib og BSC – samtidig med at der antages, at behandlingslængden (*time on treatment*, TOT) for pemigatinib er lig det gennemsnitlige estimat for progressionsfri overlevelse (PFS) – reduceres de inkrementelle omkostninger med ca. [redacted] DKK. Den markante reduktion i totale inkrementelle omkostninger skyldes primært, at behandlingslængden reduceres fra 10,6 mdr. til 5,3 mdr. i denne scenarioanalyse.

Medicinrådet vurderer, at budgetkonsekvenserne for regionerne ved anbefaling af pemigatinib som mulig standardbehandling vil være ca. [redacted] DKK i det femte år efter en anbefaling. Når analysen er udført med AIP, er budgetkonsekvenserne ca. 5,9 mio. DKK i det femte år.

Budgetkonsekvenserne er meget følsomme for ændringer i antallet af patienter, der årligt kandiderer til behandling med pemigatinib. Hvis det antages, at patientantallet er 3, reduceres de totale budgetkonsekvenser med ca. [redacted]. DKK i år 5. Hvis patientantallet opjusteres til 8 om året, stiger de totale budgetkonsekvenser med ca. [redacted]. DKK i år 5.

3. Introduktion

Formålet med analysen er at estimere de gennemsnitlige inkrementelle omkostninger pr. patient og de samlede budgetkonsekvenser for regionerne ved anbefaling af pemigatinib som mulig standardbehandling på danske hospitaler til andenlinjebehandling af patienter med lokalavanceret eller metastatisk cholangiokarcinom (CCA) med en FGFR2-fusion eller andet rearrangement.

Analysen er udarbejdet, fordi Medicinrådet har modtaget en endelig ansøgning fra Incyte Biosciences Nordic. Medicinrådet modtog ansøgningen den 2. juli 2021.

3.1 Patientpopulation

CCA er den næsthyppigste form for primær leverkræft efter hepatocellulært karcinom med ca. 200 nye tilfælde i Danmark om året og udgør omkring 3 % af alle gastrointestinale tumorer. Diagnosen er vanskelig at stille, og CCA er ofte asymptomatisk i tidlige stadier, hvilket medfører, at sygdommen ofte er dødelig, da diagnosen stilles sent. 1-års overlevelsen er ca. 50 % og 5-års overlevelsen omkring 15 % [1]. Der er p.t. ingen veletableret standardbehandling i 2. linje, og patienter tilbydes *best supportive care* (BSC) [2] eller eksperimentel behandling ved god almen status. BSC indebærer månedlige kliniske undersøgelser, symptomkontrol inkl. galdedræning og stentning af galdeveje efter behov, antibiotika, smerte- og kvalmestillende lægemidler, steroider, palliativ stråleterapi og blodtransfusioner samt anden palliativ behandling for symptomer som gulsot og hudkløe.

Pemigatinib anslås at kunne tilbydes til 3-8 patienter om året i Danmark [3].

Yderligere information om sygdomsområdet kan findes i *Medicinrådets vurderingsrapport vedrørende pemigatinib til behandling af lokalavanceret eller metastatisk cholangiokarcinom*.

3.1.1 Komparator

Medicinrådet har vurderet den kliniske værdi af pemigatinib på baggrund af følgende kliniske spørgsmål:

Klinisk spørgsmål 1:

Hvilken værdi har pemigatinib sammenlignet med *best supportive care* for patienter med lokalavanceret eller metastatisk CCA med en *fibroblast growth factor receptor 2* (FGFR2)-fusion eller andet rearrangement, som har haft tilbagefald af sygdom eller udviser refraktær sygdom efter mindst én linje systemisk behandling?

4. Vurdering af den sundhedsøkonomiske analyse

Ansøger har indsendt en sundhedsøkonomisk analyse, der består af en omkostningsanalyse og en budgetkonsekvensanalyse. I omkostningsanalysen estimeres de inkrementelle omkostninger pr. patient for pemigatinib sammenlignet med *best supportive care* (BSC). Medicinrådet vurderer nedenfor den sundhedsøkonomiske analyse, som ansøger har indsendt.

4.1 Antagelser og forudsætninger for modellen

4.1.1 Klinisk datagrundlag

Ansøger har udarbejdet en indirekte sammenligning mellem pemigatinib og BSC ved brug af en *Matching Adjusted Indirect Treatment Comparison (MAIC)*-analyse, idet der ikke findes nogen studier, der direkte sammenligner de to alternativer. Den indirekte sammenligning er udført på baggrund af data fra studierne FIGHT-202 og ABC-06 [4,5].

FIGHT-202 er et fase II-studie, hvori effekten og sikkerheden af pemigatinib blev undersøgt hos patienter med lokalavanceret eller metastatisk CCA med en FGFR2-fusion eller andet rearrangement, som har haft progression efter mindst én tidligere systemisk behandling. I den økonomiske analyse anvendes data for kohorte A fra FIGHT-202-studiet, som var patienter med FGFR2-fusion eller rearrangement, med *data-cut* i april 2020.

ABC-06 er et fase III-studie, som undersøgte effekten af tilføjet kemoterapi (mFOLFOX[1]) til eksisterende standardbehandling (*active supportive care* (ASC)) hos patienter med avanceret galdevejskræft, der er progredieret på 1. linjebehandling med cisplatin og gemcitabine. I den økonomiske analyse anvendes KM-data fra ASC-armen som proxy for samlet overlevelse (OS) for BSC, mens KM-data fra ASC+mFOLFOX-armen anvendes som proxy for progressionsfri overlevelse (PFS) for BSC. Årsagen til, at ansøger ikke anvender KM-data fra ASC-armen som proxy for PFS i modellen, er at dette data ikke er tilgængeligt i ABC-06-studiet.

Ansøger har justeret patientkarakteristika fra FIGHT-202-studiet med data fra ABC-06-studiet via MAIC-analysen, hvor OS- og PFS-KM-data fra FIGHT-202-studiet blev justeret på baggrund af hhv. ASC-armen og ASC+mFOLFOX-armen fra ABC-06-studiet.

For yderligere information om det kliniske datagrundlag, henvises til *Medicinrådets vurderingsrapport vedrørende pemigatinib til behandling af lokalavanceret eller metastatisk cholangiokarcinom*.

[1] Oxaliplatin/5-FU kemoterapi.

Ansøger påpeger, at tilstedeværelse af FGFR2-fusion eller andet rearrangement kan være en potentiel prognostisk faktor, idet CCA-patienter med FGFR2-fusion eller andet rearrangement kan have en overlevelsesfordel sammenlignet med øvrige CCA-patienter. Ansøger påpeger dog også, at denne potentielle prognostiske faktor muligvis kan forklares ved, at subpopulationen, der undersøges i denne vurdering, adskiller sig fra den generelle population ved at have en større andel af kvinder, en lavere aldersfordeling og flere patienter med intrahepatisk CCA (iCCA). I modellen er det muligt at justere overlevelsesdata, så den potentielle positive prognostiske effekt af FGFR2-fusion tages i betragtning, hvilket ansøger undersøger betydningen af i følsomhedsanalyser.

[redacted] [6].

Medicinrådets vurdering af det kliniske datagrundlag

Medicinrådet påpeger, at der er usikkerheder forbundet med at estimere omkostningerne for hhv. pemigatinib og BSC, når det kliniske datagrundlag bl.a. er baseret på et enkeltarms fase II-studie og en indirekte sammenligning, hvor det har været nødvendigt at justere for heterogenitet blandt studiepopulationerne. Endvidere har fagudvalget en klinisk forventning om, at patienter i BSC+mFOLFOX-behandling lever længere end patienter, der kun modtager BSC. I den økonomiske model er der derfor en risiko for, at PFS for BSC er overestimeret, idet disse data er baseret på patienter, som modtog både ASC og mFOLFOX i ABC-06-studiet, og ikke ASC alene. Medicinrådet anerkender dog, at det kan være svært at generere direkte evidens mellem pemigatinib og den relevante komparator, idet sygdommen er sjælden. På baggrund af dette vurderer Medicinrådet, at datagrundlaget for nuværende er det bedst tilgængelige til at vurdere effekten af pemigatinib.

På trods af at den samlede værdi af pemigatinib sammenlignet med BSC ikke kan kategoriseres, jf. vurderingsrapporten, accepterer Medicinrådet, at den økonomiske model bygger på en effektforskel mellem pemigatinib og BSC. Det skyldes, at fagudvalget fremhæver, at effekten af pemigatinib for nuværende ser lovende ud, og at der dermed er grund til at skelne mellem effekten for hhv. pemigatinib og BSC. Fagudvalget har i den kliniske sammenligning særligt lagt vægt på responsraten for behandling med pemigatinib på 37 %, med en median varighed af responset på 7,5 måneder (95 % CI 5,7-14,5), mens fagudvalget vurderer, at det er rimeligt at antage en responsrate tæt på 0 % for patienter behandlet med BSC. Medicinrådet udarbejder dog en følsomhedsanalyse, hvor der antages ikke at være forskel i effekt mellem pemigatinib og BSC, samtidig med at behandlingslængden antages at være lig PFS.

Mht. den potentielle positive prognostiske effekt af FGFR2-fusion vurderer fagudvalget, at det med det eksisterende datagrundlag ikke er muligt at vurdere størrelsen af denne, og at det er tvivlsomt, om den eventuelle effekt er af klinisk betydende relevans. På baggrund af dette vurderer Medicinrådet, at modellens overlevelsesdata ikke skal justeres i hovedanalysen mhp. at inkludere en positiv prognostisk effekt af FGFR2-fusion.

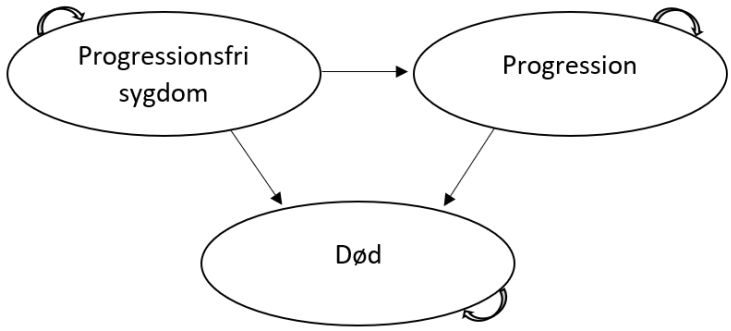
Medicinrådet udarbejder dog følsomhedsanalyser, hvor der antages at være en positiv prognostisk effekt af FGFR2-fusion.

Medicinrådet accepterer ansøgers anvendelse af studierne FIGHT-202 og ABC-06 som datagrundlag for den sundhedsøkonomiske analyse, men understreger, at der usikkerheder forbundet med at anvende en indirekte justeret sammenligning som baggrund for estimering af omkostningerne ved pemigatinib og BSC. Endvidere påpeger Medicinrådet, at der er usikkerheder forbundet med at anvende data for ASC+mFOLFOX-armen fra ABC-06-studiet som proxy for PFS for BSC-armen i den økonomiske analyse.

4.1.2 Modelbeskrivelse

Ansøger har indsendt en *partitioned survival*-model til at estimere omkostningerne forbundet med behandlingen med pemigatinib. Modellen indeholder en række sygdomsstadier, som patienterne skifter mellem i takt med sygdomsprogression. Ansøgers model består af en række stadier: progressionsfri (i behandling og ingen behandling), progression (i behandling og ingen behandling) og stadiet død.

Sygdomsstadierne og patienternes mulige transitioner mellem disse er illustreret i Figur 1.



Figur 1. Strukturen i den sundhedsøkonomiske model

Alle patienter starter i sygdomsstadiet progressionsfri (i behandling), hvori patienterne modtager behandling med enten pemigatinib eller BSC, og hvorfra deres bevægelse gennem modellen bestemmes ud fra ekstrapoleret forløbsdata. Patientens tid i stadiet progressionsfri overlevelse bestemmes ud fra PFS-data fra hhv. FIGHT-202 og ABC-06. Patienter, der er progredieret, men ikke døde, vil befinde sig i stadiet progression. Tiden, patienterne befinder sig i dette stadie, estimeres ud fra PFS- og OS-data fra hhv. FIGHT-2020 og ABC-06 som den andel patienter, der hverken er i stadierne progressionsfri eller død. Fra stadiet progression (ingen behandling) kan patienten udelukkende bevæge sig til det absorberende stadie død. Andelen af patienter i stadiet død bliver estimeret ud fra OS-data fra hhv. FIGHT-202 og ABC-06.

Medicinrådets vurdering af ansøgers model
Medicinrådet vurderer, at en *partitioned survival*-model er metodisk acceptabel at anvende til at estimere omkostningerne forbundet med patientpopulationen.

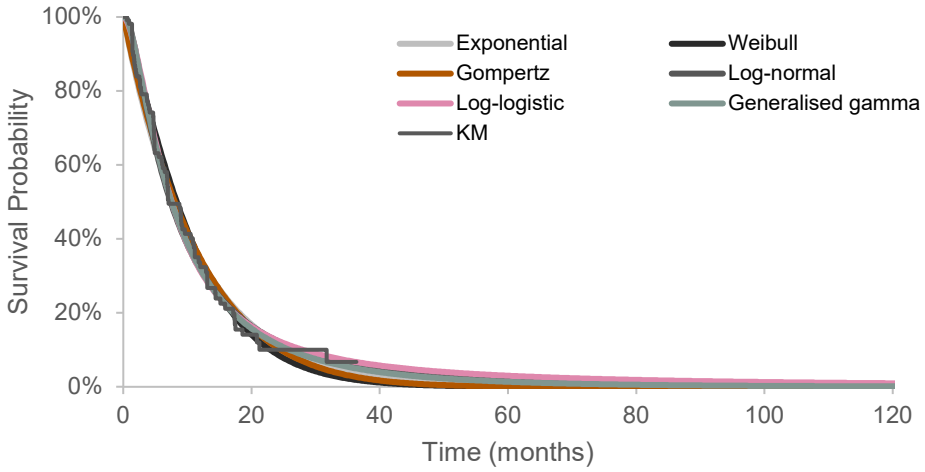
Medicinrådet accepterer strukturen af ansøgers model.

4.1.3 Ekstrapolering af forløbsdata

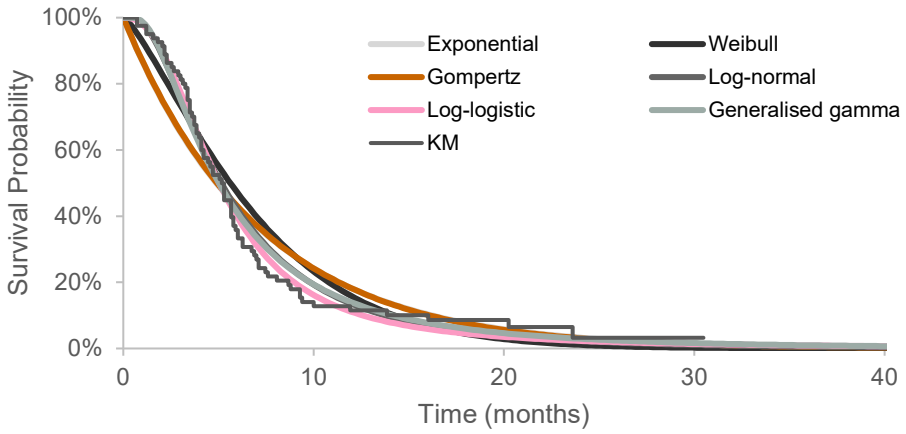
Ansøger modellerer tiden i de forskellige stadier ved anvendelse af ekstrapolerede KM-data for PFS og OS. Ansøger har ekstrapoleret forløbsdata for PFS og OS, idet opfølgningen i FIGHT-202 og ABC-06 er kortere end ansøgers anvendte tidshorisont på 40 år. Ansøger har modelleret individuelle kurver for hhv. pemigatinib og BSC. I modellen er det muligt at basere sammenligningen på både de uvægtede og vægtede hazard ratios.

Ansøger har anvendt en log-normal funktion til at ekstrapolere KM-PFS-data for både pemigatinib og BSC, se hhv. Figur 2 og Figur 3.

Ansøger pointerer, at Weibull og Gompertz har det bedste statistiske fit til KM-PFS-data for pemigatinib, mens den log-normale og log-logistiske fordeling er mest klinisk plausible. Idet den log-normale fordeling samtidig har det bedste statistiske fit på BSC-kurven, anvendes denne funktion til at ekstrapolere KM-PFS-data for begge interventioner.

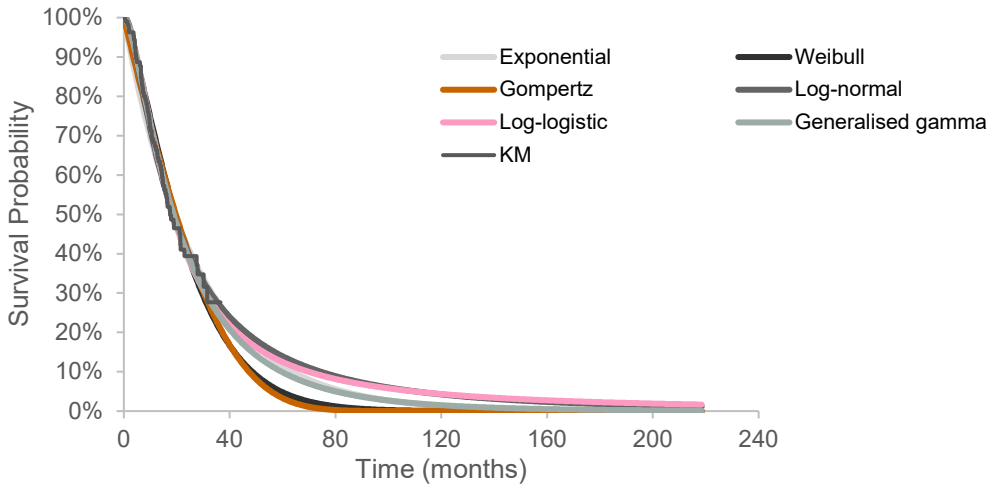


Figur 2. Ekstrapolerede KM-PFS-data for pemigatinib

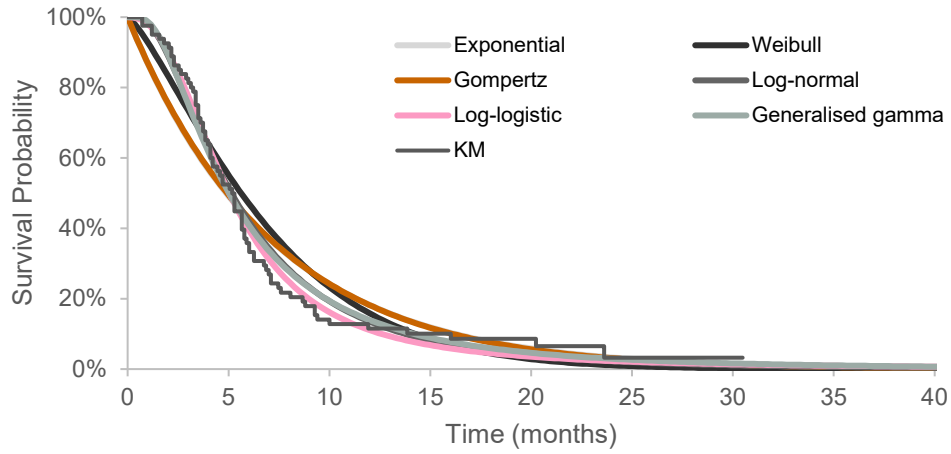


Figur 3. Ekstrapolerede KM-PFS-data for BSC

Ansøger har anvendt en log-logistisk funktion til at ekstrapolere KM-OS-data for både pemigatinib og BSC, idet denne funktion har det bedste statistiske fit på studiedata, se hhv. Figur 4 og Figur 5.

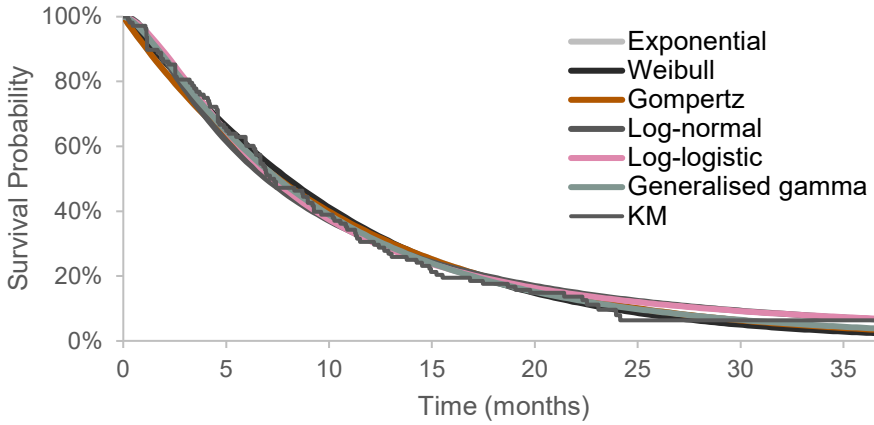


Figur 4. Ekstrapolerede KM-OS-data for pemigatinib



Figur 5. Ekstrapolerede KM-OS-data for BSC

Ansøger modellerer behandlingslængden for pemigatinib ved anvendelse af ekstrapolerede KM-data for *time on treatment* (TOT) fra FIGHT-202-studiet. Ansøger har ekstrapoleret TOT-data med en eksponentiel funktion, idet denne fordeling har det bedste statistiske fit på KM-data, og at det er den mest simple model for ekstrapolering af data. KM-TOT-data for pemigatinib fra FIGHT-202 og de ekstrapolerede kurver fremgår af Figur 6.



Figur 6. Ekstrapolerede TOT-KM-data for pemigatinib

Medicinrådets vurdering af ansøgers modelantagelser

Fagudvalget er blevet konsulteret vedr. valg af funktion til ekstrapolering af TOT-, PFS- og OS-studiedata. Det understreges af fagudvalget, at der er usikkerheder forbundet med at ekstrapolere data, hvorfor fagudvalgets vurdering skal ses som bedste kliniske bud på valg af funktion, snarere end værende en definitiv faktor for udvælgelse af funktionen. På baggrund af dette udarbejder Medicinrådet derfor også en række følsomhedsanalyser, hvor funktionerne, der anvendes til at ekstrapolere TOT-, PFS- og OS-studiedata, justeres.

Fagudvalget vurderer, at ansøgers valg af funktioner til ekstrapolering af PFS- og OS-studiedata kan være rimelige, idet den bagvedliggende antagelse for log-funktionernes hazard er mere fleksibel end de øvrige modeller, herunder at hazard kan være både ikke-konstant og ikke-monoton over tid. Medicinrådet påpeger, at der er usikkerheder forbundet med at antage en konstant hazard for tiden i behandling, hvorfor en mere fleksibel model, Weibull-funktionen, anvendes i Medicinrådets hovedanalyse.

De ekstrapolerede gennemsnitlige estimater for TOT, PFS og OS er præsenteret i Tabel 1. Estimatet for overlevelsesgevinsten afviger fra estimatet i vurderingsrapporten vedr. pemigatinib, idet overlevelsen opgøres i gennemsnit i den sundhedsøkonomiske afrapportering versus som median i vurderingsrapporten.

Tabel 1. Gennemsnitlig tid i behandling, tid til progression og samlet overlevelse

Behandling	TOT [måneder]	PFS [måneder]	OS [måneder]
Pemigatinib	10,6	12,6	33,8
BSC	-	5,3	7,3

*Time on treatment (TOT), progressionsfri overlevelse (PFS), samlet overlevelse (OS).

Medicinrådet accepterer ansøgers tilgang vedr. modelantagelser, men anvender Weibull-funktionen til at ekstrapolere TOT-studiedata for pemigatinib. Endvidere udarbejder Medicinrådet følsomhedsanalyser med andre funktioner til ekstrapolering af TOT, PFS og OS end de anvendte i hovedanalysen.

4.1.4 Analyseperspektiv

I overensstemmelse med Medicinrådets metoder har ansøger valgt et begrænset samfundsperspektiv til sin analyse. Analysen har en tidshorisont på 40 år og en cykluslængde på en uge. Omkostninger, der ligger efter det første år, er diskonteret med en rente på 3,5 % pr. cyklus. Sekretariatet har bedt ansøger om at justere modellen, så omkostningerne, der falder i år 36 og derefter, er diskonteret med en rente på 2,5 %, jf. Finansministeriets anbefalinger [7]. Ansøger har ikke imødekommet denne forespørgsel.

Medicinrådets vurdering af ansøgers analyseperspektiv
Medicinrådet ændrer tidshorisonten i analysen til 10 år, idet de totale inkrementelle omkostninger ikke ændres betydeligt efter år 10 frem til år 35 (ca. 700 DKK). Det skyldes, at størstedelen af patienterne er døde ved år 10.

Medicinrådet påpeger, at omkostningerne skal diskonteres pr. år fremfor pr. cyklus, hvorfor dette justeres i Medicinrådets analyse. Endvidere understreger Medicinrådet, at diskonteringsrenten til enhver tid skal være i overensstemmelse med Finansministeriets anbefalinger. Idet Medicinrådet ændrer tidshorisonten til 10 år, er det dog acceptabelt at anvende en årlig diskonteringsrente på 3,5 % i analysen.

Medicinrådet ændrer tidshorisonten til 10 år og diskonterer omkostningerne pr. år fremfor pr. cyklus.

4.2 Omkostninger

I det følgende præsenteres ansøgers antagelser for omkostningerne i den sundhedsøkonomiske analyse af pemigatinib sammenlignet med BSC. Ansøger har inkluderet lægemiddelomkostninger, hospitalsomkostninger og patientomkostninger. Ansøger har ikke inkluderet omkostninger forbundet med BSC-lægemidler og -procedurer, efterfølgende behandling og kommunale omkostninger.

4.2.1 Lægemiddelomkostninger

Ansøger har, jf. *Metodevejledning for omkostningsanalyser af nye lægemidler og indikationer i hospitalssektoren,* estimeret lægemiddelomkostninger på baggrund af apotekernes indkøbspris (AIP).

Doseringen af pemigatinib er baseret på produktresuméet (SPC) for lægemidlet. Den anbefalede dosis af pemigatinib er 13,5 mg, som tages én gang dagligt i 14 dage, efterfulgt af 7 dages pause uden behandling. Behandlingen med pemigatinib bør fortsættes, så længe patienten ikke viser tegn på sygdomsprogression eller uacceptabel toksicitet.

Ansøger anvender den observerede relative dosisintensitet (RDI) fra FIGHT-202-studiet på [redacted] til at afspejle den forventede gennemsnitlige dosering af pemigatinib i dansk klinisk praksis.

Ansøger har ikke inkluderet omkostninger forbundet med lægemiddelspild i analysen. Det skyldes, at ansøger antager, at der kun vil være et minimalt spild forbundet med håndtering af pemigatinib, idet lægemidlet forventes udleveret hver 3. uge til 14 dage ad gangen.

Medicinrådets vurdering af ansøgers antagelser vedr. lægemiddelomkostninger
På baggrund af konsultation med fagudvalget accepterer Medicinrådet ansøgers antagelser om RDI og lægemiddelspild. Derudover udskifter Medicinrådet AIP med sygehusapotekernes indkøbspris (SAIP) i modellen, se Tabel 2.

Tabel 2. Anvendte lægemiddelpriser, SAIP (januar 2022)

Lægemiddel	Styrke	Mg/dosis	Pakningsstørrelse	Pris [DKK]	Kilde
Pemigatinib	13,5 mg	13,5 mg	14 stk.	[redacted]	Amgros

Fagudvalget påpeger, at der ikke er defineret en stopregel for behandling med pemigatinib, men at fagudvalget normalt vil holde pause med en behandling efter 1 til 2 år.

Medicinrådet accepterer ansøgers valg vedr. lægemiddelomkostninger.

4.2.2 BSC-omkostninger

Ansøger har ikke inkluderet omkostninger forbundet med BSC-lægemidler eller -procedurer, herunder galdedræning, antibiotika, smerte- og kvalmestillende lægemidler, pal-

liativ stråling, blodtransfusioner m.v. Det skyldes, at ansøger antager, at patienterne, som modtager pemigatinib, vil modtage BSC på samme tid, og at de inkrementelle BSC-omkostninger mellem alternativerne dermed vil være 0.

Medicinrådets vurdering af ansøgers antagelser vedr. BSC-omkostninger
Fagudvalget er enig med ansøger i, at patienterne, der modtager pemigatinib, også vil modtage BSC på et tidspunkt i sygdomsforløbet, og at typen af BSC vil være ens mellem de to behandlinger. Fagudvalget påpeger dog, at behandlingen med pemigatinib kan udskyde tiden til, at patienterne oplever et behov for BSC, men har ikke mulighed for at kvantificere dette ressourceforbrug nærmere.

Medicinrådet accepterer ansøgers valg om at ekskludere omkostninger vedr. BSC-lægemidler og -procedurer.

4.2.3 Hospitalsomkostninger

Omkostninger til diagnostisk test

Ansøger har inkluderet omkostninger til diagnostisk test af FGFR2-fusion, idet denne test ikke rutinemæssigt udføres i dansk klinisk praksis hos de patienter, der tilbydes den nuværende 2. linje-standardbehandling. Ansøger pointerer, at det ikke er alle testede patienter, der vil have FGFR2-fusion eller andet rearrangement. På baggrund af data fra FIGHT-202 antager ansøger, at 8,6 % af de testede patienter vil blive identificeret med en FGFR2-fusion, hvilket svarer til, at ca. hver 8. patient testes positiv for FGFR2-fusion.

Ansøger anvender en DRG-takst til at værdisætte omkostningerne forbundet med den diagnostiske FGFR2-test svarende til 9.947 DKK (31SP02: ”Sammedagspakke: Klinisk genetisk udredning, omfattende, med svar”). Testomkostningerne er kun inkluderet i pemigatinib-armen.

Medicinrådets vurdering af ansøgers antagelser vedr. diagnostisk test
Fagudvalget er enig i ansøgers vurdering af, at en anbefaling af pemigatinib vil medføre, at patienterne systematisk vil skulle testes for detektion af FGFR2-fusion eller andet rearrangement. Fagudvalget ønsker i denne sammenhæng, at patienterne allerede skal testes, når diagnosen stilles (1. linje) – og ikke først når patienterne er progredieret og evt. kan modtage 2. linjebehandling, herunder pemigatinib. Det skyldes, at patienterne hurtigt kan progrediere, og at sundhedspersonalet hurtigere kan igangsætte 2. linjebehandling med pemigatinib, hvis de initielt kender patienternes FGFR2-status.

Fagudvalget anslår, at 60-70 patienter i alt skal testes pr. år for at finde de patienter, som kandiderer til behandling med pemigatinib. Endvidere vurderer fagudvalget, at testen bør være af typen *Next Generation Sequencing* (NGS). Til at værdisætte NGS-testen anvender Medicinrådet en enhedsomkostning på 5.000 DKK[2].

[2] Enhedsomkostningen for en NGS-test på 5.000 DKK er tidligere anvendt i færdigbehandlede vurderinger fra Medicinrådet, herunder entrectinib og larotrectinib til behandling af NTRK-fusion-positive solide tumorer.

De samlede årlige testomkostninger bliver mellem 300.000 og 350.000 DKK (60-70 patienter x 5.000 DKK), hvilket betyder, at den gennemsnitlige omkostning pr. patient, som er kandidat til behandling med pemigatinib, estimeres til at være mellem 50.000 og 58.300 DKK[3]. I Medicinrådets hovedanalyse antages det, at 60 patienter testes for FGFR2-fusion i 1. linje og dermed en testomkostning pr. patient på 50.000 DKK.

Medicinrådet accepterer ikke ansøgers tilgang vedr. omkostninger til diagnostisk test. I stedet antager Medicinrådet, at 60 patienter testes under 1. linjebehandling, og at enhedsomkostningen for en test er 5.000 DKK.

Administrationsomkostninger

Ansøger har ikke inkluderet administrationsomkostninger forbundet med håndtering af pemigatinib, idet pemigatinib administreres som orale tabletter. Ligeledes antager ansøger, at der ingen administrationsomkostninger er forbundet med BSC.

Medicinrådets vurdering af ansøgers antagelser vedr. administrationsomkostninger

Fagudvalget pointerer, at der vil være administrationsomkostninger forbundet med håndtering af pemigatinib, idet tabletterne skal udleveres af sundhedspersonalet hver 3. uge. Administrationsomkostninger burde derfor som udgangspunkt være inkluderet i analysen, men idet ansøger anvender en DRG-takst til at værdisætte ressourceforbruget forbundet med en klinisk undersøgelse, jf. følgende afsnit vedr. monitoreringsomkostninger, som ligeledes foregår hver 3. uge, accepteres ansøgers antagelser.

Medicinrådet accepterer ansøgers tilgang vedr. administrationsomkostninger.

Monitoreringsomkostninger

Ansøger har inkluderet monitoreringsomkostninger i analysen. For de patienter, der ikke er progredieret, antager ansøger, at disse vil blive monitoreret med en klinisk undersøgelse, CT-scanning og blodprøver hver tredje måned. For de patienter, der er progredieret, antager ansøger, at disse vil blive monitoreret med en klinisk undersøgelse og blodprøver hver tredje måned og en CT-scanning én gang årligt. Ansøger har inkluderet omkostninger forbundet med oftalmologisk undersøgelse, hvor det antages, at patienterne monitoreres hver anden måned i løbet af de første seks måneder efter behandlingsopstart med pemigatinib, hvorefter de monitoreres hver tredje måned. Ansøger har værdisat ressourceforbruget forbundet med monitorering ved brug af DRG-takster og Laboratoriemedicinsk Vejledning (LMV) [8].

Medicinrådets vurdering af ansøgers antagelser vedr. monitoreringsomkostninger

Fagudvalget pointerer, at patienterne, der ikke er progredieret på pemigatinib, vil blive monitoreret med en klinisk undersøgelse og blodprøver hver tredje uge fremfor hver tredje måned. Endvidere påpeger fagudvalget, at patienterne vil modtage en CT-

[3] Udregningen er baseret på, at det, jf. Medicinrådets budgetkonsekvensanalyse for pemigatinib, antages, at 6 patienter årligt vil blive behandlet med pemigatinib, hvis lægemidlet anbefales af Medicinrådet (300.000-350.000 DKK/6 patienter).

scanning hver anden eller tredje måned (spændet mellem hver anden til tredje måned skyldes, at der kan være regionale forskelle).

Hvis patienterne progredierer, vil onkologerne tage stilling til patienternes almentilstand. Såfremt det vurderes, at patienterne ikke skal igangsættes med behandling[4] efter progression på pemigatinib, vil der som udgangspunkt ikke blive foretaget yderligere monitorering, idet patienterne overgår til palliativ pleje. Hvis patienternes almentilstand gør, at de kan modtage efterfølgende behandling, vil patienterne som udgangspunkt monitoreres med en CT-scanning hver anden måned. Idet der er usikkerheder forbundet med kvantificering af den eksakte fordeling af patienter, som efter progression på pemigatinib kandiderer til hhv. palliativ pleje eller efterfølgende behandling, antager Medicinrådet, at der ingen monitoreringsomkostninger vil være forbundet med stadiet 'progression'.

Mht. frekvenserne for oftalmologisk undersøgelse vurderer fagudvalget, at ansøgers antagelser er rimelige, idet de er i overensstemmelse med SPC'et. Frekvenserne for ressourceforbruget forbundet med monitorering fremgår af Tabel 3.

Tabel 3. Ressourceforbrug forbundet med monitorering

	Pre-progression, frekvens	Progression, frekvens	Enhedsomkostning [DKK]	Kilde
Klinisk undersøgelse	Hver tredje uge	0	2.610	DRG 2021
CT-scanning	Hver tredje måned	0	2.007	DRG 2021
Blodprøver	Hver tredje uge	0	280	LMV
Oftalmologisk undersøgelse	*	0	1.028	DRG 2021

*Monitorering hver anden måned i løbet af de første seks måneder efter behandlingsopstart med pemigatinib, hvorefter patienterne monitoreres hver tredje måned.

Medicinrådet accepterer ansøgers tilgang vedr. monitoreringsomkostninger, men justerer frekvensen for klinisk undersøgelse og blodprøve ved pre-progression, så patienterne monitoreres hver tredje uge. Endvidere antager Medicinrådet, at patienterne ikke monitoreres, hvis de er progredieret.

Bivirkningsomkostninger

Ansøger har inkluderet omkostninger forbundet med de bivirkninger, der vurderes at være af grad 3 eller derover, eller bivirkninger, der vurderes som værende af signifikant klinisk betydning. For pemigatinib og BSC har ansøger benyttet de rapporterede bivirkningsrater fra hhv. FIGHT-202 og ABC-06. Ansøger har inkluderet

[4] Fagudvalget vurderer, at nogle patienter muligvis vil kunne modtage behandling med cisplatin-gemcitabine i 3. linje.

bivirkningsomkostninger, uanset årsagen til bivirkningerne, hvilket betyder, at det ikke kun er omkostningerne til de behandlingsrelaterede bivirkninger, som er inkluderet.

Ansøger værdisætter ressourceforbruget forbundet med de forskellige bivirkninger ved anvendelse af DRG 2021.

Medicinrådets vurdering af ansøgers antagelser vedr. bivirkningsomkostninger
Fagudvalget pointerer, at en række af de uønskede hændelser, som ansøger inkluderer i sin analyse, ikke observeres grundet behandling med pemigatinib og BSC, men i stedet pga. den bagvedliggende cancersygdom. Det betyder som udgangspunkt, at frekvensen for f.eks. cholangitis og anæmi bør være ens mellem de to behandlingsarme fremfor forskellig som i ansøgers analyse. Endvidere påpeger fagudvalget, at der er usikkerheder forbundet med at validere de anvendte DRG-takster, og at en bivirkning som hhv. øget alanin aminotransferase og aspartat aminotransferase kun bør fremgå én gang i analysen. På baggrund af fagudvalgets overvejelser ekskluderer Medicinrådet bivirkningsomkostninger i hovedanalysen. Denne ændring vurderes at have minimal betydning for analysens inkrementelle resultat.

Medicinrådet udarbejder dog en følsomhedsanalyse, hvor omkostninger forbundet med bivirkninger inkluderes, baseret på ansøgers antagelser om bivirkningsomkostninger. De anvendte bivirkningsfrekvenser og DRG-takster, som anvendes i følsomhedsanalysen, fremgår af afrapporteringens bilag (afsnit 10.1).

Medicinrådet ekskluderer omkostninger forbundet med bivirkninger i hovedanalysen og udarbejder en følsomhedsanalyse, hvor bivirkningsomkostningerne inkluderes.

Terminale omkostninger
Ansøger har inkluderet omkostninger til terminal pleje i analysen i form af en DRG-takst på 88.471 DKK (26MP45: ”Specialiseret Palliativ indsats, Stor”).

Medicinrådets vurdering af ansøgers antagelser vedr. terminalomkostninger
Medicinrådet ekskluderer omkostninger forbundet med terminal pleje, idet ansøger ikke har argumenteret tilstrækkeligt for, at taksten er repræsentativ for det underliggende ressourceforbrug. Ekskluderingen af de terminale omkostninger vurderes at have minimal betydning for analysens inkrementelle resultat.

Medicinrådet ekskluderer omkostninger forbundet med terminal pleje i analysen.

4.2.4 Patientomkostninger

Patientomkostninger er estimeret på baggrund af administrations- og monitoreringsbesøg på hospitalet og inkluderer patientens effektive tid på hospitalet, ventetid og transporttid. Ansøger anvender en enhedsomkostning for patienttid på 179 DKK pr. time og transportomkostninger på 100 DKK pr. besøg, jf. Medicinrådets værdisætning af enhedsomkostninger.

Ansøger antager, at patienterne gennemsnitligt bruger 3 timer på behandling af bivirkninger, ½ time på hhv. klinisk undersøgelse og blodprøver og 2 timer på en CT-scanning.

Medicinrådets vurdering af ansøgers antagelser vedr. patientomkostninger
Fagudvalget påpeger, at ansøgers antagelser om patienttid ifm. håndtering af bivirkninger er sandsynlig, men at det er usikkert at definere et eksakt estimat. Det skyldes, at ressourceforbruget forbundet med håndtering af bivirkningerne kan spænde fra et telefonopkald til flere dages indlæggelse. Vedr. de øvrige estimater for patienttid vurderer fagudvalget, at disse er rimelige, men foreslår, at de gennemsnitlige estimater for patienternes effektive tid ved klinisk undersøgelse og blodprøvetagning ændres til 1 time.

Estimaterne for patienternes effektive tid fremgår af Tabel 4.

Tabel 4. Estimat af effektiv patienttid

	Patienttid [minutter]
Bivirkninger	180
Klinisk undersøgelse	60
CT-scanning	120
Blodprøver	60

Medicinrådet accepterer ansøgers tilgang vedr. patientomkostninger, men justerer tidsforbruget for hhv. klinisk undersøgelse og CT-scanning til 60 minutter.

4.3 Følsomhedsanalyser

Formålet med følsomhedsanalyserne er at undersøge usikkerhederne i analysen og de økonomiske konsekvenser af at justere de parametre, der er usikre.

Ansøger har udarbejdet en række følsomhedsanalyser, hvor effekten af variation i forskellige parametre undersøges, se Tabel 5.

Tabel 5. Følsomhedsanalyser og beskrivelse

Følsomhedsanalyse	Beskrivelse
Tidshorisont	Ændres til 50 år.
Diskontering	Ændres til 0 %.
	Ændres til 6 %.
Prognostisk effekt af FGFR2-fusion	Antag, at der er en prognostisk effekt af FGFR2-fusion på overlevelse.
Effektivitet for komparator	Informeres via naive hazard ratios.
	Informeres via separate parametriske overlevelsesmodeller, som er fittet til ikke-justerede KM-data.

Følsomhedsanalyse	Beskrivelse
Ekstrapolering af forløbsdata	PFS for hhv. pemigatinib og BSC ekstrapoleres med Weibull-funktionen.
	OS for hhv. pemigatinib og BSC ekstrapoleres med Weibull-funktionen.
	TOT for pemigatinib ekstrapoleres med den log-logistiske funktion.
Ekskludering af testomkostninger	Omkostningerne forbundet med test af FGFR2-fusion ekskluderes.

Medicinrådets vurdering af ansøgers valg af følsomhedsanalyser
Følsomhedsanalyserne vedr. diskontering og ekskludering af testomkostninger præsenteres. Endvidere udarbejder Medicinrådet en følsomhedsanalyse, hvor bivirkningsomkostninger inkluderes, og en følsomhedsanalyse, hvor der antages at være ens effekt på PFS og OS mellem pemigatinib og BSC, samtidig med at TOT for pemigatinib antages at være lig PFS. Medicinrådet præsenterer ligeledes følsomhedsanalyser, hvor funktionerne til ekstrapolering af PFS-, OS- og TOT-studiedata ændres, og følsomhedsanalyser hvor tidshorisonten justeres til værende hhv. 3, 5 og 7 år.

Medicinrådet udarbejder følsomhedsanalyser, hvori det antages, at der er en prognostisk effekt af FGFR2-fusion.

Medicinrådet vælger at præsentere udvalgte af ansøgers følsomhedsanalyser og supplerer disse med egne følsomhedsanalyser.

4.4 Opsummering af basisantagelser

I Tabel 6 opsummeres basisantagelserne i henholdsvis ansøgers og Medicinrådets hovedanalyse.

Tabel 6. Basisantagelser for ansøgers og Medicinrådets hovedanalyse

Basisantagelser	Ansøger	Medicinrådet
Tidshorisont	40 år	10 år
Diskonteringsrate	3,5 % pr. cyklus	3,5 % pr. år
Inkluderede omkostninger	Lægemiddelomkostninger Hospitalsomkostninger Patientomkostninger	Lægemiddelomkostninger Hospitalsomkostninger Patientomkostninger
RDI	[redacted]	[redacted]
Behandlingslinje	2. linjebehandling	2. linjebehandling
Parametrisk funktion for TOT Pemigatinib:	Eksponentiel	Weibull

Basisantagelser	Ansøger	Medicinrådet
Behandlingslængde for pemigatinib	10,9 mdr.	10,6 mdr.
Parametriske funktioner for PFS		
Pemigatinib:	Log-normal	Log-normal
BSC:	Log-normal	Log-normal
Gennemsnitlig tid til progression		
Pemigatinib:	12,6 mdr.	12,6 mdr.
BSC:	5,3 mdr.	5,3 mdr.
Parametriske funktioner for OS		
Pemigatinib:	Log-logistisk	Log- logistisk
BSC:	Log-logistisk	Log-logistisk
Gennemsnitlig tid til død		
Pemigatinib:	33,8 mdr.	33,8 mdr.
BSC:	7,3 mdr.	7,3 mdr.
Inkludering af spild	Nej	Nej
Antag positiv prognostisk effekt af FGFR2-fusion	Nej	Nej

5. Resultater

5.1 Resultatet af Medicinrådets hovedanalyse

Medicinrådets hovedanalyse bygger på samme antagelser som ansøgers hovedanalyse med undtagelse af de væsentligste ændringer præsenteret ovenfor.

Den gennemsnitlige inkrementelle omkostning pr. patient bliver ca. [redacted] DKK i Medicinrådets hovedanalyse. Er analysen udført med AIP, bliver den inkrementelle omkostning pr. patient ca. 984.000 DKK.

Resultaterne fra Medicinrådets hovedanalyse er præsenteret i Tabel 7.

Tabel 7. Resultatet af Medicinrådets hovedanalyse ved sammenligning med BSC, DKK, diskonterede tal

	Pemigatinib	BSC	Inkrementelle omkostninger
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Hospitalsomkostninger	[redacted]	[redacted]	[redacted]

	Pemigatinib	BSC	Inkrementelle omkostninger
Patientomkostninger	[redacted]	[redacted]	[redacted]
Totale omkostninger	[redacted]	[redacted]	[redacted]

5.1.1 Resultatet af Medicinrådets følsomhedsanalyser

Ved samme antagelser som i Medicinrådets hovedanalyse for meromkostninger har Medicinrådet udført en følsomhedsanalyse på parametrene listet i Tabel 8.

Tabel 8. Resultatet af Medicinrådets følsomhedsanalyse sammenlignet med hovedanalysen, DKK

Scenarie		Inkrementelle omkostninger
Resultatet af hovedanalysen		[redacted]
Ens effekt på PFS og OS mellem pemigatinib og BSC (TOT = PFS)		[redacted]
Diskontering	0 %	[redacted]
	6 %	[redacted]
Tidshorisont	3 år	[redacted]
	5 år	[redacted]
	7 år	[redacted]
Inkludering af bivirkningsomkostninger		[redacted]
Ekskludering af testomkostninger		[redacted]
Antag positiv prognostisk effekt af FGFR2-fusion	Prævalens: 8,6 %	[redacted]
	Prævalens: 19,6 %	[redacted]
Ekstrapolering af OS for både pemigatinib og BSC*		
- Log-normal		[redacted]
- Gompertz		[redacted]
- Weibull		[redacted]
Ekstrapolering af PFS for både pemigatinib og BSC*		
- Log-logistisk		[redacted]
- Gompertz		[redacted]

Scenarie	Inkrementelle omkostninger
- Weibull	[redacted]
Ekstrapolering af TOT for pemigatinib*	
- Log-normal	[redacted]
- Log-logistisk	[redacted]
- Generaliseret gamma	[redacted]

* De inkrekmentelle omkostninger pr. patient præsenteres for de tre parametriske funktioner, som afviger mest fra hovedanalysens resultat.

6. Budgetkonsekvenser

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

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

Budgetkonsekvenserne udgør forskellen mellem de samlede omkostninger i de to scenarier.

6.1 Estimat af patientantal og markedsandel

Ansøger antager, at der er ca. 4 patienter om året, som kandiderer til behandling med pemigatinib. Vedr. markedsoptaget for pemigatinib antager ansøger, at dette vil være [redacted].

Medicinrådets vurdering af ansøgers budgetkonsekvensanalyse
Fagudvalget er blevet konsulteret i forhold til ansøgers antagelser om patientantal og markedsoptag, hvis pemigatinib anbefales som mulig standardbehandling, og hvis ikke pemigatinib anbefales. Fagudvalget vurderer, at markedsoptaget vil være tæt på 100 %, hvis pemigatinib anbefales af Medicinrådet. Endvidere estimerer fagudvalget, at 6 patienter pr. år forventes at være kandidater til behandling med pemigatinib til den pågældende indikation, se Tabel 9.

Tabel 9. Medicinrådets estimat af antal nye patienter pr. år

	År 1	År 2	År 3	År 4	År 5
			Anbefales		
Pemigatinib	6	6	6	6	6
BSC	0	0	0	0	0
			Anbefales ikke		
Pemigatinib	0	0	0	0	0
BSC	6	6	6	6	6

Idet det fremgår af *Medicinrådets protokol for vurdering vedrørende pemigatinib til behandling af lokalavanceret eller metastatisk cholangiokarcinom* [3], at mellem 3 og 8 patienter anslås at kunne tilbydes behandling med pemigatinib årligt, udarbejder Medicinrådet to følsomhedsanalyser, hvor patientantallet justeres fra 6 patienter til hhv. 3 og 8 patienter.

Medicinrådet har udført sin egen budgetkonsekvensanalyse, hvor patientantallet og markedsoptaget er ændret til hhv. 6 patienter pr. år og 100 % i år 1-5. Endvidere udarbejder Medicinrådet følsomhedsanalyser, hvor patientantallet justeres til hhv. 3 og 8 patienter.

6.2 Medicinrådets budgetkonsekvensanalyse

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

- Patientantallet justeres til 6 patienter.
- Markedsoptaget justeres til 100 % i år 1-5.

Medicinrådet estimerer, at anvendelse af pemigatinib vil resultere i budgetkonsekvenser på ca. [redacted] DKK i det femte år efter en anbefaling. Resultatet er præsenteret i Tabel 10.

Er analysen udført med AIP, bliver budgetkonsekvenserne ca. 5,9 mio. DKK i år 5.

Tabel 10. Medicinrådets 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]

6.2.1 Resultat af følsomhedsanalyser for budgetkonsekvensanalysen

Ved samme antagelser som i Medicinrådets hovedanalyse for budgetkonsekvenser, men med ændret patientantal til 3 og 8 patienter, vil omkostningerne i år 5 være ca. hhv. [redacted] og [redacted] DKK, se hhv. Tabel 11 og Tabel 12.

Tabel 11. Medicinrådets analyse af totale budgetkonsekvenser, hvor patientantallet antages at være 3 patienter årligt, 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]

Tabel 12. Medicinrådets analyse af totale budgetkonsekvenser, hvor patientantallet antages at være 8 patienter årligt, 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 pemigatinib er forbundet med inkrementelle omkostninger på ca. [redacted] DKK pr. patient sammenlignet med behandling med BSC. De inkrementelle omkostninger er næsten udelukkende drevet af lægemiddelomkostninger for pemigatinib; denne omkostningsgruppe udgør ca. [redacted] af de inkrementelle omkostninger. De resterende inkrementelle omkostninger er primært drevet af en forskel i hospitalsomkostninger mellem de to interventioner. Med de anvendte funktioner til ekstrapolering af studiedata medfører behandling med pemigatinib en gennemsnitlig forlængelse i PFS og OS på hhv. 7,3 mdr. og 26,5 mdr. sammenlignet med BSC. Estimatet for overlevelsesgevinsten afviger fra estimatet i vurderingsrapporten vedr. pemigatinib, idet overlevelsen opgøres i gennemsnit i den sundhedsøkonomiske afrapportering versus som median i vurderingsrapporten.

Medicinrådet påpeger, at der er usikkerheder forbundet med at estimere omkostningerne for hhv. pemigatinib og BSC, når det kliniske datagrundlag bl.a. er baseret på et enkeltarms fase II-studie og en indirekte sammenligning, hvor det har været nødvendigt at justere for heterogenitet blandt studiepopulationerne. Fagudvalget har en klinisk

forventning om, at patienter i BSC+mFOLFOX-behandling lever længere end patienter, der kun modtager BSC. I den økonomiske model er der derfor en risiko for, at PFS for BSC er overestimeret, idet disse data er baseret på patienter, som modtog både ASC og mFOLFOX i ABC-06-studiet, og ikke ASC alene. Medicinrådet anerkender dog, at det kan være svært at generere direkte evidens mellem pemigatinib og den relevante komparator, idet sygdommen er sjælden. På baggrund af dette vurderer Medicinrådet, at datagrundlaget for nuværende er det bedst tilgængelige til at vurdere effekten af pemigatinib.

På trods af at den samlede værdi af pemigatinib sammenlignet med BSC, jf. vurderingsrapporten, ikke kan kategoriseres, accepterer Medicinrådet, at den økonomiske model bygger på en effektforskel mellem pemigatinib og BSC. Det skyldes, at fagudvalget fremhæver, at effekten af pemigatinib for nuværende ser lovende ud, og at der dermed er grund til at skelne mellem effekten for hhv. pemigatinib og BSC. Såfremt der anvendes en økonomisk analyse, hvor der er effektforskel mellem pemigatinib og BSC, er de inkrementelle omkostninger per patient højere, end hvis der anvendes en analyse, hvor der ikke antages at være effektforskel. Såfremt der ikke antages at være effektforskel mellem pemigatinib og BSC – samtidig med at der antages, at TOT for pemigatinib er lig PFS – reduceres de inkrementelle omkostninger med ca. [redacted] DKK. Den markante reduktion i totale inkrementelle omkostninger skyldes primært, at behandlingslængden reduceres fra 10,6 mdr. til 5,3 mdr. i denne scenarioanalyse.

Når studiedata fra FIGHT-202 og ABC-06 ekstrapoleres med andre funktioner end de anvendte i hovedanalysen, er de totale inkrementelle omkostninger isoleret set mest følsomme ved ændring af funktion til ekstrapolering af PFS- og TOT-data.

Budgetkonsekvenserne er meget følsomme for ændringer i antallet af patienter, der årligt kandiderer til behandling med pemigatinib. Hvis det antages, at patientantallet er 3, reduceres de totale budgetkonsekvenser med ca. [redacted]. DKK i år 5. Hvis patientantallet opjusteres til 8 om året, stiger de totale budgetkonsekvenser med ca. [redacted]. DKK i år 5.

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9. Versionslog

Versionslog		
Version	**Dato**	**Ændring**
2.0	23. februar 2022	Lægemiddelprisen for pemigatinib er opdateret.
1.0	24. november 2021	Godkendt af Medicinrådet.

10. Bilag

10.1 Bivirkningsomkostninger

Se afsnit 4.2.3 for beskrivelse af dette bilag.

Tabel 13. Rapporterede bivirkningsfrekvenser ved behandling med pemigatinib og BSC samt enhedsomkostninger for bivirkningerne

	Pemigatinib [%]	BSC [%]	Enheds-omkostning [DKK]	Kilde
[redacted]	[redacted]	[redacted]	2.610	DRG 2021
[redacted]	[redacted]	[redacted]	2.610	DRG 2021
[redacted]	[redacted]	[redacted]	3.114	DRG 2021
[redacted]	[redacted]	[redacted]	2.610	DRG 2021
[redacted]	[redacted]	[redacted]	2.610	DRG 2021
[redacted]	[redacted]	[redacted]	2.610	DRG 2021
[redacted]	[redacted]	[redacted]	2.610	DRG 2021
[redacted]	[redacted]	[redacted]	18.594	DRG 2021
[redacted]	[redacted]	[redacted]	2.610	DRG 2021
[redacted]	[redacted]	[redacted]	2.610	DRG 2021
[redacted]	[redacted]	[redacted]	2.610	DRG 2021
[redacted]	[redacted]	[redacted]	2.610	DRG 2021

	Pemigatinib [%]	BSC [%]	Enheds-omkostning [DKK]	Kilde
[redacted]	[redacted]	[redacted]	2.610	DRG 2021
[redacted]	[redacted]	[redacted]	2.610	DRG 2021
[redacted]	[redacted]	[redacted]	2.610	DRG 2021
[redacted]	[redacted]	[redacted]	18.295	DRG 2021
[redacted]	[redacted]	[redacted]	2.610	DRG 2021

*Leverinfektion, øget bilirubin/basisk fosfatase og hepatitis.

10.2 Resultatet af ansøgers hovedanalyse

I ansøgers hovedanalyse bliver den inkrementelle omkostning pr. patient ca. [redacted] DKK over en tidshorisont på 40 år. Resultaterne fra ansøgers hovedanalyse er præsenteret i Tabel 14.

Tabel 14. Resultatet af ansøgers hovedanalyse, DKK, diskonterede tal

	Pemigatinib	BSC	Inkrementelle omkostninger
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Bivirkningsomkostninger	[redacted]	[redacted]	[redacted]
Hospitalsomkostninger	[redacted]	[redacted]	[redacted]
Patientomkostninger	[redacted]	[redacted]	[redacted]
Terminalomkostninger	[redacted]	[redacted]	[redacted]
Totale omkostninger	[redacted]	[redacted]	[redacted]

10.3 Resultatet af ansøgers budgetkonsekvensanalyse

Ansøger har inkluderet de samme omkostninger i budgetkonsekvensanalysen, som er inkluderet i omkostningsanalysen, dog uden patientomkostninger.

Med ovenstående antagelser om patientantal og markedsandel estimerer ansøger, at anvendelse af pemigatinib vil resultere i budgetkonsekvenser på ca. [redacted] DKK i år 5. Ansøgers estimat af budgetkonsekvenserne fremgår af Tabel 15.

Tabel 15. 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	23.02.2022
Leverandør	Incyte Biooscience Nordic
Lægemiddel	Pemigatinib (Pemazyre)
Ansøgt indikation	Pemigatinib er indiceret til 2. linjebehandling af patienter med lokalavanceret eller metastatisk CCA med en fibroblast growth factor receptor 2 (FGFR2)- fusion eller andet rearrangement.

Forhandlingsresultat

Amgros har i en genforhandling opnået følgende pris på pemigatinib (Pemazyre):

Lægemiddel	Styrke/dosis	Pakningsstr.	AIP (DKK)	Tidligere forhandlet SAIP (DKK)	Tidligere rabatprocent ift. AIP	Genforhandlet SAIP (DKK)	Genforhandlet Rabatprocent ift. AIP
Pemigatinib	4,5 mg	14 stk.	57.703,10	[redacted]	[redacted]	[redacted]	[redacted]
Pemigatinib	9 mg	14 stk.	57.703,10	[redacted]	[redacted]	[redacted]	[redacted]
Pemigatinib	13,5 mg	14 stk.	57.703,10	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

Vurdering af forhandlingsresultatet

Det er Amgros' vurdering, at Amgros har opnået den bedst mulige pris.

Relation til markedet

[redacted]

Status fra andre lande

[redacted]

Pemigatinib er anbefalet af NICE[1] i henhold til markedsføringstilladelsen som behandling til patienter med lokalavanceret eller metastatisk cholangiokarcinom med en fibroblast growth factor receptor 2 (FGFR2)-fusion eller andet rearrangement, som enten har haft tilbagefald af sygdom eller udviser refraktær sygdom efter mindst én linje systemisk behandling.
NICE konkluderer: Pemigatinib opfylder NICE kriterier for livsforlængende behandling ved livets afslutning. Estimaterne for omkostningseffektivitet er usikre, men vil sandsynligvis ligge indenfor grænserne for hvad NICE anser som værende omkostningseffektiv. Derfor anbefales pemigatinib af NICE.

Konklusion

Det er Amgros' vurdering, at vi har opnået den bedst mulige pris.

[redacted]

[1] https://www.nice.org.uk/guidance/ta722/chapter/1-Recommendations

Medicinrådet

Medicinrådets vurdering vedrørende pemigatinib til behandling af lokalavanceret eller metastatisk cholangiokarcinom

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	27. oktober 2021
Dokumentnummer	123817
Versionsnummer	1.0

Indholdsfortegnelse

1. Medicinrådets konklusion

Medicinrådet finder, at datagrundlaget ikke er tilstrækkeligt til, at den samlede værdi af pemigatinib sammenlignet med best supportive care (BSC – understøttende behandling af de symptomer, der opstår ved sygdomsprogression) til 2. linjebehandling af patienter med intrahepatisk cholangiokarcinom og en FGFR2-fusion eller andet rearrangement kan kategoriseres.

Medicinrådet finder dog, at pemigatinib kan være et bedre behandlingsalternativ end BSC til patienter med performancestatus 0 og 1. I vurderingen lægger Medicinrådet vægt på, at der på trods af et spinkelt datagrundlag er observeret, at 37 % af patienterne opnår respons ved behandling med pemigatinib, og at responset har en median varighed på 7,5 måneder. Bivirkningerne ved lægemidlet kan være alvorlige, men vurderes at kunne afhjælpes, og det forventes samtidig, at de symptomer, patienterne oplever under behandling med BSC pga. deres underliggende sygdom, udskydes ved respons på pemigatinib.

Sprog: dansk
Format: pdf
Udgivet af Medicinrådet, 28. oktober 2021

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

ASC: *Active supportive care*

BSC: *Best supportive care*

CCA: Cholangiokarcinom *(cholangiocarcinoma)*

CrCl: Kreatininclearance (*Creatinine Clearance)*

eCCA: Ekstrahepatisk cholangiokarcinom

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

EPAR: *European Public Assessment Report*

FGFR2: *Fibroblast growth factor receptor 2*

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

iCCA: Intrahepatisk cholangiokarcinom

ITT: *Intention-to-treat*

MKRF: Mindste klinisk relevante forskel

PICO: Population, intervention, komparator og effektmål (*Population, Intervention, Comparison and Outcome)*

PS: *Performance status*

PSC: Primær skleroserende cholangitis

TNM: *Tumor, node, metastases*

ULN: *Upper limit of normal*

3. Introduktion

Formålet med Medicinrådets vurdering af pemigatinib til behandling af lokalavanceret eller metastatisk cholangiokarcinom er at vurdere den værdi, lægemidlet har sammenlignet med dansk standardbehandling.

Vurderingen er udarbejdet, fordi Medicinrådet har modtaget en endelig ansøgning fra Incyte Corporation. Medicinrådet modtog ansøgningen den 2. juli 2021.

Klinisk spørgsmål 1:

Hvilken værdi har pemigatinib sammenlignet med *best supportive care* (BSC) for patienter med lokalavanceret eller metastatisk cholangiokarcinom (CCA) med en *fibroblast growth factor receptor 2* (FGFR2)-fusion eller andet rearrangement, som har haft tilbagefald af sygdom eller udviser refraktær sygdom efter mindst én linje systemisk behandling?

3.1 Cholangiokarcinom

Cholangiokarcinom er den næsthyppigste form for primær leverkræft efter hepatocellulært karcinom med ca. 200 nye tilfælde i Danmark om året og udgør omkring 3 % af alle gastrointestinale tumorer. Diagnosen er vanskelig at stille, og CCA er ofte asymptomatisk i tidlige stadier, hvilket medfører, at sygdommen ofte er dødelig, da diagnosen stilles sent. 1-års overlevelsen er ca. 50 %, og 5-års overlevelsen omkring 15 % [1]. Medianoverlevelsen for patienter, der modtager systemisk behandling, er under 1 år [2,3]. Det er svært at finde studier af medianoverlevelsen for patienter med CCA, der er kandidater til 2. linjebehandling, men i et studie af CCA og galdeblærekræft var medianoverlevelsen i 2. linje 6,2 måneder [4].

Ved udgangen af 2016 havde 478 danske patienter CCA, hvilket afspejler den lave overlevelse for denne patientgruppe. Patienter med CCA er oftest ældre (medianalderen er 71 år), og sygdommen forekommer nogenlunde lige hyppigt hos mænd og kvinder.

CCA opstår i slimhinden i galdevejene, både uden for leveren (ekstrahepatisk CCA, eCCA) og inde i leveren (intrahepatisk CCA, iCCA). For iCCA er incidens og mortalitet dog steget inden for de seneste år, mens det modsatte er tilfældet for eCCA [2,5]. En del af stigningen i iCCA skyldes sandsynligvis, at mange af de patienter, som tidligere blev diagnosticeret med ukendt primær tumor, nu bliver diagnosticeret med iCCA [6]. Ekstrahepatisk CCA opdeles yderligere i perihilar CCA (pCCA) og distal CCA (dCCA). På trods af at der findes en række veletablerede risikofaktorer for at udvikle CCA, hvoraf den mest betydende er primær skleroserende cholangitis (PSC) med eller uden samtidig inflammatorisk tarmsygdom, kan risikofaktorer forklare under 30 % af alle tilfælde, hvilket indikerer, at CCA oftest opstår sporadisk [3]. Andre mindre veletablerede risikofaktorer omfatter cirrose og kronisk viral hepatitis B- eller C-infektion. Symptomer på CCA vil typisk være ikterus (gulsot), kolestatisk hudkløe, træthed, vægttab og mavesmerter og kan bl.a. medføre risiko for cholangitis med behov for stentning af galdeveje og galdedræning [7].

TNM (tumor, node, metastases)-klassifikationen bruges til stadieinddeling og er specifik for hver undertype af CCA (iCCA, eCCA) [8]. Stadieinddelingen baseres på antallet af tumorer, vaskulær indvækst og lymfeknudemetastaser, mens tumorstørrelse ikke lader til at være afgørende for prognosen [3,5]. Dog er det eksisterende stadiesystem for iCCA utilstrækkeligt til at prædiktere langsigtet prognose og planlægge behandling [3].

3.2 Pemigatinib

Pemigatinib (handelsnavn: Pemazyre) er indiceret til 2. linjebehandling af patienter med lokalavanceret eller metastatisk CCA med en *fibroblast growth factor receptor 2* (FGFR2)-fusion eller andet rearrangement, som enten har haft tilbagefald af sygdom eller udviser refraktær sygdom efter mindst én linje systemisk behandling. Pemigatinib er formuleret som en tablet og gives i en dosis af 13,5 mg én gang dagligt i 14 dage efterfulgt af 7 dages pause. Denne cyklus gentages indtil sygdomsprogression eller uacceptable bivirkninger.

Pemigatinib virker ved at blokere enzymer (proteinkinaser), som er del af de receptorer, der kaldes *fibroblast growth factor receptorer* (FGFR). Disse receptorer findes på ydersiden af kræftcellerne og er involveret i vækst og spredning af kræftcellerne. Pemigatinib virker ved at hæmme denne proces.

For at være kandidat til behandling med pemigatinib skal patienterne have en FGFR2-fusion eller andet rearrangement, hvilket næsten udelukkende ses hos patienter med intrahepatisk CCA [9]. Pemigatinib anslås at kunne tilbydes til 6 patienter om året i Danmark, hvilket også anvendes i den sundhedsøkonomiske analyse.

I registreringsstudiet anvendes en test for FGFR2-fusion kaldet FoundationOne. Denne test skelner mellem FGFR-fusion, andet rearrangement og andre forandringer. Testen er ikke standard i Danmark, men udføres på alle de patienter, der indgår i eksperimentel behandling med tocilizumab, hvilket tilbydes alle patienter med god PS og god nyre- og leverfunktion. Den eksperimentelle behandling foregår på Herlev Hospital, og Aarhus Universitetshospital er tilbudt at deltage.

Pemigatinib er et *orphan drug*. Pemigatinib (Pemazyre) blev ikke vurderet i en accelereret proces hos European Medicines Agency (EMA), men fik i marts 2021 en betinget markedsføringsgodkendelse i EU. Markedsføringstilladelsen er betinget af, at firmaet senest i december 2021 indsender de endelige resultater af FIGHT-202-studiet og senest i december 2026 indsender resultaterne af FIGHT-302-studiet (fase 3-studie med sammenligning af virkningen og sikkerheden af pemigatinib vs. kemoterapi med gemcitabin plus cisplatin hos voksne med inoperabelt eller metastatisk cholangiokarcinom med FGFR2-omlejring).

Pemigatinib er et nyt lægemiddel og har dermed ikke andre godkendte indikationer.

3.3 Nuværende behandling

Patienter med sygdom på et meget tidligt stadie tilbydes kirurgisk fjernelse af tumor med helbredende sigte. Dette er dog kun muligt hos omkring 30 % af patienterne diagnosticeret med CCA (ca. 60 patienter årligt i Danmark), og risikoen for tilbagefald er høj [9]. For patienter med ikke-resektabel eller metastatisk sygdom (ca. 140 patienter årligt i Danmark) er standardbehandlingen i 1. linje livsforlængende behandling i form af systemisk kemoterapi med gemcitabin og cisplatin med det sigte at opnå sygdomskontrol og bevare livskvalitet. Der er p.t. ingen veletableret standardbehandling i 2. linje, og patienter tilbydes *best supportive care* (BSC) [1][3] eller – ved god almen status – eksperimentel behandling. BSC indebærer månedlige kliniske undersøgelser, symptomkontrol, inkl. galdedræning og stentning af galdeveje efter behov, antibiotika, smerte- og kvalmestillende lægemidler, steroider, palliativ stråleterapi og blodtransfusioner samt anden palliativ behandling for symptomer som gulsot og hudkløe.

4. Metode

Medicinrådets protokol for vurdering vedrørende pemigatinib til behandling af lokalavanceret eller metastatisk cholangiokarcinom beskriver sammen med *Håndbog for Medicinrådets proces og metode vedr. nye lægemidler og indikationsudvidelser*, hvordan Medicinrådet vil vurdere lægemidlets værdi for patienterne.

5. Resultater

5.1 Klinisk spørgsmål 1

5.1.1 Litteratur

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

Der foreligger ikke et direkte sammenlignende studie til besvarelse af klinisk spørgsmål 1. I protokollen var der indsat en søgestreng til at identificere og udvælge studier til en indirekte sammenligning.

Ansøger har ikke anvendt søgestrengen fra protokollen, men har i stedet anvendt sit eget systematiske litteraturreview fra 2020 til at identificere og udvælge litteratur til besvarelsen. Ansøger har udvalgt to fuldtekstartikler baseret på resultater fra to kliniske

[1] "Best supportive care (BSC)" og "Active supportive care (ASC)" er tilsvarende og af synonym betydning i denne rapport.

studier. Medicinrådets sekretariat har efterfølgende opdateret søgningen frem til maj 2021 og fandt ikke nye egnede studier.

Derudover er der inkluderet informationer fra det europæiske lægemiddelagenturs (European Medicines Agency, EMA) European Public Assessment Reports (EPAR) for pemigatinib og produktresuméer for de involverede lægemidler.

5.1.2 Gennemgang af inkluderede studier

Data fra de to inkluderede studier fremgår af Tabel 1 og beskrives efterfølgende enkeltvis.

Tabel 1. Oversigt over inkluderede studier

Publikationer	Lægemiddel	Klinisk forsøg og NCT-nummer	Population
Pemigatinib for previously treated, locally advanced or metastatic cholangiocarcinoma: a multicentre, open-label, phase 2 study. Abou-Alfa, GK et al. Lancet Oncol. 2020 [9]	Pemigatinib (single-arm)	FIGHT-202 NCT02924376	Tidligere behandlede patienter med lokalavanceret/metastatisk eller kirurgisk ikke-resektabel CCA med FGFR2-fusion
Second-line FOLFOX chemotherapy versus active symptom control for advanced biliary tract cancer (ABC-06): a phase 3, open-label, randomised, controlled trial. Lamarca, A et al. Lancet Oncol. 2021 [4]	FOLFOX vs. active *supportive care*	ABC-06 NCT01926236	Patienter med avanceret galdevejskræft, der er progredieret på behandling med cisplatin og gemcitabin

FIGHT-202

FIGHT-202 er et multicenterbaseret, enkeltarms, fase 2-studie, som undersøger effekt og sikkerhed af pemigatinib hos patienter med avanceret eller ikke-resektabel CCA, som tidligere har haft progression efter mindst en tidligere systemisk behandling. 146 patienter blev inkluderet og blev inddelt i tre kohorter afhængigt af fusionsstatus. Kohorte A, B og C bestod af patienter med henholdsvis FGFR2-fusion eller andet rearrangement (n=107), patienter med andre FGF/FGFR-ændringer (n=20) og patienter uden FGF/FGFR-ændringer (n=18). Studiet inkluderede patienter fra januar 2017 til marts 2019.

Pemigatinib blev administreret som oral tabletbehandling med en startdosis på 13,5 mg dagligt i en cyklus på 21 dage (to ugers behandling og en uges pause) frem til

progression, uacceptabel toksicitet, ønske om at udgå af studiet eller behandlers beslutning. Det var tilladt at pausere behandlingen i op til 14 dage for at kontrollere bivirkninger. Hyperfosfatæmi kunne håndteres ved kostmodifikationer, fosfatsænkende terapi eller dosismodifikationer.

Inklusionskriterierne omfattede patienter, der tidligere er progredieret på systemisk behandling, med en ECOG-performancestatus på 0-2, en forventet restlevetid på mindst 12 uger, og patienter med tidligere behandlede – og klinisk stabile – CNS-metastaser uden behov for kortikosteroidbehandling i mindst fire uger. Patienterne skulle også have en tilstrækkelig lever- og nyrefunktion (total bilirubin < 1,5 × øvre grænse for normalen (ULN) eller ≥ 2,5 × ULN ved Gilbert syndrom eller anden sygdom, der involverer leveren; aspartate aminotransferase og alanine aminotransferase ≤ 2, 5 × ULN; serum fosfat ≤ ULN og serum-calcium inden for normalområdet. Tilstrækkelig nyrefunktion defineres som kreatininclearance (CrCl) > 30 mL/min.

Eksklusionskriterierne var tidligere behandling med en selektiv FGRF-hæmmer, HIV-infektion, aktiv hepatitis B- eller C-virusinfektion, unormalt ekkokardiogram eller ukontrolleret hjertesygdom, tidligere ektopisk mineralisering eller kalcifikation og tidligere corneale eller retinale forstyrrelser.

Studiets primære endepunkt var objektiv responsrate (ORR) hos patienter med FGFR2-fusion vurderet centralt for alle patienter, som modtog mindst én dosis pemigatinib. Sekundære endepunkter var ORR i de øvrige kohorter, progressionsfri overlevelse (PFS), varighed af respons (DoR), sygdomskontrolrate (DCR (andelen af patienter med sygdomskontrol)), samlet overlevelse (OS) og farmakokinetik. Derudover blev sikkerhed og tolerabilitet vurderet. Tumorrespons blev vurderet ved uafhængigt review v. RECIST 1.1. Sygdom blev vurderet ved CT (eller MRI-scanning afhængigt af investigators ønske) hver 6. uge i de første 12 uger og derefter hver 9. uge.

Studiets eksplorative endepunkter var at vurdere karakteristika, som kunne have indflydelse på respons, resistens og sikkerhed, og blev målt ved brug af tumor- og blodprøver taget ved baseline og under behandling. Derudover blev livskvalitet vurderet ved hjælp af værktøjerne EORTC-QLQ-C30 og EORTC-QLQ-BIL21 (sidstnævnte kun USA, UK, Tyskland og Korea).

Ved data-cut i marts 2019 var median opfølgningstid i kohorte A 15,4 måneder (IQR 9,3-19,0) og median behandlingstid 7,2 måneder (3,9-10,9) [9]. Kohorte A inkluderer patienter med henholdsvis FGFR2-fusion eller andet rearrangement (n=107) og er den kohorte fra studiet, der er relevant for Medicinrådets vurdering. I EMAs EPAR præsenteres data fra en opdateret analyse med data-cut i april 2020, hvor median opfølgningstid i kohorte A var 27,91 måneder. Ved data-cut i 2020 er der inkluderet én ekstra patient, og ITT-populationen er derfor 108 patienter i stedet for 107 patienter som i den publicerede studie-artikel[9] .

ABC-06

ABC-06 er et randomiseret, ublindet fase 3-studie, som undersøger effekten af at få tilføjet kemoterapi (FOLFOX) til eksisterende standardbehandling (*Active Supportive Care* (ASC), herefter refereret til som *best supportive care* (BSC)), hos 162 patienter med avanceret galdegangskræft, som er progredieret efter 1. linjebehandling med cisplatin og gemcitabine. I indeværende vurdering af pemigatinib anvendes kun BSC-armen som komparator, idet den afspejler nuværende dansk klinisk praksis.

Patienterne blev randomiseret 1:1 til BSC plus FOLFOX eller BSC alene.
BSC bestod af tidlig identifikation og behandling af galdevejsrelaterede komplikationer og kræftrelateret symptombehandling, fx drænage af galdeveje, antibiotika, smertestillende, steroider, kvalmestillende, anden palliativ symptomkontrol, palliativ strålebehandling og blodtransfusion.
FOLFOX-regimet indebar behandling med kemoterapi hver 2. uge i op til 12 cykler over 24 uger og bestod af intravenøs behandling med oxaliplatin 85 mg/m^2, L-folinsyre 175 mg (eller folinsyre 350 mg) og fluorouracil 400 mg/m^2 på dag 1 og fluorouracil 2.400 mg/m^2 som kontinuerlig infusion opstartet på dag 1 og afsluttet på dag 3.

Inklusionskriterier var histologisk eller cytologisk verificeret lokalavanceret eller metastatisk galdegangskræft (inkl. cholangiokarcinom (intrahepatisk + ekstrahepatisk), galdeblærekarcinom og *ampullary carcinoma*, se tabel 2), hvor der var dokumenteret radiologisk sygdomsprogression ved behandling med cisplatin og gemcitabin i 1. linje. Behandling med andre systemiske behandlinger (inkl. genbehandling med cisplatin og gemcitabine) var ikke tilladt. Patienter, der var opstartet behandling med 1. linje cisplatin og gemcitabin, men hvor behandling med cisplatin var stoppet pga. toksicitet, kunne indgå i studiet.
Patienterne skulle have en ECOG-performancestatus på 0-1 og en forventet restlevetid på mindst tre måneder samt tilstrækkelig hæmatologisk funktion og tilstrækkelig nyre- og leverfunktion uden eksisterende infektion eller utilstrækkelig *"biliary drainage"*.
Patienter med klinisk evidens for metastatisk sygdom i hjernen og patienter med hjertesygdom blev ekskluderet.

Studiets primære effektmål for begge behandlingsgrupper var samlet overlevelse, og sekundære endepunkter var PFS og radiologisk respons (kun målt hos patientgruppen i behandling med BSC plus FOLFOX), mens begge behandlingsgrupper blev vurderet i forhold til bivirkninger og livskvalitet. Patienterne i BSC plus FOLFOX-gruppen blev undersøgt ved radiologisk evaluering ved behandlingsstart, hver 12. uge under behandling samt efter endt behandling og indtil sygdomsprogression. Patienter i BSC-gruppen alene blev ikke regelmæssigt radiologisk evalueret, men scanning var tilladt ved klinisk indikation.

Studie- og patientkarakteristika

Tabel 2. Baselinekarakteristika FIGHT-202, kohorte A og ABC-06, BSC-kohorte

	FIGHT-202 Kohorte A (n=107)	ABC-06 BSC (n=81)
Køn		
Kvinde (%)	65 (61 %)	44 (54 %)
Alder, år		
Median	56 (26-77)	65 (59-72)
< 65	82 (77 %)	-
Interval		26-81
Platinresistente		47 (58 %)
Platinfølsomme		34 (42 %)
Sygdomsstadie[§]		
Lokalavanceret		15 (19 %)
Metastatisk	88 (82 %)	66 (81 %)
Tumorplacering		
Intrahepatisk	105 (98 %)	38 (47 %)
Ekstrahepatisk	1 (1 %)	19 (23 %)
Galdeblære	-	17 (21 %)
Ampulla[§§]	-	7 (9 %)
Andet/manglende data	1 (1 %)	-
Histologi		
Adenokarcinom		74 (91 %)
Andre[§§§]		7 (9 %)
ECOG-performancestatus		
0	45 (42 %)	28 (35 %)
1	57 (53 %)	52 (64 %)
2	5 (5 %)	-
Mangler	-	1 (1 %)
Tidligere operation	38 (36 %)	38 (47 %)
Tidligere strålebehandling	28 (26 %)	-
Antal tidligere systemiske behandlinger for avanceret metastatisk sygdom[§§§§]		
1	65 (61 %)	
2	29 (27 %)	
≥ 3	13 (12 %)	
Tidligere cisplatin og gemcitabin	-	81
Varighed, måneder		4,8 (2,9-5,3)
≥ 6 måneder		6 (7 %)

[§]Stratifikationsfaktor, [§§]Distalt cholangiokarcinom, [§§§]Planocellulær, adenoplanocellulær og ikke-specificeret, [§§§§]Maksimalt 5 tidligere behandlinger hos patienter med FGFR2-fusion.

5.1.3 Studiernes sammenlignelighed

Fagudvalget har følgende kommentarer til studiernes sammenlignelighed på tværs og i forhold til en tilsvarende dansk population:

Tumor:
I FIGHT-202 var studiepopulationen begrænset til patienter med avanceret eller ikke-resektabel CAA, som var progredieret efter mindst én tidligere systemisk behandling, og hovedparten af patienternes tumorer var intrahepatiske (98 %). I ABC-06 var patienter med forskellige typer af avanceret galdegangskræft inkluderet (CCA (70 %), galdeblærekræft (21 %) og ampulla (distalt cholangiokarcinom) (9 %)).

Mutationsstatus:
Kohorte A i FIGHT-202-studiet inkluderer udelukkende patienter med FGRF2-fusioner. I ABC-06 er andelen af patienter med disse mutationer ikke rapporteret. Andelen af patienter i ABC-06 med iCCA var 47 % (n=38), og heraf må andelen med FGFR2-fusion antages at være meget begrænset. Det er estimeret, at omkring 10-16 % af patienter med iCCA har FGFR2-fusion, hvilket i så fald kan omregnes til maks. 6 patienter i ABC-06 med FGFR2-fusion.
Jf. protokollen er der studier, som associerer tilstedeværelse af FGRF2-fusioner med en bedre prognose[10]. Medicinrådet bad ansøger redegøre herfor, da dette forhold kan have indvirkning på tolkningen af effektforskelle ved sammenligning med ABC-06, hvor FGFR2-fusion ikke er et inklusionskriterie.

Ansøger har fremhævet et studie af Jain et al. [12], der undersøger den prognostiske effekt af FGFR2-fusion. Studiet inkluderer 374 patienter med forskellige typer af avanceret galdegangskræft, hvoraf 95 havde FGFR-fusion (heraf 63 med FGFR2). Der sås en længere overlevelse hos patienter med FGFR-fusion sammenlignet med patienter uden FGFR-fusion (37 mdr. (95 % CI 24-65) vs. 20 mdr. (95 % CI 17-26)) [12]. Når patienter, der tidligere var behandlet med en FGFR-hæmmer (N=36), blev ekskluderet, var de tilsvarende tal henholdsvis 30 og 20 måneders median overlevelse ($p < 0.003$). Overlevelsen for patienter med forskellige typer af FGFR-fusion adskilte sig dog ikke fra hinanden [12]. En af begrænsningerne ved studiet – udover at det er retrospektivt og baseret på et begrænset antal patienter – er, at overlevelsesdata er kalkuleret samlet for patienter i forskellige behandlingslinjer, som også har modtaget forskellige typer behandling. Det kan betyde, at den bedre overlevelse hos patienter med en form for FGFR-fusion muligvis kan tilskrives en bedre prognose hos de patienter, der er tidligere i deres sygdomsforløb, snarere end for den patientgruppe, der er aktuel for indikationen i denne vurdering.

Herudover har sekretariatet fundet et review fra 2020, der omhandler den prognostiske betydning af FGFR2-fusion [10]. Dette review understøtter den manglende viden om betydningen af FGFR2, idet nogle studier har vist længere overlevelse hos patienter med FGFR2-fusion, mens andre ikke har fundet nogen sammenhæng [10].

Fælles for de inkluderede studier i reviewet, der også inkluderer ovenstående studie af Jain et al., er, at de er retrospektive, baseret på meget få patienter, inkluderer flere

undertyper af galdegangskræft eller flere forskellige typer af FGFR-fusion, samt at ingen af studiepopulationerne er repræsentative for indikationen for pemigatinib, da ingen af studierne er baseret på tidligere behandlede patienter, der har haft tilbagefald af sygdom eller udviser refraktær sygdom.

Udover ovenstående studie inkluderer reviewet et studie fra 2014 baseret på 12 CCA-patienter med FGFR2-fusion, for hvem der sås en længere medianoverlevelse (123 mdr. (95 % CI, 51-123 mdr.)) sammenlignet med CCA-patienter uden FGFR2-fusion (37 mdr. (95 % CI, 24-49 mdr.)) [11]. Dette var dog baseret på en patientgruppe, der kunne behandles kirurgisk og dermed adskiller sig markant mht. prognose end patientgruppen for nærværende indikation.

Derudover henvises til to studier, baseret på henholdsvis 3 og 7 CCA-patienter med FGFR2-fusion, som finder, at der ikke er en sammenhæng mellem FGFR2-fusion og overlevelse [13,14].

På baggrund af ansøgers svar og det tilgængelige data vedrørende dette spørgsmål vurderer fagudvalget, at FGFR2-fusioner medfører en vis grad af positiv prognostisk værdi, men at omfanget af denne er uklar og muligvis ikke klinisk relevant.

Overvejelser om dette forhold gennemgås yderligere under andre overvejelser, afsnit 6.3.

Performance status:
Patienterne i FIGHT-202-studiet kunne indgå med en PS på 0-2, mens patienterne i ABC-studiet alle havde en PS på 0-1. Dog er det kun 5 % (n=5) af patienterne i FIGHT-202-studiet, der har PS 2. Fagudvalget bemærker, at forskellen ikke vurderes at påvirke resultaterne i væsentlig grad, og at størstedelen af patienterne i Danmark, som forventes at blive tilbudt behandling med pemigatinib, vil være i PS 0-1.

Tidligere behandling:
I Kohorte A i FIGHT-202-studiet var 61 % af patienterne behandlet med én tidligere linje systemisk behandling, mens 27 % var behandlet to gange, og 12 % var behandlet 3 gange eller derover (maks. 5 behandlinger). 69 patienter (65 %) i kohorte A er tidligere behandlet med gemcitabine plus cisplatin. I ABC-studiet er alle patienter tidligere behandlet med gemcitabine plus cisplatin. Fagudvalget bemærker, at det ikke er muligt at vurdere betydningen af antallet af tidligere behandlingslinjer ift. effekten af pemigatinib hos patienterne, da flere tidligere behandlingslinjer både kan skyldes, at patientens sygdom er mere fremskreden, og at sygdommen ikke er så aggressiv, så patienten har kunnet tåle flere behandlinger.

Senere behandlingslinjer:
Det var tilladt for patienterne i FIGHT-202 at modtage behandling efter stop af pemigatinib. For 35 patienter i hele FIGHT-202 er der information om efterfølgende behandlinger. Det var tilladt for patienterne i ABC-06 at modtage eksperimentel behandling ved progression (i fase 1-studier). 8 (10 %) ud af de 81 patienter i BSC-armen

modtog efterfølgende behandling med kemoterapi uden for protokol, mens 3 patienter (4 %) modtog eksperimentel behandling.

Tabel 3. Sammenligning af anvendte studier

	FIGHT-202	ABC-06
Studiedesign	Fase 2, single-arm	Randomiseret fase 3, multicenter, ublindet
Population	Cholangiokarcinom, inkl. FGFR2-ændringer	Galdegangskræft, kun patienter fra Storbritannien
Intervention	Pemigatinib	mFOLFOX + BSC
Komparator	-	BSC alene
Primært endepunkt	ORR	OS
Sekundære endepunkt	Responsvarighed, PFS (RECIST 1.1), sygdomskontrolrate, OS	PFS, (RECIST 1.1), radiologisk respons, uønskede hændelser, livskvalitet
Median opfølgningstid	27,91 måneder	21,7 måneder

Fagudvalget vurderer, at de anvendte studier, på trods af stor heterogenitet, må antages at være den bedste mulighed for en sammenligning mellem behandling med pemigatinib og BSC.

5.1.4 Databehandling og analyse

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

Datagrundlaget for vurderingen består af et fase 2-studie (FIGHT-202) uden kontrolarm og data fra et fase 3-studie (ABC-06), som sammenligner BSC med kemoterapi som tillæg til BSC. Jf. afsnit 5.1.2 er studiepopulationen i ABC-06 ikke direkte sammenlignelig med den relevante population i det kliniske spørgsmål (svarende til indikationen for pemigatinib). Datagrundlaget er meget heterogent, og der findes ikke en direkte sammenligning mellem pemigatinib og BSC. Analyseresultaterne i denne vurdering skal derfor fortolkes med forbehold.
I det følgende gennemgås datagrundlaget for de ønskede effektmål i denne vurdering.

Overlevelse:
For effektmålet OS har ansøger indsendt data fra en indirekte sammenligning af pemigatinib vs. *best supportive care* ved en *Matching Adjusted Indirect Comparison* (MAIC-analyse). Ved en MAIC-analyse er det muligt at justere for udvalgte forskelle i baselinekarakteristika mellem studiernes patientpopulationer, som forventes at kunne

påvirke effekten af interventionen (*effect modifiers*), eller som har prognostisk betydning (*prognostic factors*). Denne metode giver kun mening i en sammenligning af to eller flere lægemidler, når der findes tilgængelige data på individniveau for mindst det ene lægemiddel. Dernæst skal der justeres for alle effektmodificerende (og prognostiske) variable, da analysen ellers vil være *biased*.

I ansøgers MAIC-analyse er data på patientniveau fra FIGHT-202 justeret i forhold til forskelle i patientkarakteristika fra ABC-06, og sammenligningerne er udført ved vægtede analyser (*parametric survival models and Cox proportional hazard models*).
Der er i MAIC-analysen justeret for parametrene alder, køn, ECOG-performancestatus og albuminniveau. Analysen er ikke justeret for FGFR2-fusion, da der ikke er screenet for denne fusion i ABC-06. Dog er antallet af patienter med FGFR2-fusion i ABC-06-studiet formodentlig meget begrænset (se afsnit 5.1.3).
Ansøger beskriver, at patienterne i den vægtede FIGHT-202-population er ca. 10 år ældre, at en større andel var mænd, samt at en større andel havde performancestatus 0-1 og et lavere albuminniveau end i den oprindelige FIGHT-202-population. Baseret på disse karakteristika skriver ansøger, at det ikke er klart, hvordan justeringen påvirker den vægtede analyse ift. en naiv ikke-statistisk sammenligning. Dette begrundes med, at en population med flere patienter med performancestatus 0-1 og med lavere albuminniveau kan påvirke effekten positivt, mens en population med højere alder kan påvirke effekten negativt.

Både resultater for den vægtede og uvægtede analyse vil blive præsenteret i resultatgennemgangen.

Tabel 4. Sammenligning af baselinekarakteristika – Pemigatinib (FIGHT 202) vs. BSC (ABC-06)

Behandling (studie)	N	Alder	Køn (andel mænd)	ECOG	ALB-35
Pemigatinib ujusteret (FIGHT-202)	108	55,2	38,9	95,4	78,7
Pemigatinib vægtet (FIGHT-202)	54,2	65,0	46,0	100,0	74,0
BSC (ABC-06)	81,0	65,0	46,0	100,0	74,0

Responsrater og PFS:
Det var ikke muligt for ansøger at foretage en MAIC-analyse for effektmålene responsrate og PFS, da der i ABC-06 ikke var indsamlet data for PFS og responsrate for patienterne i BSC-armen. Effektmålene ORR og PFS kan derfor ikke kategoriseres, jf. Medicinrådets metoder, og data gennemgås i stedet kvalitativt.

Uønskede hændelser:
Ansøger har ikke fortaget en sammenligning mellem pemigatinib og *best supportive care* vedrørende effektmålet uønskede hændelser. Effektmålet kan derfor ikke kategoriseres, jf. Medicinrådets metoder, og data gennemgås i stedet kvalitativt.

Livskvalitet:
Ansøger har indsendt en præsentation fra ASCO 2021 vedr. livskvalitet fra FIGHT-202 [15]. Livskvalitetsdata for ABC-06-studiet er endnu ikke publiceret. Effektmålet kan derfor ikke kategoriseres, jf. Medicinrådets metoder, og data gennemgås i stedet kvalitativt.

Opfølgningstider:
Ansøger har i sin ansøgning anvendt resultater fra det første data-cut i FIGHT-202 fra april 2019. I EMAs EPAR er der opgivet resultater fra FIGHT-202 med et data-cut i april 2020 for effektmålene ORR, DoR, PFS og median OS. Jf. protokollen ønsker Medicinrådet at anvende resultater med længst mulig opfølgningstid. Ansøger har efter forespørgsel fra Medicinrådet efterfølgende indsendt opdaterede data baseret på et data-cut i april 2020, hvilket anvendes i denne rapport.

5.1.5 Evidensens kvalitet

Der er primært tale om en kvalitativ sammenligning på baggrund af et ukontrolleret studie for interventionen. Der findes ikke velvaliderede værktøjer til at vurdere evidensens kvalitet for non-komparative studier. Der er derfor hverken udarbejdet en Risk of Bias-profil eller en GRADE-profil. På baggrund af disse forhold vil evidensens kvalitet dog som udgangspunkt være meget lav.

5.1.6 Effektestimater og kategorier

I tabellen herunder fremgår de absolutte og relative effektforskelle, de foreløbige og aggregerede kategorier, den samlede kategori og den samlede kvalitet af evidensen for klinisk spørgsmål 1.

Tabel 5. 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	
Samlet overlevelse (OS)	Median overlevelse (3 mdr.)	Kritisk	12,2 mdr.	Kan ikke kategoriseres	HR: 0,21 (0,15-0,29)	Stor merværdi	Kan ikke kategoriseres
	Overlevelsesrate efter 6 måneders behandling (10 %-point)		53,5 %-point	Kan ikke kategoriseres			
Objektiv responsrate	Andel patienter, som opnår objektiv respons (30 %-point)	Kritisk	Ikke opgjort	Kan ikke kategoriseres	Ikke opgjort	Kan ikke kategoriseres	Kan ikke kategoriseres
Livskvalitet	EORTC QLQ-C30 (≥ 10 point)	Kritisk	Ikke opgjort	Kan ikke kategoriseres	Ikke opgjort	Kan ikke kategoriseres	Kan ikke kategoriseres
Uønskede hændelser	Andel patienter med grad 3-4 uønskede hændelser (5 %-point)	Vigtig	Ikke opgjort	Kan ikke kategoriseres	Ikke opgjort	Kan ikke kategoriseres	Kan ikke kategoriseres
	Kvalitativ gennemgang af uønskede hændelser (narrativ vurdering)		Se side 22 for gennemgang af bivirkningsprofil				
Konklusion							
Samlet kategori for lægemidlets værdi	Kan ikke kategoriseres						
Kvalitet af den samlede evidens	Meget lav						

Samlet overlevelse

Som beskrevet i protokollen er effektmålet samlet overlevelse kritisk for vurderingen af lægemidlets værdi for patienterne, fordi sygdommen er forbundet med høj dødelighed og forventet kort restlevetid for patienterne. Det er derfor afgørende, at behandlingen kan forlænge patienternes levetid. Fagudvalget ønskede effektmålet opgjort som median OS, hvilket afspejler OS for den samlede patientpopulation, og ved overlevelsesrate efter 6 måneder, som viser, hvor stor en gruppe af patienterne der opnår en længerevarende effekt af behandlingen. Hvis data for medianoverlevelse ikke er tilgængeligt, ønskede fagudvalget at se data for median PFS. Data for PFS er udeladt i følgende afsnit, da vi har modtaget data for medianoverlevelse. Det bemærkes dog, at der i den økonomiske analyse er udført en MAIC-analyse for PFS-data, hvori FOLFOX-armen fra ABC-06-studiet anvendes. Medicinrådet fastsatte i protokollen, at en forskel på henholdsvis 3 måneder og 10 %-point var klinisk relevante forskelle for median OS og overlevelsesrate.

Median OS

Ansøger har til MAIC-analysen beregnet median OS for både den vægtede og ujusterede population i FIGHT-202 (Tabel 6). Estimaterne stammer fra den seneste opfølgning, som også anvendes i EPAR med en median opfølgningstid på 27,1 måneder for pemigatinib. Data for BSC-armen fra ABC-06-studiet har en median opfølgningstid på 21,7 måneder. I ansøgningen indgår også en overlevelseskurve baseret på samme data-cut (Figur 1).

Tabel 6. Median OS for den ujusterede og vægtede patientpopulation fra FIGHT-202 samt ujusteret median OS fra ABC-06 baseret på data fra data-cut i april 2020

Behandling (studie)	N/ ESS	Events	Median (95 % CI)
Pemigatinib ujusteret (FIGHT-202)	108	63	17,48 (14,42-22,93)
Pemigatinib vægtet (FIGHT-202)	54,2	39	17,38 (14,82-30,13)
BSC (ABC-06)	81,0	74	5,18 (4,10-5,78)

Overlevelseskurve

Median overlevelse er i den vægtede analyse 17,38 måneder for patienter behandlet med pemigatinib og 5,18 måneder for patienter, der har modtaget BSC, hvilket giver en forskel i medianoverlevelse på 12,2 måneder mellem behandlingerne og dermed overstiger den fastsatte MKRF. Dog er der ikke udført en statistisk analyse for forskellen, og på den baggrund kan den foreløbige værdi af pemigatinib vedr. medianoverlevelse ikke kategoriseres efter Medicinrådets metoder.

Overlevelsesrate ved 6 måneder

Efter 6 måneder var overlevelsesraten efter behandling med pemigatinib i FIGHT-202 88,6 % (80,8-93,4), og i BSC-armen i ABC-06-studiet var den 35,5 % (25,2-46,0), hvilket giver en absolut forskel på 53,1 %-point, som derved overstiger MKRF (10 %-point). Dog er der ikke udført en statistisk analyse af forskellen, og de 53,1 %-point kan derfor ikke bruges som et solidt estimat for forskellen, men blot som en indikation af effekten. Derfor kan den foreløbige værdi af pemigatinib vedr. overlevelsesrate ikke kategoriseres efter Medicinrådets metoder.

Den relative effektforskel fra ansøgers vægtede MAIC-analyse fra april 2020 viser en HR på 0,21 (CI 95 %: 0,15-0,29), og baseret på den relative effektforskel har pemigatinib en **stor merværdi** for effektmålet samlet overlevelse.

Samlet vurdering af effektmålet OS
Fagudvalget vurderer, at den samlede værdi vedr. effektmålet OS for behandling med pemigatinib sammenlignet med BSC ikke kan kategoriseres, jf. Medicinrådets metoder. Den relative forskel mellem behandlingerne (HR 0,21 (95 % CI 0,15-0,29)) indikerer en stor merværdi, men fagudvalget fremhæver her, at datagrundlaget, som den bygger på, er spinkelt. Den mulige positive prognostiske effekt af FGFR2-fusion er med det eksisterende datagrundlag ikke mulig at vurdere størrelsen af. Fagudvalget vurderer dog, at det er tvivlsomt, om den prognostiske effekt er af klinisk betydende relevans (se afsnit 5.3.1 og 6.3).

På trods af betydelige usikkerheder ved sammenligningen fremhæver fagudvalget dog, at effekten af pemigatinib ser lovende ud, idet median OS og OS-rate ved 6 måneder er væsentligt højere for patienter behandlet med pemigatinib end for patienter, der har modtaget BSC.

Fagudvalget oplyser, at der pågår et klinisk randomiseret fase 3-studie, hvor behandling med pemigatinib direkte sammenlignes med dansk standardbehandling (cisplatin/gemcitabin) til patientgruppen i 1. linje.

Objektiv responsrate
Som beskrevet i protokollen er effektmålet ORR kritisk for vurderingen af lægemidlets værdi for patienterne, da effektmålet belyser behandlingsrespons og afspejler interventionens effekt på tumorstørrelse. Derudover vurderer fagudvalget, at et væsentligt tumorsvind ofte vil bevirke en reduktion i patientens sygdomsbyrde, og selv en mindre reduktion af tumorbyrden i galdeveje vil lindre ikterus (gulsot), kolestatisk hudkløe, reducere behov for stentning af galdeveje og mindske risiko for cholangitis.

Jf. RECIST, vers. 1.1 [16], defineres komplet og partielt respons således:

- Komplet respons (CR): Klinisk og billeddiagnostisk sygdomsfri. Alle tumorlæsioner (defineret som mål-læsioner ved første kontrol) er væk, og ingen nye er fremkommet.
- Partielt respons (PR): Mindst 30 % reduktion af tumorlæsionernes størrelse sammenlignet med baseline.

Objektiv respons (OR) opnås for en patient, hvis responset for en patients sygdom er klassificeret som CR eller PR, og den objektive responsrate (ORR) defineres som CR + PR delt med det samlede patientantal.

Respons ved behandling med pemigatinib sås hos 37,0 % (CI 95 % 27,94-46,86) af patienterne (data-cut i april 2020). Der er ikke målt respons for BSC-armen i ABC-06-studiet. Fagudvalget vurderer dog, at det er rimeligt at antage, at responsraten hos patienter i 2. linje, der ikke modtager andet end symptomlindrende behandling, er tæt på 0 %. Ud fra denne betragtning må det formodes, at forskellen i responsrate mellem patienter behandlet med pemigatinib og patienter i BSC-behandling er større end den fastsatte MKRF på 30 %-point. Dog er det ikke muligt at lave en foreløbig kategorisering på denne baggrund, da forskellen bygger på en antagelse og ikke observerede hændelser

fra et klinisk studie. Derfor kan effekten af pemigatinib vedr. effektmålet responsrate ikke kategoriseres efter Medicinrådets metoder.

Ved data-cut i april 2020 havde 4 patienter (3,7 %) opnået komplet respons og 36 patienter (33,3 %) et partielt respons. I EPAR præsenteres også median varighed af respons (DoR) på 8,08 måneder (95 % CI: 5.65, 13.14), hvilket suppleres med en DoR ≥ 6 måneder hos 23 patienter, der responderede (57,5 %) og en DoR ≥ 12 måneder hos 10 patienter, der responderede. DoR er et udtryk for, hvor stor en procentdel af de patienter, som har et komplet eller partielt respons, der har et vedvarende respons efter henholdsvis 6 og 12 måneder.

Fagudvalget bemærker, at objektiv responsrate i dette tilfælde vurderes at være et meget relevant effektmål, idet patienter med FGFR2-fusion kan have en bedre prognose end andre patienter med CCA (se afsnit 5.1.3 og 6.3 for yderligere detaljer). Da data for komparator indeholder patienter med og uden FGFR2-fusion, kan det medføre usikkerhed i vurderingen af effektmålet overlevelse, men ikke i tilsvarende grad for ORR.

Samlet vurdering af effektmålet ORR
Fagudvalget vurderer, at pemigatinibs effekt vedr. effektmålet ORR samlet set ikke kan kategoriseres, jf. Medicinrådets metoder. Fagudvalget vurderer dog, at responsraten i FIGHT-202-studiet indikerer, at der er en positiv effekt ved behandling med pemigatinib.

Livskvalitet
Som beskrevet i protokollen er effektmålet livskvalitet kritisk for vurderingen af pemigatinibs værdi for patienterne, da livskvalitet har stor betydning for den enkelte patient – især idet behandlingen er livsforlængende og ikke kurativ. Derudover forventes dette effektmål at kunne give en indikation af, hvorvidt bivirkningerne påvirker patientens livskvalitet.

Livskvalitet blev i protokollen ønsket opgjort som ændring i point på scoringsskalaen i spørgeskemaet EORTC QLQC30, der går fra 0-100. Ansøger har ikke indleveret data opgjort på ændring i point, men henviser til en poster præsenteret på ASCO-konferencen i 2021 med resultater baseret på 100 af de 107 patienter i kohorte A i FIGHT-202-studiet. Disse resultater indikerer, at patienter med enten komplet respons (CR), delvist respons (PR) eller stabil sygdom (SD) oplevede marginale ændringer i livskvalitet fra baseline (gennemsnitlig ændring fra baseline) målt ved ”*overall health status scores over time*”.

I EPAR står derudover, at der er tilgængelige data for gennemsnitlig og median ændring fra baseline målt ved EORTC QLQ-C30 og QLQ-BIL21, og at disse ikke viser nogen konsistente tendenser.

Samlet vurdering af effektmålet livskvalitet
Fagudvalget vurderer, at pemigatinib samlet set har en værdi vedr. livskvalitet, der ikke kan kategoriseres, jf. Medicinrådets metoder.

Fagudvalget bemærker, at det ikke er muligt at konkludere noget på baggrund af det tilgængelige data for livskvalitet, men at der ikke ser ud til at være nogen markante

ændringer fra baseline, og at der derudover ikke er noget, der tyder på, at pemigatinib påvirker livskvaliteten negativt.

Uønskede hændelser
Som beskrevet i protokollen er effektmålet uønskede hændelser vigtigt for vurderingen af lægemidlets værdi for patienterne. Vægtningen af effektmålet som vigtigt skyldes, at patienterne har en dårlig prognose og mange symptomer, og at fagudvalget derfor forventer, at patienterne vil tolerere et vist niveau af bivirkninger. Fagudvalget ønskede bivirkninger belyst ved antallet af grad 3-4 uønskede hændelser defineret ved CTCAE og derudover en kvalitativ vurdering.

Uønskede hændelser grad 3-4
59,8 % af patienterne behandlet med pemigatinib oplevede uønskede hændelser grad 3-4. I ABC-06 oplevede 35 (43 %) af patienterne en grad 3-hændelse og 3 (4 %) en grad 4-hændelse.

Ansøger har ikke angivet et relativt effektestimat for forskellen mellem antallet af uønskede hændelser ved behandling med pemigatinib vs. BSC, og pemigatinib kan derfor ikke tildeles en foreløbig værdi vedr. effektmålet uønskede hændelser grad 3-4.

Kvalitativ gennemgang
Til den kvalitative gennemgang er anvendt produktresume og EMAs EPAR for pemigatinib.

For pemigatinib (alle inkluderede patienter i FIGHT-202) var de mest almindelige bivirkninger hyperfosfatæmi (60,5 %), alopecia (hårtab) (49,7 %), diarré (46,9 %), negletoksicitet (44,9 %), træthed (43,5 %), kvalme (41,5 %), dysgeusi (smagsforstyrrelser) (40,8 %), stomatitis (mundbetændelse) (37,4 %), forstoppelse (36,7 %), mundtørhed (34,0 %), tørre øjne (27,9 %), artralgi (ledsmerter) (25,9 %), hypofosfatæmi (23,1 %), tør hud (21,8 %) og palmar-plantar erytrodysæstesi-syndrom (hånd/fod-syndrom) (16,3 %).

De mest almindelige alvorlige bivirkninger var hyponatriæmi (2,0 %) og stigning i blodkreatinin (1,4 %). Ingen alvorlige bivirkninger førte til dosisreduktion af pemigatinib. En alvorlig bivirkning med hyponatriæmi (0,7 %) førte til dosisafbrydelse. En alvorlig bivirkning med kreatininstigning i blodet (0,7 %) førte til seponering af pemigatinib.

Alvorlige bivirkninger i form af øjenlidelser var nethindeløsning (0,7 %), non-arteritisk iskæmisk opticusneuropati (0,7 %) og okklusion af nethindearterien (0,7 %).

Bivirkninger af særlig interesse
I FIGHT-202 var der særlig interesse for følgende bivirkninger: hyper- og hypofosfatæmi, serøs nethindeløsning og negletoksicitet.

Hyper- og hypofosfatæmi
Hyperfosfatæmi blev rapporteret hos 60,5 % af alle patienter behandlet med pemigatinib (57,9 % i kohorte A sammenlignet med 65,0 % og 66,7 % i kohorte B og C). Ingen af reaktionerne var alvorlige (≥ grad 3) eller førte til seponering af pemigatinib. Dosisafbrydelse forekom hos 1,4 % af patienterne og reduktion hos 0,7 % af patienterne.

Håndtering af hyperfosfatæmi er angivet i produktresumeet. Fagudvalget bemærker, at hyperfosfatæmi ikke er noget, som fylder meget i klinikken, og at det kan afhjælpes ved hjælp af kost og evt. medicin.

Hypofosfatæmi blev rapporteret hos 25,2 % i kohorte A. Ingen af hændelserne var alvorlige, medførte seponering eller dosisreduktion.

Serøs nethindeløsning
Serøs nethindeløsning forekom hos 4,8 % af alle patienter behandlet med pemigatinib. Reaktionerne var generelt ikke alvorlige (grad 1-2) (3,4 %), men hos én patient (0,7 %) blev der observeret alvorlig (grad 3-4) nethindeløsning. To bivirkninger med nethindeløsning (0,7 %) og løsning af øjets pigmentepitel (0,7 %) førte til dosisafbrydelse. Ingen af reaktionerne førte til dosisreduktion eller seponering af pemigatinib.
Fagudvalget finder ikke, at det er muligt at konkludere, om tilfældet af alvorlig nethindeløsning, der blev observeret hos én enkelt patient, kan tilskrives en bivirkning af pemigatinib. Fagudvalget er opmærksom på, at der i produktresuméet er beskrevet en procedure for kontrol af patienternes øjne ved opstart og under behandling med pemigatinib.

Negletoksicitet
Negletoksicitet var primært ikke alvorlig (grad 1-2). Ingen hændelser var alvorlige eller førte til seponering. Få patienter måtte pausere behandlingen eller dosisjustere (4,1 % og 3,4 %). De oftest rapporterede hændelser (≥ 5 %) i kohorte A var onychomadesis (svampeinfektion) (12,1 %), misfarvning af negle (11,2 %), onycholysis (negleplade er separeret fra neglelaget) (9,3 %), negledystrofi (dårlig negledannelse) (9,3 %), paronychia (bløddelsinfektion i neglevolden) (8,4 %) og onychoclasis (knækkede negle) (8,4 %).

Best supportive care
BSC bestod i studiet af tidlig identifikation og behandling af galdevejsrelaterede komplikationer og kræftrelateret symptombehandling, fx dræning af galdeveje, antibiotika, smertestillende, steroider, kvalmestillende, anden palliativ symptomkontrol, palliativ strålebehandling og blodtransfusion.
42 (52 %) patienter i BSC-armen oplevede en grad 3-5-hændelse. Heraf var 35 en grad 3-hændelse og 3 en grad 4-hændelse. 4 (5 %) patienter døde pga. infektion eller *"biliary event"*. De grad 3-5-hændelser, som oftest blev rapporteret, var: anoreksi (7 %), anæmi (1 %), diarré (2 %), opkastning (5 %), hypertension (1 %), *"biliary events"* (21 %), infektioner (6 %), fatigue (7 %) og neutropeni (1 %).
Fagudvalget vurderer, at disse hændelser ved behandling med BSC stemmer overens med, hvad de ser i klinikken.

Samlet vurdering vedr. effektmålet uønskede hændelser
Fagudvalget vurderer, at pemigatinib samlet set har en værdi vedr. uønskede hændelser, der ikke kan kategoriseres. Fagudvalget vurderer dog, at bivirkningerne ved pemigatinib generelt er mulige at afhjælpe. Fagudvalget er opmærksom på risikoen for udvikling af nethindeløsning og alvorligheden heraf.

Fagudvalget vurderer, at de behandlingskrævende symptomer, sygdommen medfører under nuværende standardbehandling (BSC), forventes at blive udskudt ved respons på pemigatinib, hvilket antages at have en positiv indflydelse på patienternes livskvalitet.

5.1.7 Fagudvalgets konklusion

Fagudvalget vurderer, at den samlede værdi af pemigatinib sammenlignet med BSC til 2. linjebehandling af patienter med cholangiokarcinom ikke kan kategoriseres, jf. Medicinrådets metoder.

Vurderingen er baseret på et enkeltarms fase 2-studie af pemigatinib hos CCA-patienter med FGFR2-fusion eller andet rearrangement og BSC-armen i et fase 3-studie med patienter med avanceret galdegangskræft som komparator. De to studier er meget heterogene, og datagrundlaget for sammenligningerne er derfor meget usikkert.

Fagudvalget anser dog datagrundlaget som det for nuværende bedst tilgængelige til at vurdere effekten af pemigatinib. Der pågår i øjeblikket et klinisk randomiseret fase 3-studie, hvor behandling med pemigatinib i 1. linje sammenlignes *direkte* med dansk standardbehandling (cisplatin/gemcitabin) til patienter med cholangiokarcinom med FGRF2-fusion eller andet rearrangement.

Dog vurderer fagudvalget, at pemigatinib er et bedre behandlingsalternativ end *best supportive care* til en patientgruppe, som p.t. ikke har et behandlingstilbud. Fagudvalget begrunder dette med følgende:

For det kritiske effektmål "samlet overlevelse" er der fundet forskelle i henholdsvis median overlevelse (12,2 mdr.) og overlevelsesrate (53,5 %-point), som oversteg de mindste klinisk relevante forskelle, og den relative forskel (HR: 0,21 (0,15-0,29)) indikerede en stor merværdi. Dog bemærker fagudvalget, at muligheden for en positiv prognostisk værdi af FGFR-2-fusion medfører yderligere usikkerhed på effektmålet overlevelse.

For det kritiske effektmål "objektiv responsrate" er responsraten ved behandling med pemigatinib 37 %, mens responsraten hos patienter i 2. linje, der ikke modtager andet end symptomlindrende behandling, antages at være tæt på 0 %.

For det kritiske effektmål "livskvalitet" var det ikke muligt at konkludere noget på baggrund af det tilgængelige data.

For det vigtige effektmål "uønskede hændelser" er bivirkningsprofilerne meget forskellige. Bivirkningerne ved pemigatinib vurderes generelt at være mulige at afhjælpe i klinikken, og der er opmærksomhed på risikoen for udvikling af nethindeløsning. Samtidig vurderes det, at de behandlingskrævende symptomer, sygdommen medfører, og som behandles via BSC, forventes at blive udskudt, når patienterne oplever respons under behandling med pemigatinib. Dette antages at have en positiv indflydelse på patienternes livskvalitet.

6. Andre overvejelser

6.1 Test for FGFR2-fusion

Medicinrådet anmodede i protokollen for vurdering af pemigatinib ansøger om at gøre rede for, hvilken metode man anvender ved test for FGFR2-fusion, og om den stemmer overens med metoden i det kliniske studie. Endvidere ønskede Medicinrådet, at ansøger gjorde rede for omkostningerne ved en test og kom med et estimat for antallet af patienter, der skal testes for at finde én patient med FGFR2-fusion. Medicinrådet ønskede desuden, at ansøger redegjorde for disse forhold, idet omkostninger til implementering af lægemidlet skal indgå som del af den sundhedsøkonomiske analyse.

Ansøger skriver, at de har haft kontakt til lokale eksperter på Herlev Hospital, Odense Universitetshospital og Aarhus Universitetshospital, og at svaret er baseret på deres udtalelser (se bilag 1). Fagudvalget tager ansøgers svar til efterretning og vurderer, at den bedste måde at identificere FGFR2-fusion er ved at anvende en test baseret på væv og ikke blod. Derudover opfordrer fagudvalget til, at alle patienter med cholangiokarcinom får foretaget en test, umiddelbart efter diagnosen med CCA er blevet fastlagt, så de hurtigt er klar til at modtage behandling med pemigatinib i tilfælde af, at de efter 1. linjebehandling kandiderer til 2. linjebehandling med pemigatinib.

6.2 Dosisreduktion

Medicinrådet ønsker, at ansøger gør rede for eventuelle dosisreduktioner ved behandling med pemigatinib.

Fagudvalget har gennemgået ansøgers svar og vurderer, at det er beskedent, at omkring 20 % af patienter behandlet med pemigatinib bliver dosisreduceret. Dog er der en del patienter, der bliver pauseret (42,5 % i kohorte A+B+C samlet) på grund af bivirkninger, og pauseringen er på mellem 1 og 37 dage. I EPAR er det angivet, at *"gastrointestinale disorders"* (diarré) er den hovedsagelige årsag til pauseringer. Fagudvalget lægger desuden vægt på, at dosisintensiteten stadig er tæt på komplet, hvilket må betyde, at pausering er af kort varighed.

Det fulde svar fra ansøger er vedlagt som bilag (Bilag 1).

6.3 Prognose

Medicinrådet ønskede, at ansøger beskrev, hvorvidt CCA-patienter med FGFR2-fusion har en bedre prognose end CCA-patienter uden FGFR2-fusion, og redegjorde for den eventuelle betydning af dette for de forskellige effektmål [10]. Herunder skulle ansøger redegøre for fordelingen af patienter med og uden FGFR2-fusion i litteraturen, som beskriver effekten af komparator.

Fagudvalget har gennemgået ansøgers svar (bilag 1) og vurderer, at data tyder på, at FGFR2-fusioner medfører en vis grad af positiv prognostisk værdi, men at omfanget af denne er uklar og muligvis ikke klinisk relevant.

I tillæg til dette gør fagudvalget opmærksom på, at effekten af 1. linjebehandling med cisplatin og gemcitabin er undersøgt i et fase 3-studie fra 2010 blandt patienter med avanceret/metastatisk cholangiokarcinom, galdeblærekræft eller kræft i ampulla [17]. I studiet var median PFS for patientgruppen 8,0 måneder (95 % CI; 6,6-8,6). Fagudvalget gør opmærksom på, at median PFS for denne patientpopulation – uden overvægt af patienter med FGFR2-fusion – ikke er markant længere end median PFS for patienter i FIGHT-202 med FGFR2-fusion, der modtager samme behandling i 1. linje (median PFS 5,7 måneder (CI 95 % 4,6-9,1)). Dette kan indikere, at patienter med FGFR2-fusion ikke nødvendigvis har en bedre prognose end patienter uden FGFR2-fusion, men at den bedre prognose kan tilskrives den målrettede behandling med pemigatinib.

Det fulde svar fra ansøger er vedlagt som bilag (Bilag 1).

6.4 Behandling ved performancestatus 2 (PS2)

Medicinrådet ønsker, at ansøger redegør for behandling af patienter med PS2.

Ansøger har ikke kunnet identificere data specifikt for patienter med PS2.

Fagudvalgets konklusion:

Fagudvalget bemærker, at EMA ikke har indskrænket indikationen på baggrund af performancestatus, men at det på baggrund af det lave antal af patienter med PS2 i FIGHT-202 (n=5 (5 %)) ikke er muligt at vurdere effekten af pemigatinib for patienter med PS2 (se afsnit 5.1.3). Fagudvalget forventer dog, at behandling med pemigatinib hovedsageligt vil blive tilbudt patienter i god performancestatus, men at det ikke kan udelukkes, at enkelte patienter med PS2 vil være kandidater til behandling.

6.5 Begrænsning i datagrundlaget

Medicinrådet skønnede i protokollen, at datagrundlaget for vurderingen kunne være begrænset grundet den diagnostiske indikation med FGFR2-fusion og designet af det studie, der ligger til grund for EMAs vurdering af pemigatinib. Medicinrådet ønskede i protokollen derfor en opgørelse, som sammenlignede PFS- og ORR-data for den behandling, patienterne modtog i 1. linje umiddelbart inden pemigatinib, med behandlingen med pemigatinib. Medicinrådet ønskede også en opgørelse over varigheden af responset (*duration of response*).

Ansøger har leveret data for PFS i 1. linjebehandling med pemigatinib i FIGHT-202 baseret på et konferenceabstract præsenteret på ASCO 2020 af Bibeau et al. [18]. Ansøger har ikke leveret data for ORR ved 1. linjebehandling og heller ikke for varighed af respons. Varighed af respons i 2. linjebehandling med pemigatinib er rapporteret i

FIGHT-202-studiet [9] og beskrevet i det følgende. Ansøgers fulde svar er vedlagt som bilag 1.

PFS i 1. og 2. linjebehandling hos patienter med FGFR-2-fusion
Ud af de 107 patienter i kohorte A i FIGHT-202, som blev behandlet med pemigatinib, var der 65 patienter, der kun havde modtaget én tidligere linje af behandling. For disse patienter var median PFS i 2. linjebehandling med pemigatinib 7,03 måneder (95 % CI 4,9-11,1). Median PFS ved 1. linjebehandling med gemcitabin og cisplatin for samme patienter (n=69) var 5,7 måneder (95 % CI 4,6-9,1).

Der var derudover data for 39 patienter i kohorte A, der havde modtaget en anden 2. linjebehandling end pemigatinib (ikke oplyst hvilken). For disse patienter var median PFS 4,2 måneder (95 % CI 3,0-5,3).

Disse resultater indikerer, at PFS ved 2. linjebehandling med pemigatinib er længere end PFS med nuværende standardbehandling i 1. linje for samme patientgruppe og også længere end ved anden 2. linjebehandling end pemigatinib for denne patientgruppe.

Varighed af respons hos patienter med FGFR-2-fusion
For de 38 patienter, der havde opnået et respons (CR n=3, PR n= 35) af behandlingen ved første data-cut i april 2019, var median varighed af responset (DoR) 7,5 måneder (95 % CI 5,7-14,5). Ved data-cut i april 2020 havde 4 patienter (3,7 %) opnået komplet respons og 36 patienter (33,3 %) et partielt respons. I EPAR præsenteres også median varighed af respons (DoR) på 8,08 måneder (95 % CI: 5.65, 13.14), hvilket suppleres med en DoR ≥ 6 måneder hos 23 patienter, der responderede (57,5 %) og en DoR ≥ 12 måneder hos 10 patienter, der responderede. DoR er et udtryk for, hvor stor en procentdel af de patienter, som har et komplet eller partielt respons, der har et vedvarende respons efter henholdsvis 6 og 12 måneder.

Fagudvalgets konklusion:

Fagudvalget vurderer, at evidensen tyder på, at patienterne har væsentlig længere tid til sygdomsprogression ved behandling med pemigatinib end ved den behandling, de har modtaget umiddelbart inden. Der tages forbehold for, at der ikke er foretaget en statistisk sammenligning, og at estimaterne er forbundet med usikkerhed pga. det begrænsede datagrundlag.

7. Relation til behandlingsvejledning

Der findes ikke en relevant behandlingsvejledning.

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9. Sammensætning af fagudvalg og kontaktinformation til Medicinrådet

Medicinrådets fagudvalg vedrørende leverkræft

Forvaltningslovens § 3, stk. 2, har været anvendt i forbindelse med udpegning af medlemmer til dette fagudvalg.

Sammensætning af fagudvalg	
Formand	**Indstillet af**
Britta Weber *Afdelingslæge*	Lægevidenskabelige Selskaber
Medlemmer	**Udpeget af**
Kan ikke udpege en kandidat, der opfylder Medicinrådets habilitetskrav	Region Nordjylland
Gerda Elisabeth Villadsen *Overlæge, klinisk lektor*	Region Midtjylland
Merete Krogh *Overlæge*	Region Syddanmark
Lone Galmstrup Madsen *Overlæge*	Region Sjælland
Kirsten Kjeldgaard Vistisen *Overlæge*	Region Hovedstaden
Sidsel Marcussen *Klinisk farmaceut*	Dansk Selskab for Sygehusapoteksledelse
Niels Jessen *Professor, overlæge*	Dansk Selskab for Klinisk Farmakologi
Rozeta Abazi *Overlæge*	Dansk Selskab for Gastroenterologi og Hepatologi
Amy Daugaard Asmussen *Udviklingsansvarlig sygeplejerske, MHH*	Inviteret af formanden
Finn Ole Larsen *Overlæge*	Inviteret af formanden
Tóra Haraldsen Dahl *Patient/patientrepræsentant*	Danske Patienter
Marijanne Nord Madsen *Patient/patientrepræsentant*	Danske Patienter

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10. Versionslog

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

Medicinrådet

Application for the assessment of Pemazyre (pemigatinib) for the treatment of adults with locally advanced or metastatic cholangiocarcinoma with a fibroblast growth factor receptor 2 (FGFR2) fusion or rearrangement that have progressed after at least one prior line of systemic therapy

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

Contents

1. Basic information

Kontaktoplysninger	
Navn	**Fredrik Neij**
Titel	Nordic Director Market Access
Ansvarsområde	Reimbursement, pricing, health economics, negotiation
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Ansvarsområde	+45 51 59 05 24
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Overview of the pharmaceutical	
Proprietary name	Pemazyre
Generic name	Pemigatinib
Marketing authorization holder in Denmark	Incyte Biosciences Distribution B.V. Paasheuvelweg 25 1105 Amsterdam, Netherlands
ATC code	L01EX20
Pharmacotherapeutic group	Other protein kinase inhibitors
Active substance(s)	Pemigatinib
Pharmaceutical form(s)	Oral tablets
Mechanism of action	Pemigatinib is a potent and selective FGFR1, 2, and 3 inhibitor. Pemigatinib blocks autophosphorylation and activation of major FGF/FGFR signalling pathways, inhibiting the growth of cells with FGFR fusions/rearrangements.
Dosage regimen	4,5 mg/9 mg/13.5 mg (one tablet) once daily for two weeks, followed by one week with no treatment (treatment cycles of 21 days)

Overview of the pharmaceutical	
Therapeutic indication relevant for assessment (as defined by the European Medicines Agency, EMA)	Pemazyre monotherapy is indicated for the treatment of adults with locally advanced or metastatic cholangiocarcinoma with a fibroblast growth factor receptor 2 (FGFR2) fusion or rearrangement that have progressed after at least one prior line of systemic therapy.
Other approved therapeutic indications	n/a
Will dispensing be restricted to hospitals?	No
Combination therapy and/or co-medication	No
Packaging – types, sizes/number of units, and concentrations	4.5 mg x 14 tablets 9 mg x 14 tablets 13.5 mg x 14 tablets
Orphan drug designation	Yes (EMA number: EU/3/18/2066, August 24, 2018)

2. Abbrevations

Abbreviation / term	Definition
AE	Adverse event
AIC	Akaike information criterion
AIP	Pharmacy retail price
AS	Absolute shortfall
ASC	Active symptom control
BIC	Bayesian information criterion
BTC	Biliary tract cancer
CCA	Cholangiocarcinoma
CEAC	Cost-effectiveness acceptability curves
CEM	Cost-effectiveness model
CI	Confidence interval
CT	Computerised tomography
CUA	Cost-utility analysis
DSU	Decision Support Unit
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal growth factor receptor
EORTC-QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30
EQ-5D-3L	EuroQol 5-Dimensions 3-Levels
ESMO	European Society for Medical Onchology
FGFR	Fibroblast growth factor receptor
FU	Fluorouracil
HR	Hazard ratio
HRQoL	Health-related quality of life
iCCA	Intrahepatic cholangiocarcinoma
ICER	Incremental cost-effectiveness ratio
IPD	Individual patient-level data
IRC	Independent Review Committee
ITC	Indirect treatment comparison
KM	Kaplan-Meier
LY	Life year
MAIC	Matching Adjusted Indirect Comparison
mFOLFOX	Oxaliplatin, L-folinic acid and Fluorouracil with active symptom control
MO	Mobility
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
ORR	Objective response rate
OS	Overall survival
OWSA	One-way sensitivity analyses
PCR	Polymerase chain reaction
PD	Progressed disease
PF	Progression-free
PFS	Progression-free survival
PH	Proportional hazards
PPS	Post-progression survival
PRP	Pharmacy maximum sale price
PSA	Probabilistic sensitivity analyses
PSM	Parametric survival model
QALY	Quality-adjusted life year
RDI	Relative dose intensity
SD	Standard deviation
TA	Technology appraisal
TOT	Time on treatment
TSD	Technical support document
UA	Usual activities
VAT	Value added tax
WTP	Willingness-to-pay

3. Summary

Cholangiocarcinoma (CCA) is a rare malignancy with a poor prognosis. Survival for CCA has not improved in the last three decades and most patients with advanced CCA who go on to second-line treatment do not survive the next year. Current treatment options for patients who have progressed after first-line treatment are limited. For patients in good general condition and who have received a response to first-line treatment, a second trial of chemotherapy may be considered. However, there is no established standard treatment in second-line and current regimens are associated with toxicity, low response rates, rapid progression and a median overall survival (OS) of less than one year.

Fibroblast Growth Factor Receptor 2 (FGFR2) fusions and rearrangements are involved in the pathogenesis of CCA and are found almost exclusively in intrahepatic CCA (iCCA). The incidence of FGFR2 fusions or rearrangements varies in the existing literature but is estimated at 10-16% of patients with iCCA.

The majority of patients who progress after first-line treatment are rarely eligible for further chemotherapy. According to Swedish data on patients diagnosed with iCCA 2017-2019, only 31% of patients were planned to receive curative surgery, 33% were planned to receive medical antitumoral treatment but as many as 35% were planned for no antitumoral treatment. In second-line treatment, there are even more patients where best supportive care with active symptom control is the only option. Thus, the need for new treatment options for these patients is great.

Pemazyre (pemigatinib) is a selective, potent, oral inhibitor of FGFR1, 2 and 3 indicated for the treatment of patients with advanced or metastatic CCA with an FGFR2 fusion or rearrangement that has progressed after at least one line of previous systemic treatment. In the FIGHT-202 study, Pemazyre reported unmatched response rates with clinically meaningful and long-lasting responses in CCA patients. Side effects were manageable with a favourable safety and toxicity profile.

The number of patients who may be eligible for treatment with Pemazyre is small and an estimated 3-8 patients per year are estimated to meet the criteria for treatment. The company's forecasts estimate that 1-3 patients per year will receive treatment with Pemazyre.

As there is no established standard treatment in the second line of treatment guidelines, the cost analysis is based on a comparison between treatment with Pemazyre and active symptom control (ASC). In summary, the results suggest that Pemazyre has a significant clinical benefit in a group of selected patients who have a poor prognosis and for whom there are few effective treatment options. However, this advantage is associated with additional costs compared to available alternatives.

The results of the cost analysis are consistent with findings from the clinical trial. The base case showed that pemigatinib yielded higher life years when compared to ASC. The health gains associated with pemigatinib came with a higher lifetime cost compared to ASC where the primary cost driver was treatment duration.

In the base case analysis, the incremental cost was 1,019,108 DKK compared to ASC. A range of sensitivity analyses have been explored to test the impact of altering elements in the model structure. The analyses indicated that the results were most sensitive to changes in the parameters contributing to resource use in the pemigatinib arm as well as the choice of curve for extrapolating TOT for pemigatinib.

Pemazyre was approved in April 2020 in the United States and by the European Commission on March 29 2021.

4. Literature search

Please find the systematic literature review in the attached report “Clinical SLR in rrCCA.pdf”

4.1 Relevant studies

Table 1 Relevant studies included in the assessment.

Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)	Relevant for clinical question <x>*
Pemigatinib for previously treated, locally advanced or metastatic cholangiocarcinoma: a multicentre, open-label, phase 2 study. Abou-Alfa, GK et al. Lancet Oncol. 2020[1]	FIGHT-202	NCT02924376	Start: January 16, 2017 Estimated completion: June 11, 2021	1
Second-line FOLFOX chemotherapy versus active symptom control for advanced biliary tract cancer (ABC-06): a phase 3, open-label, randomised, controlled trial. Lamarca, A et al. Lancet Oncol. 2021[2]	ABC-06	NCT01926236	Start: February 2014 Completion: January 2019	1

*when multiple clinical questions are defined in the protocol

4.2 Main characteristics of included studies

Table A2 Main study characteristics FIGHT-202	
Trial name	FIGHT-202
NCT number	NCT02924376
Objective	Evaluate the Efficacy and Safety of Pemigatinib in Subjects With Advanced/Metastatic or Surgically Unresectable Cholangiocarcinoma Including FGFR2 Translocations Who Failed Previous Therapy
Publications – title, author, journal, year	Pemigatinib for previously treated, locally advanced or metastatic cholangiocarcinoma: a multicentre, open-label, phase 2 study. Abou-Alfa, GK et al. Lancet Oncol. 2020[1]
Study type and design	A Phase 2, Open-Label, Single-Arm, Multicenter Study Patients aged 18 years or older with disease progression following at least one previous treatment and an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2 recruited from 146 academic or community-based sites in the USA, Europe, the Middle East, and Asia were assigned to one of three cohorts: patients with FGFR2 fusions or rearrangements, patients with other FGF/FGFR alterations, or patients with no FGF/FGFR alterations. All enrolled patients received a starting dose of 13·5 mg oral pemigatinib once daily (21-day cycle; 2 weeks on, 1 week off) until disease progression, unacceptable toxicity, withdrawal of consent, or physician decision. The primary endpoint was the proportion of patients who achieved an objective response among those with FGFR2 fusions or rearrangements, assessed centrally in all patients who received at least one dose of pemigatinib
Follow-up time	Median follow-up = 17.8 months (IQR 11.6–21.3)

Table A2 Main study characteristics
FIGHT-202

Population (inclusion and exclusion criteria)	• Histologically or cytologically confirmed cholangiocarcinoma. • Radiographically measurable or evaluable disease per RECIST v1.1. • Tumor assessment for FGF/FGFR gene alteration status. • Documented disease progression after at least 1 line of prior systemic therapy. • Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2. • Life expectancy ≥ 12 weeks.
Intervention	All enrolled patients (Total n=146, Cohort A, n = 107; Cohort B, n =20; Cohort C, n =18) received a starting dose of 13.5 mg oral pemigatinib once daily (21-day cycle; 2 weeks on, 1 week off)

Baseline characteristics

	FGFR2 fusions or rearrangements (n=107), Cohort A
Age, median (range), years	56 (26 to 77)
<65	82 (77%)
65 to <75	20 (19%)
≥75	5 (5%)
Sex	
Male	42 (39%)
Female	65 (61%)
Region	
North America	64 (60%)
Western Europe	32 (30%)
Rest of world†	11 (10%)
Race	
White	79 (74%)
Asian	11 (10%)
Black or African American	7 (7%)
American Indian or Alaska Native	0
Other or data missing	10 (9%)
ECOG performance status	
0	45 (42%)
1	57 (53%)
2	5 (5%)
Metastatic disease	
Yes	88 (82%)
No	16 (15%)
Missing or not evaluable	3 (3%)
Number of previous systemic therapies for advanced mtetastatic disease‡	
1	65 (61%)
2	29 (27%)
≥3	0,13 (12%)
Previous cancer surgery	38 (36%)
Previous radiotherapy	28 (26%)
Cholangiocarcinoma location◊	
Intrahepatic	105 (98%)
Extrahepatic	1 (1%)
Other or data missing	1 (1%)
History of hepatitis	
Hepatitis B	4 (4%)
Hepatitis C	1 (1%)
Sites of disease	
Liver	101 (94%)
Lymph nodes	57 (53%)
Lung	58 (54%)
Bone	21 (20%)
Ascites	8 (7%)
Pancreas	7 (7%)
Pleural effusion	4 (4%)
Skin or subcutaneous tissue	2 (2%)
Bladder	0
Colon	1 (1%)
Other	31 (29%)

Table A2 Main study characteristics
FIGHT-202

Primary and secondary endpoints	The primary endpoint of this study was to determine the overall response rate (ORR) of Pemazyre in subjects with FGFR2 rearrangements or fusions based on the central genomics laboratory results who had progressed on at least 1 previous treatment (Cohort A). ORR was defined as the proportion of subjects who achieved a CR; disappearance of all target lesions) or a partial response (PR; ≥30% decrease in the sum of the longest diameters of target lesions) based on RECIST version 1.1. Clinical response was determined by an independent radiological review committee (IRC). Secondary endpoints were ORR in subjects with FGF/FGFR alterations other than FGFR2 translocations (Cohort B), ORR in all subjects with FGF/FGFR alterations (Cohorts A and B), ORR in subjects negative for FGF/FGFR alterations (Cohort C [US only]), progression free survival (PFS, first dose to progressive disease (PD) or death; all cohorts), duration of response (DOR, time from the date of CR or PR until PD; all cohorts), disease control rate (DCR, CR+PR + SD; all cohorts), overall survival (OS, first dose to death of any cause; all cohorts), population pharmacokinetics (all cohorts). Safety and tolerability was assessed by evaluating the frequency, duration and severity of AEs; through a review of findings of physical examinations, changes in vital signs and electrocardiograms; and through clinical laboratory blood and urine sample evaluations (all cohorts), The exploratory endpoints of the study were profiling of tumor and blood samples for baseline and on-treatment characteristics associated with response, resistance and safety. This included examination of plasma markers and tumor and blood cell characteristics. Comparison of local genomic testing results versus central genomic testing results. QoL evaluations utilizing the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 and EORTC QLQ-BIL21 questionnaires. EORTC QLQ-BIL21 were only administered to subjects enrolled in the US, UK, Italy, Germany and Korea. Patient reported QoL outcomes were assessed to provide an important understanding of the patients' perspective and treatment experience.
Method of analysis	Efficacy was assessed in all patients with centrally confirmed FGF/FGFR status who received at least one dose of pemigatinib. The safety population included all patients who received at least one dose of pemigatinib. A futility analysis was planned for when approximately 25 patients with FGFR2 fusions or rearrangements had enrolled and had at least one post-baseline tumour assessment or had permanently discontinued treatment. Enrolment in this cohort could have been stopped if two or fewer of the 25 patients enrolled had achieved a response, for which there was a less than 10% probability of the proportion of patients with an objective response being greater than 15% based on a 60-patient cohort. Although the trial was initially designed to enroll 60 patients with FGFR2 fusions or rearrangements, a protocol amendment was later approved (Oct 3, 2017) that allowed enrolment in this cohort to be increased to approximately 100 patients. This sample size was estimated based on the current treatment landscape of cholangiocarcinoma, to ensure an adequate population for safety assessments and robust response data. A sensitivity analysis of the proportion of patients with FGFR2 fusions or rearrangements who achieved an objective response was done based on the first 60 patients enrolled as per the original protocol, and on the additional patients enrolled after the protocol amendment to increase the sample size. With an assumed proportion of patients with an objective response of 33%, a sample size of 100 patients was estimated to provide a greater than 95% probability of having a 95% CI with a lower limit of 15%. 15% was considered the minimum clinically meaningful proportion of patients with an objective response, based on proportions of patients with an objective response reportedby previous studies of patients with cholangiocarcinoma. In patients with other FGF/FGFR alterations or no FGF/FGFR alterations, up to 20 patients were planned to be enrolled to provide a greater than 80% probability of observing at least four responders in each cohort if the underlying proportion of patients with an

Table A2 Main study characteristics FIGHT-202	
	objective response was 30%. The study was not designed to make statistical comparisons between cohorts. For the primary endpoint, patients with insufficient baseline or on-study disease assessment data were considered non-responders and were included in the denominators for the calculation of the proportion of patients with an objective response. No formal hypothesis testing or inferential analyses were done. The 95% Cis for effect sizes were estimated using the Clopper-Pearson method. Exploratory subgroup analyses of the proportion of patients with an objective response and progression-free survival were done for patients with FGFR2 fusions or rearrangements to assess the consistency of the pemigatinib treatment effect on the basis of predefined demographic and disease characteristics. Exploratory (post-hoc) pharmacodynamics analyses were also done to assess the associations between exposure and changes in serum phosphate from baseline, and between changes in serum phosphate from baseline and the proportion of patients with an objective response.
Subgroup analyses	Exploratory subgroup analyses of the proportion of patients with an objective response and progression-free survival were done for patients with FGFR2 fusions or rearrangements to assess the consistency of the pemigatinib treatment effect on the basis of predefined demographic and disease characteristics. Stratification was done for age, sex, race, region, ECOG status, metastatic disease, lines of prior therapy and FGFR2 rearrangement partner.

Table A2 Main study characteristics ABC-06	
Trial name	ABC-06
NCT number	NCT01926236
Objective	To determine if patients with ABC (Advanced Biliary tract Cancers) benefit with respect to survival from the addition of mFOLFOX chemotherapy to ASC (Active Symptom Care) in the second-line setting after progression to first-line treatment with CisGem. This study will establish the standard of care for patients with ABC who have progressed on first line CisGem chemotherapy.
Publications – title, author, journal, year	Lamarca A et al. Lancet Oncol. 2021[2]
Study type and design	A phase 3, open-label, randomized controlled study from 20 sites in the UK Patients were eligible if they were aged 18 years or older and had histologically or cytologically verified locally advanced or metastatic biliary tract cancer (including cholangiocarcinoma, gallbladder carcinoma, and ampullary carcinoma) with documented radiological disease progression to previous first-line cisplatin and gemcitabine chemotherapy. Any other form of first-line systemic chemotherapy or additional line of first-line chemotherapy (including rechallenge with cisplatin and gemcitabine) was not allowed. Patients who had been started on firstline cisplatin and gemcitabine for whom the cisplatin was stopped due to toxicity (with continuation of gemcitabine) were eligible.
Follow-up time	Median follow-up = 21.7 months (IQR 17.2–30.8)

Table A2 Main study characteristics
ABC-06

Intervention

162 patients were randomly assigned (1:1) to ASC plus FOLFOX or ASC alone.

- Biliary drainage, antibiotics, analgesia, steroids, antiemetics,
- Other palliative treatment for symptom control, palliative radiotherapy (eg, for painful bone metastases)
- Transfusion of blood products

FOLFOX chemotherapy:

Every 2 weeks for a maximum of 12 cycles: Treatment took place over 2 days:

- Oxaliplatin 85 mg/m²
- L-folinic acid 175 mg (or folinic acid 350 mg; 2-h intravenous infusion concurrently with oxaliplatin infusion)
- Fluorouracil 400 mg/m² (5–10 min bolus) completed on day 1, and fluorouracil 2400 mg/m² as continuous intravenous infusion starting on day 1 and finishing on day 2

Baseline characteristics

		ASC	ASC + FOLFOX
Basal characteristics	Female	44 (54%)	38 (47%)
	Male	37 (46%)	43 (53%)
	Age (range)	65 (26-81)	65 (26-84)
	Platinum r/r	47 (58%)	54 (67%)
	Platinum sensitive	34 (42%)	27 (33%)
Disease stage	Locally advanced	15 (19%)	14 (17%)
	Metastatic	66 (81%)	67 (83%)
Tumour site	Intrahepatic	38 (47%)	34 (42%)
	Extrahepatic	19 (23%)	26 (32%)
	Gallbladder	17 (21%)	17 (21%)
	Ampulla	7 (9%)	4 (5%)
Histology	Adenocarcinoma	74 (91%)	73 (90%)
	Others	7 (9%)	8 (10%)
ECOG performance status	0	28 (35%)	25 (31%)
	1	52 (64%)	55 (68%)

Primary and secondary endpoints

Primary outcome: Overall survival

Secondary outcome: Progression-free survival, response rate, toxicity, quality of life, costs of health and social care, health status, quality adjusted life years (QALYs)

Method of analysis

The study was powered to show a benefit in overall survival with the addition of FOLFOX to ASC in the intention-to-treat population. 148 death events were required for a hypothesised hazard ratio (HR) of 0·63 with 80% power and 5% two-sided α; since minimal (<3%) loss to follow-up was envisaged, the required sample size was 162 patients. At the time of the study design, the assumed 12-month overall survival rate for patients assigned to ASC alone was 10% (derived from the 24-month overall survival rate from the cisplatin and gemcitabine group in the ABC-02 study,2 given that the first 12 months were taken up with first-line effect), and the median overall survival was assumed to be 4 months (derived from the difference between overall survival [12 months] and progression-free survival [8 months] in the ABC-02 study2). The hypothesised HR was equivalent to an increase in median overall survival from 4 months to 6·4 months.

Table A2 Main study characteristics ABC-06	
	The study was expected to recruit across 20 centres and recruitment was expected to be completed in 28 months (from February, 2014, to August, 2016). Because of slower than anticipated recruitment, the study period was extended to allow the required sample size to be reached (protocol version 6.0; July 26, 2017). From the start of recruitment to final analysis of the findings, eight protocol amendments were submitted and approved (appendix p 2). None of these amendments affected the sample size or primary or secondary endpoints. The final study protocol (version 7.0) is available in the appendix. Analysis of the primary endpoint (overall survival) was done with multivariable Cox regression adjusted for the stratification factors (platinum sensitivity, serum albumin concentration, and disease stage); HRs for each stratification factor are also provided, adjusted by the other stratification factors and treatment group. Proportional hazard assumptions were assessed with plots of Schoenfeld residuals and one-step tests on trend. No interim analysis of the primary endpoint was planned. Median overall survival, progression-free survival, and survival rates at 3 months (progression-free survival) and at 6 and 12 months (both progression-free survival and overall survival) were derived from Kaplan-Meier estimates. Surviving patients were censored at their time of last follow-up. Radiological response data were summarised by best recorded response, complete response, partial response, stable disease, progressive disease, or death. Efficacy and safety analyses were done in the intention-to-treat population. Prespecified subgroup analyses by stratification factors for overall survival and progression-free survival were done, together with post-hoc subgroup analyses by primary tumour site and ECOG performance status. A post-hoc sensitivity analysis for overall survival using the stratification categories provided by local investigators at the time of randomisation was also done. Two-sided p<0·05 was considered significant.
Subgroup analyses	Subgroup analyses was done for overall survival stratified by platinum sensitivity, albumin levels, disease stage, primary tumour site and ECOG performance status

5. Clinical questions

5.1 Hvilken værdi har pemigatinib sammenlignet med best supportive care

Hvilken værdi har pemigatinib sammenlignet med best supportive care for patienter med lokalavanceret eller metastatisk CCA med en fibroblast growth factor receptor 2 (FGFR2)-fusion eller andet rearrangement, som har haft tilbagefald af sygdom eller udviser refraktær sygdom efter mindst én linje systemisk behandling?

5.1.1 Population

Patienter med lokalavanceret eller metastatisk CCA med en FGFR2-fusion eller andet rearrangement, som enten har haft tilbagefald af sygdom eller udviser refraktær sygdom efter mindst én linje systemisk behandling, og som har en ECOG-performance status ≤ 2 og tilstrækkelig lever- og nyrefunktion (se afsnit 2.3).

5.1.2 Intervention

Pemigatinib administreres i cyklusser af 13,5 mg per oral tablet én gang dagligt i 14 dage, efterfulgt af 7 dages pause.

5.1.3 Komparator

Best supportive care.

5.1.4 Presentation of relevant studies

Table A3a Results of study FIGHT-202

Trial name:	*FIGHT-202*										
NCT number:	NCT02924376										
				Estimated absolute difference in effect			**Estimated relative difference in effect**			**Description of methods used for estimation**	**References**
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Median survival (months)	Cohort A	107	21.1 (14.8–not estimable)								Abou-Alfa et al[1]
Survival rate after 6 months	Cohort A	107	89%								Abou-Alfa et al[1]
Median progression free survival (PFS, months)	Cohort A	107	6.9 (6.2–9.6)								Abou-Alfa et al[1]
Proportion of patients, which achieves objective response	Cohort A	107	35.5% (26.50–45.35)								Abou-Alfa et al[1]
EORTC QLQ-C30	Cohort A	107									
Proportion of patients with grade 3-4 adverse events	Cohort A	107	64%								Abou-Alfa et al[1]

Table A3a Results of study ABC-06

Trial name:	*ABC-06*										
NCT number:	NCT01926236										
				Estimated absolute difference in effect			**Estimated relative difference in effect**			**Description of methods used for estimation**	**References**
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Median survival (months)	ASC	81	5.3 (4.1–5.8)								Lamarca et al[2]
Survival rate after 6 months	ASC	81	35.5%								Lamarca et al[2]
Median progression free survival (PFS, months)	ASC	81	n/a								
Proportion of patients, which achieves objective response	ASC	81	n/a								
EORTC QLQ-C30	ASC	81									
Proportion of patients with grade 3-4 adverse events	ASC	81	n/a								

5.2 Comparative analyses: Matched-adjusted indirect comparison

5.2.1 Feasibility assessment

In the absence of randomised controlled trials comparing the efficacy of pemigatinib directly to the standard of care, an indirect treatment comparison (ITC) is warranted to provide relative treatment effect evidence. Sources of information for the efficacy of the current standard of care were identified using literature identified through a rapid review and a clinical systematic literature review.

Data from the ABC-06 trial and individual trials from a systematic review and meta-analysis (Lamarca et al. 2014) were found as potential evidence for an ITC.[3, 4] A historical treatment comparison within FIGHT-202 was considered unfeasible due to a lack of overall survival (OS) and progression-free survival (PFS) (time to progression [TTP] only) data.

The validity of the ITCs relies on whether there are systematic differences between intervention and comparator study populations regarding baseline or disease characteristics that are treatment effect modifiers. The choice of trials for inclusion in the matching-adjusted indirect treatment comparison (MAIC) was based on the following criteria:

- Availability of Kaplan–Meier (KM) plots for OS and PFS (must have both)
- Minimum sample size (n ≥20)
- Eastern Cooperative Oncology Group (ECOG) 0–1 close to 100% – this is due to the high percentage in FIGHT-202 and matching being difficult on this variable (must be 80% ECOG 0–1)
- Intrahepatic CCA% as high as possible – as above, FIGHT-202 is 98% for this variable and thus will be difficult (impossible) to match on
- The treatment used is representative of the standard of care (SOC)

Out of the 22 studies in the Lamarca review, seven presented a KM plot for both OS and PFS. The baseline characteristics of these studies are presented in Table 1.

Table 1: Baseline characteristics

Study	FIGHT-202	ABC-06	ABC-06	Suzuki 2013	Lim 2012	Chiorean 2012	Yi 2012	Kobayashi 2012	Croitoru 2012	Walter 2013
Patients, N	107	81	81	41	50	25	56	55	46 with 2L	96
Treatment	Pemigatinib	ASC	ASC + mFOLFOX+ASC	S-1	iFAM	Erlotinib and docetaxel	Sunitinib	S-1	5-FU-based, Gem-based	Gem + 5-FU
FGFR2+, N	107	NR	NR	NR	NR	NR	NR	NR	NR	NR
Median age, years (range)	56 (26–77)	65 (26–81)	65 (26–84)	67 (35–78)	57 (26–72)	64 (41–76)	55 (38–75)	69 (39–81)	N/A	57 (23–79)
Men, %	39	46	53	65	66	60	66	57	N/A	46
Intrahepatic CCA, N (%)	105 (98)	38 (47)	34 (42)	10 (24)	15 (30)	NR	35 (63)	15 (27)	N/A	31 (32)
ECOG PS 0–1, %	95	100	100	95	64	NR	93	98	N/A	NR

Key: 2L, second line; ASC, active symptom control; CCA, cholangiocarcinoma; ECOG PS, Eastern Cooperative Oncology Group performance status; FGFR2+, fibroblast growth factor receptor 2-positive; FU, fluorouracil; iFAM, infusional 5-fluorouracil, doxorubicin and mitomycin-C; mFOLFOX+ASC, oxaliplatin, L-folinic acid and fluorouracil; NR, not reported

The two arms in ABC-06, Suzuki 2013 and Lim 2012 were used in the analysis due the availability of KM curves for digitization being available, the arms in the study being considered more representative of established SOC and the availability of baseline characteristics considered for matching. Of the clinical trials identified via the pragmatic review, four (Suzuki et al. 2013, Lim et al. 2012, Yi et al. 2012 and Chiorean et al. 2012) contained KM curves for digitization, and the remaining Lamarca study was excluded. Notably, patients in ABC-06, Suzuki 2013 and Lim 2012 were assigned to FOLFOX, S-1 (tegafur, gimeracil and oteracil) chemotherapy and iFAM (infusional 5-fluorouracil, doxorubicin and mitomycin-C) chemotherapy, respectively, while Yi 2012 investigated the second-line use of sunitinib (a newer therapy, not considered standard care). Chiorean was excluded due to not reporting mean intrahepatic CCA or ECOG to be used in matching.

5.2.2 Estimation of MAIC weights

To make an adjusted comparison between pemigatinib and the comparative evidence source(s), individual pemigatinib-treated patients were assigned statistical weights that adjust for their over- or underrepresentation relative to that observed in each comparative evidence source. After weighting, average baseline characteristics were balanced for the pemigatinib-treated patients and the comparative evidence source.

Weights were be derived using a MAIC, a form of propensity score weighting.[5] The propensity score logistic regression model estimates the odds of being enrolled in the pemigatinib trial or the comparative evidence source. A method of moments is utilized to allow a propensity score logistic regression model to be estimated without individual patient data (IPD) for the comparative evidence source. The model will be estimated based on IPD available for the pemigatinib-treated patients and the published summary data available for the comparative evidence sources.

Following the estimation of weights, it is necessary to explore their distribution. Rescaled weights (specified in Equation 1) will be explored via the use of histograms to determine whether the specific patient(s) or groups of patients (based on covariate values) are over- or underrepresented in the analysis. The use of scaled weights aids interpretation; a scaled weight > 1 implies that an individual carries more weight in the re-weighted sample than in the original sample, while a scaled weight < 1 implies that an individual carries less weight.

Equation 1: Calculation of rescaled weights

$$Rescaled\ weight_i = \frac{weight_i}{\sum_{i=1}^{n} weight_i} \times N$$

The robustness of the analyses will also be considered by approximating the effective sample size (ESS). For a weighted estimate, the ESS is the number of independent non-weighted individuals that would be required to provide an estimate with the same precision as the weighted sample estimate.[6] The calculation of the ESS approximation is specified in Equation 2. A small ESS is an indication that the weights are highly variable due to a lack of population overlap, and that the estimate may be unstable.

Equation 2: Calculation of the effective sample size[5]

$$Effective\ sample\ size\ (ESS) = \frac{\left(\sum_{i=1}^{n} weight_i\right)^2}{\sum_{i=1}^{n} weight_i^2}$$

[redacted]

5.3 Results per PICO (clinical question)

Table A4 Results referring to <clinical question x>								
Results per outcome:	*Attach forest plots and statistical results as a separate file.* *Results from the comparative analysis should be given in the table below, if possible.*							
		Absolute difference in effect			**Relative difference in effect**			**Methods used for quantitative synthesis**
	Studies included in the analysis	**Difference**	**CI**	***P* value**	**Difference**	**CI**	***P* value**	
Median survival (months)	FIGHT-202, Cohort A v.s. ABC-06, ASC	21.1 months v.s. 5.3 months	NA	NA	HR: 0.163	0.0099–0.249		
Survival rate after 6 months	FIGHT-202, Cohort A v.s. ABC-06, ASC	89% v.s. 35.5%	NA	NA	NA			
Median progression free survival (PFS, months)	FIGHT-202, Cohort A v.s. ABC-06, ASC	6.9 v.s. n/a	NA	NA	NA			

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Table A4 Results referring to <clinical question x>				
Proportion of patients, which achieves objective response	FIGHT-202, Cohort A v.s. ABC-06, ASC	35.5% v.s. n/a		
EORTC QLQ-C30	FIGHT-202, Cohort A v.s. ABC-06, ASC			
Proportion of patients with grade 3-4 adverse events	FIGHT-202, Cohort A v.s. ABC-06, ASC	64% v.s. n/a		

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7. Appendices A Addressing Medicinrådets "other considerations"

In "Medicinrådets protokol for vurdering vedrørende pemigatinib til behandling af lokalavanceret eller metastatisk cholangiokarcinom" a number of considerations are listed. We attemt to respond to these considerations here.

7.1 Consideration 1

Medicinrådet ønsker, at ansøger gør rede for, hvilken metode man anvender ved test for FGFR2-fusion, og om den stemmer overens med metoden i det kliniske studie. Endvidere ønsker Medicinrådet, at ansøger gør rede for omkostningerne ved en test og kommer med et estimat for antallet af patienter, der skal testes, for at finde én patient med FGFR2-fusionen. Medicinrådet ønsker, at ansøger redegør for disse forhold, idet omkostninger til implementering af lægemidlet skal indgå som del af den sundhedsøkonomiske analyse.

7.1.1 Incyte response

CCA is treated at Herlev Hospital, Odense University Hospital and Aarhus University Hospital, Skejby. Comments below are from local experts working at each of these hospitals.

According to local lab expert at Herlev Hospital, the Foundation Medicine (FMI) uses Illumina, which initially was very different from other analysis in this area. This has however now changed. At Herlev Hospital they are in the process of implementing the Archer DX panel which is equally qualified in finding FGFR alterations as the analyses performed by FMI in relation to Study INCB 54828-202

At Odense University Hospital the PreCode protocol is currently enrolling cancer patients for which no other treatment is available, according to local CCA treating physician this panel including 500 genes will most likely be used for CCA patients beyond 1 line. As an alternative samples can be shipped for analysis at either Aarhus or Herlev (when Archer DX is made available)).

At Aarhus University Hospital, Skejby at MOMA (Molekylærmedicinsk Afdeling/ Kræftafdelingen) tissue and blood samples are analysed using Whole Exome Sequencing (and shortly Whole Genome Sequencing) detecting mutations and RNA fusions. The method is not tested against FoundationOne/FMI and as FMI don't make their pipeline public the bioinformatics and molecular biology tools are unknown. When benchmarking against commercially available tests the analysis done at MOMA scores high. Pathologists have the option to use the Archer RNA fusion panel when requested by treating physician. It is being considered to initiate NGS for CCA patients earlier on through OPRA. This according to a physician at MOMA and a CCA treating physician.

Since FGFR2 testing is not part of standard clinical practice in Denmark, a cost for FGFR2 testing may need to be realised within the cost-effectiveness model for patients in the intervention arm. This cost is only applied to the intervention arm because, in current clinical practice, patients would not need to be tested for FGFR2 fusions or rearrangements before receiving current standard of care. Additionally, since not everyone tested would be positive for FGFR2 translocations, more than one person may need to be tested to treat one person with pemigatinib. To calculate the number of patients that must be tested before one pemigatinib-eligible patient is identified, an FGFR2+ translocation frequency of 8.6% was used.[7] This results in approximately twelve tests being conducted per patient treated with pemigatinib. The total cost per test used in the model is 14,972.00 DKK.

7.2 Consideration 2

Medicinrådet ønsker, at ansøger gør rede for eventuelle dosisreduktioner ved behandling med pemigatinib.

7.2.1 Incyte response

All participants enrolled in Study INCB 54828-202 received pemigatinib 13.5 mg QD on a 2 weeks-on/1-week-off schedule.

[redacted]

[redacted] Taken together, efficacy and exposure-response data from Study INCB 54828-202 support 13.5 mg as the optimal starting dose in FGFR2-rearranged cholangiocarcinoma.

7.3 Consideration 3

Medicinrådet ønsker, at ansøger beskriver, hvorvidt CCA-patienter med FGFR2-fusion har en bedre prognose end CCA-patienter uden FGFR2-fusion og redegør for den eventuelle betydning af dette for de forskellige effektmål [16]. Herunder skal ansøger redegøre for fordelingen af patienter med og uden FGFR2-fusion i litteraturen, som beskriver effekten af komparator.

7.3.1 Incyte response

7.3.1.1 The Role of FGFR2

FGFR2 alterations have been highlighted as actionable molecular alterations in cholangiocarcinoma[8, 9]. In the United State and Europe, FGFR2 fusions have been observed in 10% to 16% of patients and almost exclusively within intrahepatic cholangiocarcinoma[9-11]. Comprehensive genomic profiling identified FGFR2 genomic alterations in 11% of 3634 cholangiocarcinoma patients using the FoundationOne assay, with 85% of those alterations being fusions[12] and in 14% of 195 cholangiocarcinoma patients using the MSK-IMPACT platform[13]. The differences seen in this study for some of the genomic alterations highlight the importance of early molecular profiling in disease course to ensure the best-guided decisions in therapy selection to patients with advanced iliary cancers.

The natural history of cholangiocarcinoma with FGFR alterations and the prognostic role of FGFR alterations are not fully characterized. There are no prospective data on prognostic and predictive impact of those alterations but several retrospective studies have evaluated this important question. Retrospective studies have shown that FGFR alterations (predominantly FGFR2 rearrangements or fusions), contrary to the general cholangiocarcinoma population, occur more frequently in younger women and seem to confer more indolent disease[9, 14], although its predictive role to standard chemotherapy regimens is not known. Furthermore, the role played by FGFR2 fusions as compared to either other FGFR alteration or wild type patients on the endpoint of survival is not well-characterized.

A retrospective analysis assessed 377 patients with cholangiocarcinoma by next-generation sequencing or fluorescence in situ hybridization (Jain et al 2018). Ninety-five subjects had FGFR alterations, where FGFR2 fusions were the most frequent alteration (N = 63 FGFR2 fusions, 11 with other FGFR2 alterations). Consistent with previous retrospective studies[9, 14], FGFR alterations occurred more frequently in intrahepatic cholangiocarcinoma versus extrahepatic cholangiocarcinoma. These patients tended to be younger females who presented at an earlier stage (TNM I/II vs III/IV 35.8% vs 22%, respectively) and were associated with longer survival compared with patients without FGFR alterations (median OS from date of diagnosis until death 37 vs 20 months, respectively; $p < 0.001$). This difference remained significant after excluding 36 patients treated with FGFR inhibitors (30 vs 20 months, respectively; $p < 0.003$). Patients with any FGFR alteration had a better OS with FGFR-targeted therapy (44.8 months) than those who did not receive FGFR-targeted therapy (24.3 months; $p = 0.01$). The PFS data were available only in a subset of patients (n = 177) who received first-line chemotherapy for systemic disease. Progression-free survival with first-line chemotherapy showed no statistically significant difference between the FGFR genetically altered and FGFR wild-type subgroups (33.9 vs 24.5 weeks; $p = 0.074$). One of the limitations of this study is that despite separating out patients with specific FGFR2 fusions, the survival data was calculated via all lines of therapy, which may indicate an enhanced survival only among patients in the earlier course of disease. Many of the early stage patients (43%) had been resected and received adjuvant therapy which may have conferred extended survival due to the curative intent of these procedures.

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There are no adequately powered, controlled studies on the role that a FGFR2 abnormality plays in overall survival in FGFR2-altered cholangiocarcinoma patients, or in 1L PFS or 2L PFS to definitively conclude that those with an FGFR2 fusion or rearrangement have better prognosis. However, multiple papers which are limited by sample size seem to yield results which trend toward a prognostic role played by those with FGFR abnormalities. Despite the lack of statistically significant conclusions that can be drawn individually, data suggest that FGFR2 fusions/rearrangement provide some degree of positive prognostic value, though magnitude is questionable and may be clinically irrelevant. While the totality of the evidence is suggestive of some degree of positive prognosis for these patients compared to their wild type counterparts, literature published from retrospective studies is limited to small samples sizes, imperfect definitions of survival, and lack of balance between groups, while attempts at analyzing these relationships from clinical trials is limited by selection bias inherent in inclusion criteria which limits the generalization to all patients with CCA, with or without FGFR altered disease.

Because of the rarity of cholangiocarcinoma, and furthermore the small proportion of cholangiocarcinoma patients with FGFR2 fusions or rearrangements, the directionality of the prognostic factor may be implied based on a number

of studies showing similar trends, despite statistical power often lacking. As previously described, some papers may conflate the likelihood of patients with FGFR2 driven disease being younger with evidence that the genomic alteration itself is truly prognostic. Nevertheless, studies highlighting the differences in OS or in PFS from 1L indicate that the role of a driving FGFR2 fusion or rearrangement may confer some extended surv]ival. It remains unclear if the role FGFR2 plays in the prognosis of the patient is constant, or if it changes throughout the course of the disease journey.

There appears to be no scientific controversy that patients with FGFR2 altered disease are afforded additional survival with the exposure to FGFR-targeted therapy [8]. This is further confirmed with the results of the pemigatinib trial, with an ORR of 36% [redacted] In patients with an advanced illness like intrahepatic cholangiocarcinoma, it is completely unexpected that patients would have any tumor reduction, and would likely progress much faster than was seen in the trial. Despite lack of a comparator arm in the trial, it is understood that these patients are benefiting from the targeted therapy afforded them.

7.4 Consideration 4

Medicinrådet ønsker, at ansøger redegør for behandling af patienter med PS2.

7.4.1 Incyte response

[redacted]

7.5 Consideration 5

Medicinrådet skønner, at datagrundlaget for vurderingen kan være begrænset grundet den diagnostiske indikation med FGFR2 fusion og designet af det studie, der ligger til grund for EMAs vurdering af pemigatinib. Medicinrådet ønsker en opgørelse, som sammenligner PFS og ORR-data for den behandling, patienterne modtog i første linje umiddelbart inden pemigatinib, med behandlingen med pemigatinib.

7.5.1 Incyte response

In the work by Bibeau and colleagues [15], the following is presented:

A total of 66 patients enrolled in FIGHT-202 (Study INCB 54828-202) had complete data on prior second line systemic treatment for advanced/metastatic CCA; of these, 39 were enrolled in cohort A

- Among CCA patients with FGFR2 fusions/rearrangements, median PFS on prior second-line systemic therapy was 4.2 (95% confidence interval [CI], 3.0–5.3) months

  – Among the 65 patients enrolled in cohort A who had only 1 line of prior therapy, median PFS on pemigatinib as second-line therapy in FIGHT-202 was 7.0 (95% CI, 4.9–11.1) months

PFS on prior first-line therapy for patients in cohort A was comparable with the reported literature in an unselected population

- PFS on prior second-line therapy is numerically shorter than PFS in patients treated with pemigatinib second-line in the FIGHT-202 trial

Table 2 PFS by line of treatment

	Cohort A (n = 107) FGFR2 Fusions/Rearrangements	Chohort B (n = 20) Other FGF/FGFR Genetic Alterations	Cohort C (n = 18) No FGF/FGFR Genetic Alterations
Prior first-line therapy			
1L gemcitabine + cisplatin, n	69	12	13
Median PFS (95% CI), mo	5.7 (4.6–9.1)	3.9 (1.6–6.4)	2.8 (1.6–17.7)
1L NOT gemcitabine + cisplatin, n	33	7	3
Median PFS (95% CI), mo	4.1 (2.3–6.5)	7.4 (3.1–14.0)	5.1 (1.3–5.5)
Prior second-line therapy			
Evaluable patients, n	39	8	6
Median PFS (95% CI), mo	4.2 (3.0–5.3)	3.0 (1.1–9.9)	5.9 (2.4–12.5)

Table 3 PFS prior second line treatment compared to PFS following pemigatinib as second-line treatment

	Pre-FIGHT-202 Enrolment Prior Second-line Systemic Cancer Therapy (n = 39)	Enrolled in FIGHT-202 Pemigatinib as Second-Line Cancer Therapy (n = 65)
Age, median (range), years	51.5 (27–76)	54.7 (25–75)
Sex, n (%)	13 (33)	26 (40)
Men	26 (67)	39 (60)
Women		
Region, n (%)		
North America	23 (59)	39 (60)

Western Europe	14 (36)	17 (26)
Rest of World	2 (5)	9 (14)
ECOG PS, n (%)		
0	17 (44)	27 (42)
1	21 (24)	37 (57)
2	1 (3)	1 (2)
Prior cancer surgery, n (%)	21 (54)	16 (25)
Prior radiation, n (%)	13 (33)	11 (17)
CCA location, n (%)		
Intrahepatic	38 (97)	64 (98)
Extrahepatic	0	1 (2)
Other/Missing	1 (3)	0
Median PFS, (95% CI), months	4.2 (3.0–5.3)	7.0 (4.9–11.1)

In conclusion:

- PFS following first-line therapy in patients enrolled in FIGHT-202 is consistent with previously published results
- There is little information regarding the treatment outcome of patients with CCA harboring *FGFR2* fusions or rearrangements in the second-line metastatic setting
- Among patients enrolled in the FIGHT-202 trial, 39 patients with *FGFR2* fusions or rearrangements had received at least 2 prior lines of therapy before enrolling in the trial. On prior second-line systemic therapy for advanced/metastatic CCA, the median PFS was 4.2 (95% CI, 3.0-5.3) months
- Among patients who received pemigatinib as their second-line therapy in the trial setting, a median PFS of 7.0 (95% CI, 4.9-11.1) months was observed, suggesting that second-line treatment with pemigatinib results in a numerically longer PFS than second-line treatment before pemigatinib
- Further research is warranted in the real-world setting to characterize the second-line treatment outcomes of patients with *FGFR2* alterations outside of a clinical trial

[redacted]

[redacted]

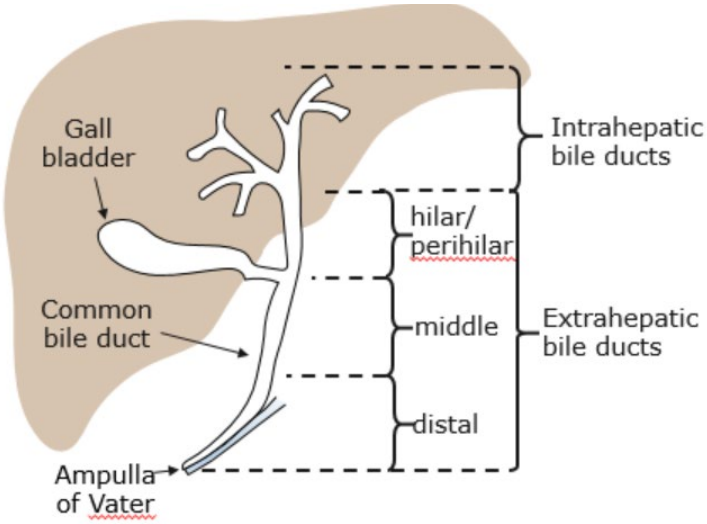
9. Appendix C: Disease background, patient population and the intervention

9.1 The medical condition and patient population

9.1.1 CCA description, etiology and classification

CCA comprise a group of cancers with different anatomical locations and pronounced inter-tumoral and intra-tumoral heterogeneity. CCA is a rare malignancy that arises in connection to the bile ducts and show various degrees of cholangiocyte differentiation. The biliary tract is a network of ducts facilitating the movement of bile; connecting the liver, gallbladder and pancreas.[16] CCAs are classified based on anatomical location as intrahepatic (iCCA) and extrahepatic (eCCA). Extrahepatic CCA is further divided into hilar/perihilar (pCCA) or distal (dCCA).[17] Intrahepatic CCAs originate from the biliary tree within the liver.[18] Perihilar/hilar tumors, also called Klatskin tumors, occur at or near the junction of the right and left hepatic ducts. Distal tumors arise from the extrahepatic bile ducts, above the ampulla of Vater (Figure 6).[19]

Figure 6. Location of CCA primary tumor and sub-classification



In the 10th edition of International Classification of Disease (ICD), CCA is classified in the category C22 (Malignant neoplasm of liver and intrahepatic bile ducts) with C22:1 being intrahepatic bile duct carcinoma.[20] The classification of CCA is associated with some difficulties when evaluating epidemiological data. First, the revision of tumor coding in the second version of ICD Oncology (ICD-O) have resulted in misclassification of hilar/Klatskin tumors as iCCA rather than eCCA. Second, CCA is often diagnosed at an advanced stage and the discrimination of intrahepatic and extrahepatic location in these cases are challenging. This is important to bear in mind when interpreting epidemiological data in CCA.[21] Correct classification of iCCA and eCCA is of importance since FGFR2 fusions, the target alteration for Pemazyre, are predominantly found in iCCA.

9.1.2 Genetic heterogeneity by classification

CCA is a disease with high genomic heterogeneity. The most common genetic alterations associated with iCCA are fibroblast growth factor receptor (FGFR), isocitrate dehydrogenase (IDH) 1/2 and AT-rich interactive domain-containing protein 1A (ARID1A), while eCCA is associated with KRAS, SMAD4 and tumor protein 53 (TP53) (Table 5).[14, 22-24]

Table 5. Common genetic mutations for iCCA and eCCA[22]

Genetic mutation	Frequency (%) in all tumors tested	
	iCCA	eCCA
IDH 1/2	14-36%	0%
BAP 1	9%-25%	4%-10%
KRAS	9%-24%	40%-47%
TP53	3%-38%	18%-45%
PBRM1	11%-17%	4%-11%
ARID1A	11%-36%	5%-16%
EGFR amplification	7%	0%
HER2	0%-2%	0%-20%
VEGF overexpression	42%	31%
PIK3CA	4%-6%	9%
BRAF	4%-22%	6%
FGFR translocation	6%-45%*	0%-5%
MCL1 amplification	16%-21%	NR
PTEN	1%-11%	4%
FBXW7	1%-6%	4%-15%
CDK6	7%	NR
CDKN2A	7%	15%
BRCA 1/2	4%	NR
SMAD4	1%-4%	11%-25%
mTOR	26%	40%

*Amendment to Kayhanian et al., 2017; changed from 50% to 45% (Sia et al., 2015)
ARID1A, AT-rich interactive domain-containing protein 1A; BAP1, BRCA1 associated protein-1; CDK6, cyclin-dependent kinase 6; BRCA, BReast CAncer; CDKN2A, cyclin-dependent kinase Inhibitor 2A; EGFR, epidermal growth factor receptor; FBXW7, F-box/WD repeat-containing protein 7; FGFR, fibroblast growth factor receptor; HER2, human epidermal growth factor 2; IDH, isocitrate dehydrogenase; mTOR, mammalian Target Of Rapamycin; PBRM1, protein polybromo-1; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; PTEN, phosphatase and tensin; TP53, tumor protein 53; VEGF, vascular endothelial growth factor

Comprehensive genomic profiling has identified several potentially actionable oncogenic alterations in patients with CCA, including the genes encoding for FGFR.[13]

9.1.3 Epidemiology

9.1.3.1 Incidence and prevalence of CCA

CCA is a rare cancer, although it is the most common primary malignancy of the bile duct and the second most common primary hepatic cancer. CCA consists of a heterogeneous group of tumors that account for 3% of all gastrointestinal (GI) tumors.[25, 26] Incidence of CCA varies worldwide, with incidence rates of 2.8 per 100,000 in the US and 0.5-3.36 per 100,000 in Europe.[27, 28] The highest incidence rates are seen in Thailand (>80 cases per 100,000) due to the prevalence of liver fluke (Opisthorchis viverrini) infections in this region, which often result in CCA.[27] Such infections are not related to FGFR2 fusions in CCA, the target alteration for Pemazyre.

An analysis of CCA-specific data from the SEER-18 registry demonstrated the increasing incidence of CCA over the last 40 years.[28] Overall age-adjusted incidence rates of CCA in the US increased by 65% from 1973-2012.[27, 28] In Europe, data have also shown that the incidence of iCCA has increased; however, the incidence of eCCA has decreased or remained stable. [27, 29] The age-adjusted incidence rate of iCCA in Europe in 2007 was 1.6 per 100,000 for men and 1.5 for women, increasing from 1.2 in men and 1.0 women in 1998.[30] The increase in CCA is likely due to a combination of factors including improved diagnostic techniques and increased incidence of risk factors including hepatitis C, obesity, diabetes and alcohol use.[26, 28, 31, 32]X

Prevalence data is rarely reported for CCA. Due to the low overall survival (OS) in this patient population, on average less than 12 months, prevalence data are similar to incidence data. For example, an analysis of SEER data 2000-2011 found incidence and prevalence of iCCA to be 1.6 per 100,000.[33]

9.1.3.2 Incidence and prevalence of CCA with FGFR2 fusions

Somatic alterations in *FGFR* can lead to aberrant FGFR signalling, which can drive tumorigenesis by enhancing cellular proliferation, migration, survival, and invasion, as well as angiogenesis.[34] FGFR2 fusions and rearrangements are frequently identified genetic alterations among patients with CCA, occurring in 10-16% of patients and are almost exclusively present in iCCA.[9, 10, 35] The frequency of FGFR2-fusion varies in the literature as described in Table 6.[9, 10, 13, 24, 35-40] Javle *et al* presented results from a large cohort of 3634 CCA patients with 9% FGFR2 fusions identified using comprehensive genomic profiling (FoundationOne assay).[12] Incidence of FGFR2 fusions is highest among younger patients than those of the overall CCA population, and there is a predominance in women.[23, 24, 40].

Table 6. Frequency of FGFR2 fusion genes in iCCA populations

Reference	Country	N	% FGFR2 fusions
Jiao et al. 2013 [39]	USA	32	13*
Churi et al. 2014 [14]	USA	55	6
Graham et al. 2014 [9]	USA	96	13**
Ross et al. 2014 [35]	USA	28	11
Javle et al. 2016 [24]	USA	412	7
Goyal et al. 2017 [40]	USA	32	28
Lowery et al. 2018 [13]	USA	158	10
Jain et al. 2018 [8]	USA	273	22
Javle et al. 2019 [12]	USA	3634†	9
TCGA 2017 [10]	USA, Canada	32	16
Sia et al. 2015 [36]	USA, Spain, Italy	107	45
Arai et al. 2014 [37]	Japan	66	14
Nakamura et al. 2015 [38]	Japan	109	6

FGFR, fibroblast growth factor receptor; TCGA, The Cancer Genome Atlas; US, United States
*FGFR somatic mutation; **FGFR translocation; † CCA population

9.1.3.3 Risk factors

Risk factors for CCA are dominated by diseases affecting the liver, gallbladder and surrounding tissues (Table 7).[27, 41, 42] Inflammation of the bile ducts, caused by such diseases, can increase the frequency of oncogenic mutations leading to malignant cells.[29] However, in most instances, the development of CCA is spontaneous.[29]

There exists a divergence in risk factors between overall CCA and CCA with FGFR2 fusions specifically (Table 7). Indeed, CCA with FGFR2 fusion is more likely to occur in women and with a lower age of peak incidence.[24]

Table 7. Risk factors for overall CCA versus CCA with FGFR2 fusion [24, 27, 41, 42]

Overall CCA	CCA with FGFR2 fusion
Male	Female
Increases with age	Lower age of peak incidence
Primary sclerosing cholangitis	
Cholelithiasis	
Liver fluke infestation; *O. viverrini* and *C. sinensis* (iCCA)	
Choledochal cysts	
Liver disease: cirrhosis, NASH, hepatitis B/C (iCCA)	
Inflammatory bowel disease includes ulcerative colitis and Crohn's disease	
Rare diseases of the liver and bile duct including polycystic liver disease and Caroli syndrome	
Metabolic disorders: diabetes, dyslipidemia	
Life-style: alcoholism, smoking, obesity	

iCCA, intrahepatic cholangiocarcinoma; NASH, non-alcoholic steatohepatitis

9.1.4 Clinical presentation, diagnosis

9.1.4.1 Clinical presentation

CCA remains a diagnostic challenge and is most commonly diagnosed at an unresectable or advanced/metastatic disease stage.[43, 44] This is due to the generally asymptomatic nature of early stage disease and its nonspecific clinical presentation at a late or advanced stage.[32, 45, 46] The asymptomatic/non-specific nature of the disease means 19% to 43% of iCCA are actually diagnosed incidentally.[29]Patients with intrahepatic masses may present with abdominal pain, malaise, night sweats, weight loss and loss of appetite.[29] Approximately one third of patients are diagnosed with advanced disease and >65% with unresectable disease and at least half have lymph node metastases.[17, 47] Diagnosis at advanced stage means patients are ineligible for the only curative treatment option, which is surgical resection. Furthermore, of those patients considered resectable, 10% to 45% are found to be unresectable during explorative laparotomy.[29]

9.1.4.2 Diagnosing patients with CCA

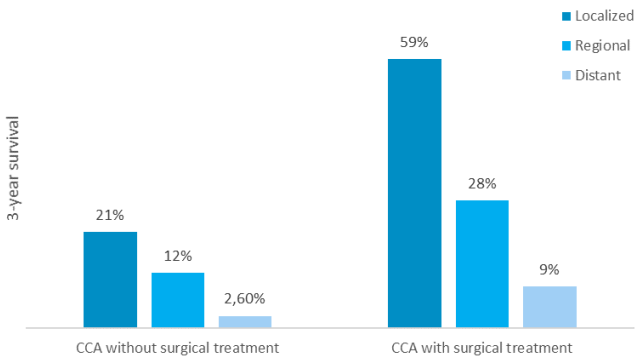
Imaging is the main method of diagnosis for CCA and it is recommended that patients have combined magnetic resonance imaging (MRI) and magnetic resonance cholangiopancreatography with contrast enhanced high resolution computed tomography (CT) and fluorodeoxyglucose positron emission tomography (FDG-PET) with or without CT (FDG-PET/CT).[17, 18, 48] There is no specific diagnostic blood test for CCA; however, in advanced disease, non-specific markers of malignancy such as albumin, erythrocyte sedimentation rate, C-reactive protein and haemoglobin may be altered.[17] Abnormal liver function tests are also usually undertaken. Overall, biopsy is usually not necessary for patients undergoing resection.[19] Endoscopic retrograde cholangiopancreatography (ERCP)-guided biopsy is recommended for distal tumors where palliation is indicated. Though imaging is usually sufficient to differentiate iCCA and hepatocellular carcinoma (HCC), diagnosis can be challenging if cirrhosis of the liver is present. It is

important that results are conclusive given the differences in management and prognosis of iCCA versus other primary hepatic tumors.[29] In such cases, biopsy is undertaken.

9.1.4.3 Prognostic factors and burden of disease

Bile duct cancers are staged based on the Tumor/Node/Metastasis (TNM) Classification of Malignant Tumors and is specific for every subtype of CCA.[18] Prognosis of CCA is dependent on stage of disease at diagnosis and location of primary tumor.[49] However, existing staging system for iCCA is not sufficient for clear treatment planning or to predict long term prognosis. Tumor size seem to be of less prognostic importance compared to multiple tumors, vascular infiltration and lymph node invasion.[48] CCAs are generally asymptomatic in early stages and a high percentage of patient are diagnosed with unresectable disease compromising the effective therapeutic options for these patients. In the US, 3-year survival for patients with disease metastasized to 1 or 2 lymph nodes is 50% while patients with disease metastasized to 3 or more lymph nodes is 0%.[50] In the UK, 20-50% of patients will live at least 5 years if bile duct cancer is diagnosed as surgically resectable but only 2% will be alive after 5 years for patients with unresectable disease.[51] Figure 7 shows that with or without surgical intervention, 3-year survival is still dependent on stage.

Figure 7. CCA 3-year survival by stage, with and without surgical treatment [44]



We have failed to find country specific numbers for Denmark, but in Sweden, only 22% of patients with iCCA received treatment with a curative intent in 2019 and the majority of patients are only candidates for pharmacological anti-tumoural intervention or palliative therapy.[52] The probability of survival decreases dramatically for patients not suitable for surgical intervention as illustrated in Figure 8.

Figure 8. Survival curves for patients diagnosed with iCCA in 2009-2018 in Sweden. The treatment groups are non-comparable due to selection to different treatment interventions; planned surgery, no planned intervention, planned pharmacological intervention.[53]

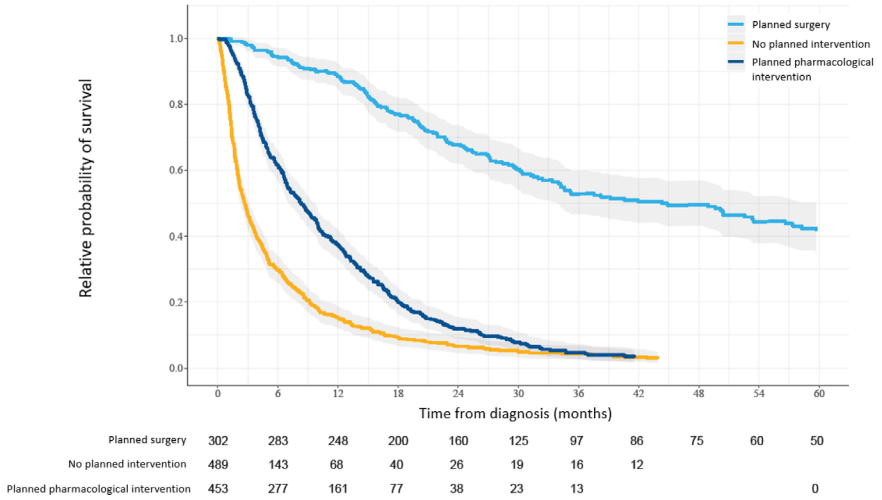


Table 8 illustrates the limited treatment options available for patients diagnosed with iCCA. Swedish registry data from 2017-2019 show that 31% of the patients were planned for/or received a treatment with curative intent, i.e. surgery. However, only 33% of the patients were planned to receive an anti-tumoral therapy whereas 35% of the patients were not planned for any anti-tumoral therapy (active symptom control) illustrating the need for further treatment options for patients diagnosed with an advanced disease.[52]

Table 8 Swedish treatment options for patients with iCCA.

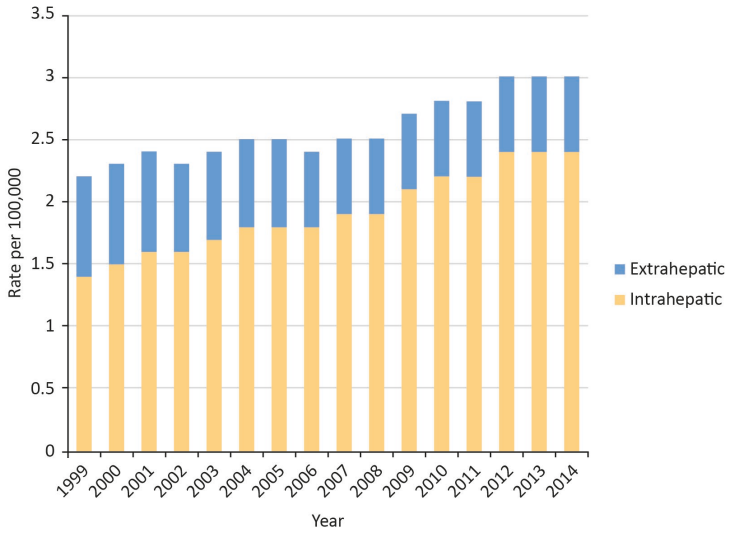
	Planned non-curative treatment		Curative/Other		All CCC
Time period	No planned (%)	Medical (%)	Curative (%)	Other (%)	Total (%)
2017-2019 Total	189 (34.7)	180 (33.0)	171 (31.4)	5 (0.9)	545 (100)
2009-2016 Total	400 (36.9)	335 (30.9)	325 (30.0)	23 (2.1)	1,083 (100)

Number of intrahepatic CCA patients planned for/or received curative treatment (ablation, resection and/or transplantation) and number of patients not planned for curative treatment, grouped into ”Planned for medical anti-tumoral treatment and/or chemoembolization” alternatively ”No planned” treatment. The group ”Other” includes patients that cannot be placed in any of the other categories.[52]

9.1.4.4 Mortality

CCA accounts for about 20% of the deaths from hepatobiliary cancers, which cause 13% of the total cancer mortality worldwide.[27] iCCA accounts for the majority of CCA mortality, and the increasing CCA mortality rate (Figure 9).[54-57]

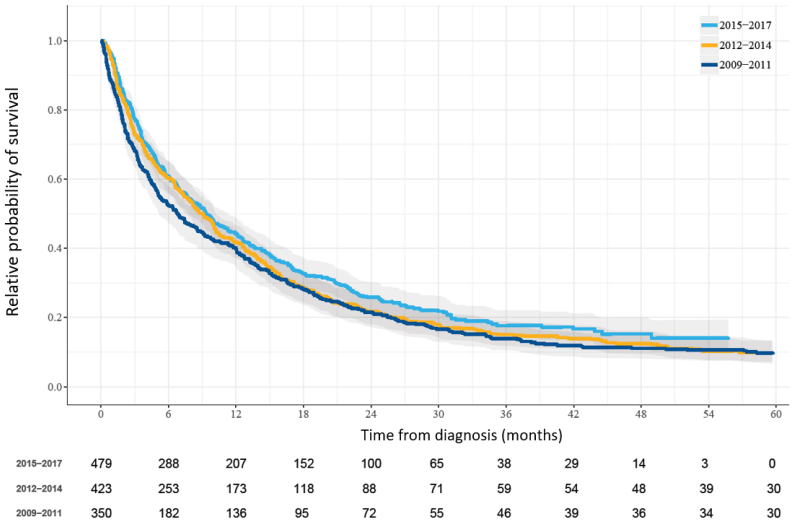
Figure 9. Mortality from CCA for those aged 25+ in the US between 1999 and 2014 [54]



Globally, 5-year survival for patients with early diagnosis is 80-100% and for resectable disease 10-40%. However, for overall CCA this value drops dramatically to approximately 5%.[58, 59]

Due to the lack of any new interventions introduced to the market, especially for unresectable or advanced/metastatic CCA patients, survival rates has remained the same since the current first-line standard of care (SOC) was established (note: SOC (GemCis) was established following the ABC-02 trial: Valle *et al.* Cisplatin plus Gemcitabine versus Gemcitabine for Biliary Tract Cancer).[57, 60] Registry data from Sweden show little improvement in survival rates for patients diagnosed in 2009 compared to 2017 with a 1-year survival rate of approximately 40% (Figure 10).[53] This again emphasize the need for new treatment options in this patient population.

Figure 10. Survival for patients diagnosed with iCCA grouped by year of diagnosis [53]



9.1.4.5 Morbidity

Symptoms associated with CCA are usually non-specific and become most apparent at advanced disease stages. The subclassifications of CCA have different symptoms due to the varying primary tumor locations (Table 9).[61-70]

Table 9. Presenting symptoms for CCA by subclassification [61-70]

Symptoms	Overall CCA	iCCA	eCCA/hCCA
Jaundice	40.2-90%	8.3†-19%	79-93%†
Weight loss	31-52%	20-58%†	50-51%†
Abdominal pain	32.8-83.2%	27-67%†	21-39%†
Pain - unspecified	54%	24%	NR
Fatigue	46%	NR	NR
Fever	7-32.7%	8.3†-20%	7%†
Vomiting	9%	17†-33%	7%†
General/unspecified	NR	NR	16.3%
Anorexia	51.4-57%	10-33%†	61.4%†
Pruritus	25-44%	6-8.3%†	28%†

CCA, cholangiocarcinoma; eCCA, extrahepatic cholangiocarcinoma; hCCA, hilar cholangiocarcinoma; iCCA, intrahepatic cholangiocarcinoma; NR, not reported; †Figures calculated from Yusoff et al., 2012 [62]

The most common presenting symptoms in overall CCA are jaundice and associated pruritis.[63, 64, 67, 68, 70] When looking at iCCA and eCCA separately, there is a disparity in symptoms. Jaundice is commonly seen in patients with eCCA as the tumor location often leads to blockage of bile drainage.[61, 62, 69] However, jaundice is rarely seen in iCCA which instead usually presents with abdominal pain and weight loss.[65, 66] Somjaivong *et al.*, 2011 found abdominal pain or dyspepsia, fatigue, and lack of appetite to be most distressing for CCA patients above other symptoms.[71]

9.1.4.6 Quality of life (QoL)

As CCA is a cancer with a poor prognosis, remaining QoL can be important factor when deciding treatment. As CCA is not detected until late in the disease stage, symptoms and QoL issues develop rapidly. Emotional functioning and fatigue worsen in the first 6 months of diagnosis.[72] Patients with advanced disease have been shown to have lower overall health-related quality-of-life (HRQoL) compared to those with early-stage disease.[73] QoL in patients with CCA is most affected by disease-related symptoms and the side effects of treatments but also the uncertainty/anxiety surrounding the treatment options and outcomes.[71] Lower HRQoL is associated with higher frequency of symptoms at diagnosis and clinical depression in patients with hepatobiliary cancer.[74]

HRQoL scores for patients with CCA have been found to be lower than scores for patients with breast cancer or head and neck cancer. Particularly, CCA patients were found to have a level of uncertainty higher than head and neck, breast and cervical cancer patients. This may be due to the reoccurring symptoms and few treatment options with limited effectiveness.[71]

9.1.5 Patient populations relevant for this application

The approved indication for Pemazyre reads:

Pemazyre, som monoterapi, er indiceret til behandling af voksne med lokalt fremskredent eller metastatisk cholangiocarcinom med en fibroblastvækstfaktorreceptor 2 (FGFR2)-fusion eller -omlejring, som er progredieret efter mindst én tidligere linje systemisk behandling.[75] (Adults with locally advanced or metastatic cholangiocarcinoma with a fibroblast growth factor receptor 2 (FGFR2) fusion or rearrangement that have progressed after at least one prior line of systemic therapy)

9.2 Current treatment options and choice of comparator(s)

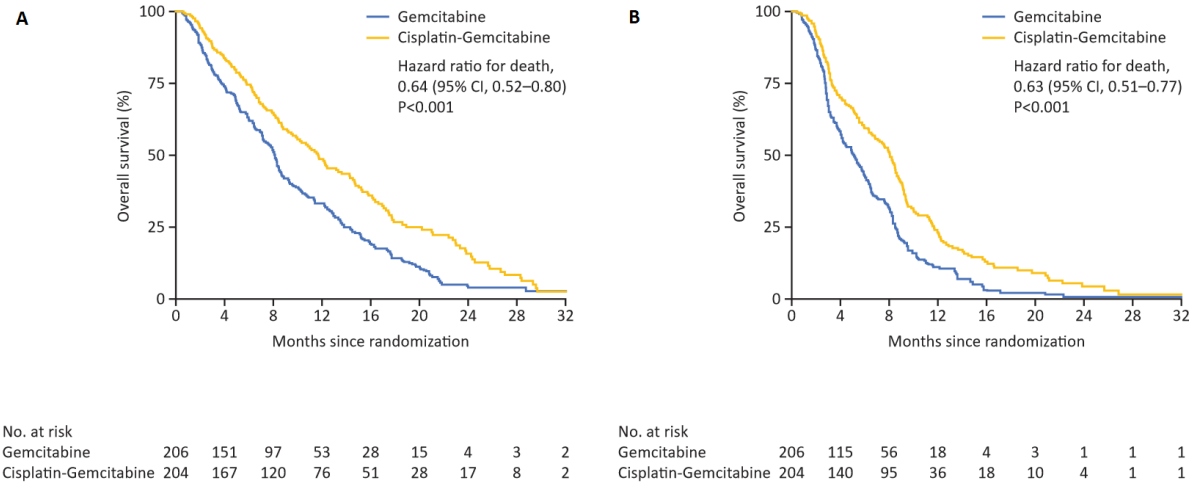
9.2.1 Treatment goals

For patients with CCA, surgery is the only potentially curative option but only a minority of patients qualify for surgery.[18, 19] Patients with unresectable or advanced/metastatic disease can only be provided with palliative chemotherapy, with modest survival expectations. Indeed, the primary aim of palliative chemotherapy is symptom control and to maintain QoL.[49, 76]

9.2.2 Treatment for recurrent and/or metastatic disease

Current SOC for first-line therapy was established in 2009/2010 following the results of the advanced biliary cancer (ABC)-02 trial.[60] The ABC-02 was a phase III UK study of 410 patients with locally advanced or metastatic disease. However, the patient cohort was not restricted specifically to patients with CCA but also included patients with gallbladder and ampullary carcinoma. Overall, the results indicated that the combination treatment of GemCis was more effective than gemcitabine alone. Median OS was 11.7 months for GemCis and 8.1 months for gemcitabine alone ($p < 0.001$) (Figure 11a). Median PFS was 8.0 months for GemCis and 5.0 months for gemcitabine alone ($p < 0.001$) (Figure 11b).[60]

Figure 11. Outcomes for patients with biliary tract cancer who received GemCis versus gemcitabine alone in ABC-02; a) OS, b) PFS [60]



ABC, advanced biliary cancer; CI, confidence interval

Since 2010, there have been further ABC trials in first-line therapy, ABC-03 and -04, yet none have shown additional clinical benefit over GemCis.[77, 78]

ABC-06, a randomized phase III, multi-center, open-label study, has recently been completed, the aim of which was to establish the SOC for patients with advanced biliary tract cancer who have progressed on first-line GemCis. Active symptom control (ASC) plus 5-fluorouracil (5-FU), leucovorin and oxaliplatin (mFOLFOX) compared to ASC alone improved OS after progression to GemCis with a clinically meaningful increase in 6 month and 12 month OS rate.[79] Median OS was 6.2 months and 6 months and 12 month OS-rate were 50.6% and 25.9% respectively, for the ASC+mFOLFOX arm. For the ASC arm, median OS were 5.3 months, 6 months and 12 months OS rate were 35.5% and 11.4% respectively.[79] However, patient performance status, response and tolerability to first line therapy needs to be taken into consideration when evaluating risk/benefit for 2nd line therapy and currently best supportive care (BSC) or active symptom control (ASC) is often the only option after development of resistance to first-line chemotherapy.[80]

As the ABC clinical trials included a heterogeneous group of biliary tract patients, outcomes are not specific to CCA alone, which is distinct from other biliary tract cancers by etiology, management and prognosis.

Current, systemic chemotherapies can result in high rates of severe adverse events (SAEs), leading to high discontinuation rates. A systematic literature review conducted mid-2017 looking at treatment outcomes found the most common SAEs are severe haematological abnormalities or toxicities (Table 10).[81] In a retrospective analysis of chemotherapy outcomes for unresectable iCCA and hCCA, 30% of patients receiving GemCis discontinued therapy due to toxicity, with the most common reason being elevated creatinine.[82]

Table 10. Severe adverse events reported across studies with regimens including systemic chemotherapy [81]

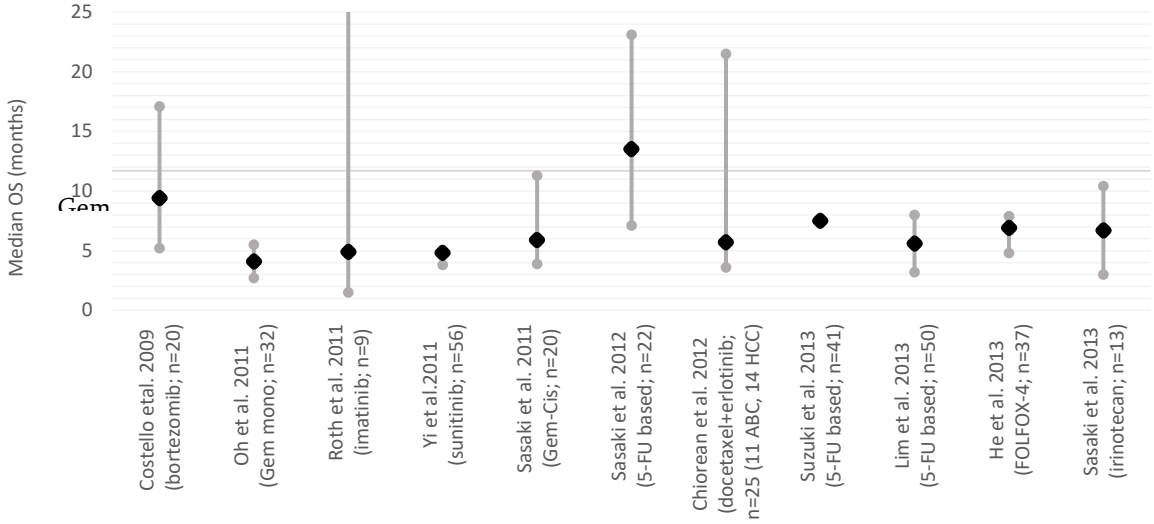
Frequently experienced SAEs across studies	% Patients experiencing event
Anemia	6.8% - 54% [83-86]
Hematologic abnormalities or toxicities	38.5%- 52.2% [87, 88]
Neutropenia	20% - 36% [83, 85, 86, 89]
Asthenia	6.8% - 33% [84, 90]
Cholangitis	30% [89]
Fatigue	11.4% - 20% [83, 85, 87]
Hepatic Toxicity	20% [84]
Performance status decrease	11.3%-15.5% [84]
Skin Toxicity	6.6% - 13.6% [84, 87]

SAE, serious adverse event

Evidence for second-line chemotherapy is lacking in quality and quantity. A systematic review of second-line chemotherapy in advanced biliary cancer found 14 phase II clinical trials.[3] The authors concluded that there was insufficient evidence to establish a SOC for second-line chemotherapy due to the small patient cohorts, variation in chemotherapy regimen, lack of consensus on primary endpoint, heterogeneity of patients and poor outcomes.

Figure 12 illustrates the poor survival outcomes of second-line chemotherapy treatment of advanced biliary cancer (*not only CCA*) from Lamarca *et al.*, 2014.[3] Mean PFS and mean OS were 3.2 months and 7.2 months, respectively.

Figure 12. Median overall survival in phase II single arm clinical trials in second-line chemotherapy treatment of advanced biliary cancer [3]



5-FU, 5-fluorouracil; ABC, advanced biliary tract; FOLFOX-4; oxaliplatin+5-FU+ leucovorin; GemCis, gemcitabine + cisplatin; HCC, hepatocellular carcinoma; mono, monotherapy; OS, overall survival

In agreement with the study above, a systematic literature review of current treatments and outcomes specifically in patients with advanced CCA identified 71 studies, and only ten investigated second-line therapy.[91] Of these studies, half were non-interventional and the studies that were interventional had only small patient cohorts (mean n=30; range 11-53). Overall, the poor quality and heterogeneity of evidence does not allow meaningful conclusions on treatment effect to be drawn, resulting in insufficient evidence to establish second-line SOC.[18] In Sweden, there is no established SOC for second-line treatment. As described in Section 2.4, less than half of the patients not suitable for curative intent were planned to receive anti-tumoral treatment in the first line setting with the majority receiving best supportive care. Even fewer patients are considered suitable for 2nd line treatment based on the risk/benefit ratio and patient performance status as well as response and tolerability to first line treatment.

9.2.3 Real-world treatment patterns

Low treatment rates are seen in patients with unresectable or advanced/metastatic CCA due to limited treatment options.[43, 92, 93] For CCA, SEER data between 1988 and 2009 indicated that 84% of patients undertook no-interventional treatment.[92] For iCCA in the US between 2000 and 2008, 66.4% of patients received no therapy or best supportive care (BSC).[43] [redacted].[94]

For many patients cytotoxic chemotherapy is not a viable option due to poor prognosis, poor performance status (PS) or intolerance to the treatment.[43, 92, 93, 95] [redacted].[94]

9.2.4 Treatment guidelines for advanced/metastatic disease

9.2.4.1 Biliary Cancer: ESMO Clinical Practice Guidelines 2016 [18]

Systemic chemotherapy is the treatment of choice for patients with locally advanced or inoperable disease; combination chemotherapy for PS 0-1 patients and monotherapy for PS 2 patients

Cisplatin/gemcitabine is the reference chemotherapy regimen for good PS (0-1) patients; oxaliplatin may be substituted for cisplatin where there is a concern about renal function

Gemcitabine monotherapy may be considered for PS 2 patients

There is no established second-line chemotherapy regimen; patients should be encouraged to participate in clinical trials

There is no established evidence to support the use of targeted therapies; patients should be encouraged to participate in clinical trials

Radiotherapy may be considered in patients with localised disease, after first-line chemotherapy; patients should be encouraged to participate in clinical trials

Radioembolisation may be considered in patients with inoperable iCCA, usually after first-line chemotherapy; patients should be encouraged to participate in clinical trials

There is no established second-line systemic therapy following progression after first-line treatment although fluoropyrimidine-based therapy (either in monotherapy or in combination with other cytotoxics) is sometimes used. A systematic review including 761 patients showed disappointing median PFS (3.2 months; 95% CI: 2.7–3.7) and response rates (7.7%; 95% CI: 4.6–10.9); the mean OS was 7.2 months (95% CI: 6.2–8.2) and no recommendation could

be made about the most appropriate second-line regimen.[3] Moreover, the magnitude of benefit to patients (if any) over best supportive care is not known; results of study NCT01926236 (ABC-06) will inform this question.

9.2.4.2 NCCN Clinical Practice Guidelines in Oncology; Hepatobiliary Cancers, 2021 [96]

For unresectable/metastatic disease primary treatment options include:

- Systemic therapy: Preferred regimen is gemcitabine + cisplatin.
  - Other recommended regimens include: 5-fluorouracil + oxaliplatin, 5-fluorouracil + cisplatin, capecitabine + cisplatin, capecitabine + oxaliplatin, gemcitabine + albumin-bound paclitaxel, gemcitabine + capecitabine, gemcitabine + oxaliplatin, gemcitabine + cisplatin + albumin-bound paclitaxel
  - Single agents: 5-fluorouracil, capecitabine or gemcitabine.
  - Useful in certain circumstances: For *NTRK* gene fusion-positive tumors: entrectinib or larotrectinib. For MSI-H/dMMR tumors: Pembrolizumab
- Clinical trial
- Consider locoregional therapy such as EBRT or arterially directed therapies
- Best supportive care

Subsequent-line therapy for biliary tract cancers if disease progression:

Systemic therapy: Preferred regimen FOLFOX. Other recommended regimens include FOLFIRI, regorafenib or regimens listed in "other recommended regimens" in first line setting (treatment selection depends on clinical factors including previous treatment regimen/agent and extent of liver dysfunction).

In the section "Useful in Certain Circumstances", pemigatinib is recommended for CCA with *FGFR2* fusions or rearrangements (Category 2A; Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.)

9.2.4.3 Danish guidelines, cholangiocarcinoma [97]

The Danish guidelines for the treatment of cholangiocarcinoma states the following:

Treatment of non-resectable bile duct cancer:

- Gemcitabine and cisplatin are recommended as first-line treatment of patients with good general condition (PS 0-1)
- Second line treatment can only be recommended in protocol

As we understand, "in protocol" should be interpreted as the patient being included in a clinical trial.

9.2.5 Limitations in current treatments and unmet needs

The first-line SOC, gemcitabine + cisplatin for patients with unresectable or advanced/metastatic CCA provides limited efficacy with ORR of 25% and median OS of 11.7 months.[60] This first-line therapy is established based on a trial (ABC-02) in a mixed population of biliary tract cancer, including gallbladder and ampullary carcinoma as well as CCA. Therefore, this first-line therapy was not established specifically for CCA. Also, a high proportion of patients' progress on first-line therapy.

There is no second-line SOC established due to lack of high-level evidence and a lack a differentiation between the current options in terms of efficacy. Many patients receive only best supportive care. The first randomized controlled trial (RCT) in second-line advanced biliary tract cancer, ABC-06, has been completed, and the results indicate that

ASC+mFOLFOX may become second-line SOC.[79] However, as with all ABC trials, these results are not CCA specific and the median OS of 6.2 months is still poor.

Treatment for patients with unresectable or advanced/metastatic CCA consist of systemic chemotherapy combinations with poor safety profiles. Systemic chemotherapies have high discontinuation rates as a result of severe side effects such as hematological toxicities and neuropathy, for only modest improvements in survival. For many patients cytotoxic chemotherapy is not a viable option due to poor prognosis, poor performance status (PS) or intolerance to the treatment.[43, 92, 93] This has led to low treatment rates in this patient population and a need for new therapies.

CCA includes subclassifications based on primary tumor location; iCCA and eCCA. Each has a different prognosis and requires different management; however, palliative chemotherapy care is currently the same for both iCCA and eCCA.

Within iCCA and eCCA there exists high genetic heterogeneity. Due to the genetic heterogeneity of CCA, molecularly targeted therapies have the potential for patient selection and to increase survival with fewer side effects and lower discontinuation rates compared to systemic chemotherapies. Several targeted therapies are under investigation for advanced CCA, against various molecular targets, with promising results, including FGFR inhibitors. FGFR2-fusions are found in 10-16% of CCA tumors, almost exclusively in iCCA.[10, 13, 36, 37]

Pemazyre (pemigatinib) is a selective oral inhibitor of FGFR that offers a non-chemotherapy treatment option to a selected group of patients with CCA who have FGFR2-fusions or rearrangements.

9.3 The intervention

9.3.1 Pemazyre product overview

Pemazyre is a novel, targeted oral therapy for the treatment of unresectable or advanced/metastatic CCA with FGFR2 fusions after failure of at least one prior line of treatment.

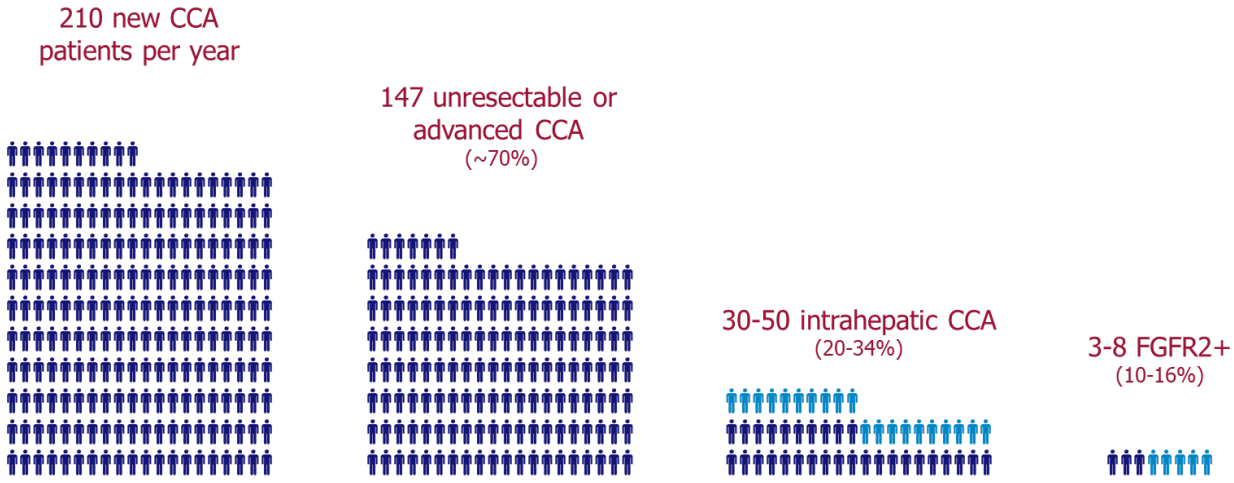
9.3.2 Indication

Pemazyre monotherapy is indicated for the treatment of adults with locally advanced or metastatic cholangiocarcinoma with a fibroblast growth factor receptor 2 (FGFR2) fusion or rearrangement that have progressed after at least one prior line of systemic therapy.

9.3.3 Orphan designation and estimated Pemazyre patient population

Orphan designation EU/3/18/2066 was granted by the European Commission to Incyte for pemigatinib for the treatment of biliary tract cancer. In Denmark, we estimate that 3-8 patient per year are eligible for pemigatinib as illustrated in Figure 13. There are many uncertainties in the estimation that needs to be taken into consideration. FGFR2 fusion testing is not done in clinical routines. However, with Pemazyre approved we estimate that 80% of patients will be tested for FGFR2 fusions at relapse/recurrent disease after 1st line therapy. There is no established standard of care (SOC) chemotherapy regimen in 2nd line and the majority of patients get best supportive care. Pemazyre can be used in later lines, i.e >2 line setting but due to even lower number of patients getting >2 line therapy we have not estimated these numbers.

Figure 13. Patient funnel estimating number of eligible patients for Pemazyre per year.



References:

[98] [99] [99, 100] [9, 10, 35, 101, 102]

Prevalence data for CCA are very rarely reported. Due to the overall survival (OS) in this patient population being on average less than 12 months, prevalence data are similar to incidence data. Incidence of CCA varies worldwide, with incidence rates of 2.8 per 100,000 in the US and 0.5-3.36 per 100,000 in Europe.[27, 28] The highest incidence rates are seen in Thailand (>80 cases per 100,000) due to the prevalence of liver fluke (Opisthorchis viverrini) infections in this region, which often result in CCA.[27] Such infections are not related to FGFR2 fusions in CCA, the target mutation for Pemazyre.

Incyte estimate the number of patients that treated with Pemazyre to be 3 patients per year in Denmark.

Table 11 Estimated number of patients eligible for treatment

Year	2021	2022	2023	2024	2025
Number of patients in Denmark who are expected to use the pharmaceutical in the coming years	1	3	3	3	3

9.3.4 Mechanism of action (MoA)

9.3.4.1 Fibroblast Growth Factor Receptor (FGFR)

The Fibroblast Growth Factor (FGF)/FGFR signalling pathway plays a critical role in cell proliferation, differentiation, migration, and survival. Genetic alterations in FGFR, including activating mutations, gene amplifications, and chromosomal rearrangements, have been described in a range of cancers including CCA, bladder, myeloid/lymphoid, and other malignancies.[34, 103-110] These genetic alterations lead to aberrant FGFR signalling, which drive tumorigenesis by enhancing cellular proliferation, migration, survival, invasion, and angiogenesis.[34, 111, 112] FGFR2 fusions or rearrangements have been identified as oncogenic drivers in iCCA patients.[9, 13, 37]

9.3.4.2 FGFR2 fusion analysis

The FGFR family consists of four transmembrane receptors (FGFR1 to FGFR4) that can form gene fusions with different fusion partners.[111, 113] Although multiple fusion partners have been identified, in most cases, the 5′ exons of FGFR2, containing the intact kinase domain, are fused in-frame to a 3′ partner.[37] Of all the FGF receptors, FGFR2 gene fusions can have multiple and inconsistent genomic breakpoint locations with their partners,[114-117] and they show the broadest range of 3' fusion partners, including BICC1, AHCYL1, CIT, CCDC6, CASP7, AFF3, OFD1 and CCAR2 etc. Many of these fusion partners contain dimerization domains, suggesting that the resulting fusions may demonstrate constitutive ligand-independent activation.[118] Additionally, FGFR2 gene fusions contain intronic regions of variable length that are fusion-agnostic.[114-116, 119, 120] All these structural considerations require an appropriately designed test to detect FGFR2 fusions, so that these genetic rearrangements can act as effective biomarkers for patient selection and stratification.

9.3.4.3 Pemazyre inhibition of FGFR

Selectively inhibiting FGFR2 activity in patients with iCCA harboring FGFR2 rearrangements or fusions is a promising individualized therapeutic approach that represents a landmark in the management of iCCA.[102, 121] Pemazyre is a small molecule kinase inhibitor of FGFR1, 2 and 3. Pemazyre inhibits FGFR phosphorylation and signalling and selectively decreases cell viability in cancer cell lines with activating FGFR genetic alterations, including point mutations, amplifications, and fusions or rearrangements. In preclinical studies, Pemazyre exhibited anti-tumor activity in mouse xenograft models of human tumors with FGFR1, FGFR2, or FGFR3 activation including a patient-derived xenograft model of CCA that expressed an oncogenic FGFR2-Transformer-2 beta homolog (TRA2b) fusion protein.

9.3.4.4 Dosing and administration

Pemazyre is administered as a 13.5 mg oral tablet taken once daily for 14 days followed by 7 days off therapy.[122] The tablets should be taken at approximately the same time every day. Patients should not crush, chew, split or dissolve the tablets. Pemazyre may be taken with or without food. Treatment should be continued as long as the patient does not show evidence of disease progression or unacceptable toxicity.

9.4 Efficacy and safety

9.4.1 Clinical development plan

Pemazyre is being investigated as a monotherapy in three key clinical trials in CCA:

1. **Study Fight-202 (pivotal trial)** is an ongoing Phase 2, open-label, single-arm, multicenter study, assessing the efficacy and safety of Pemazyre monotherapy in advanced/metastatic or unresectable CCA, including patients with FGFR2 fusion and other FGF/FGFR alterations who failed at least one previous therapy (NCT02924376).
[redacted] **Study Fight-302** is an ongoing Phase 3, open-label, randomized, controlled, multicenter study, assessing the efficacy and safety of Pemazyre monotherapy versus GemCis in first-line treatment of patients with unresectable or advanced/metastatic CCA with FGFR2 rearrangement (NCT03656536). [redacted]
[redacted] **Study Fight-101** is an ongoing Phase 1/2, open-label, dose-escalation study, assessing the pharmacokinetics/pharmacodynamics (PK/PD) and safety, tolerability, and preliminary efficacy of Pemazyre in patients with refractory advanced malignancy (NCT02393248). [redacted]
    - Fight-202 (pivotal trial)

Fight-202 study was published in Lancet Oncology in May 2020 with a data cutoff date of March 22, 2019 with a median follow-up of 17·8 months[redacted]

9.4.2 Study design and population

A Phase 2, open-label, single-arm, multinational study to evaluate the efficacy and safety of Pemazyre in subjects with advanced/metastatic or surgically unresectable CCA including FGFR2 rearrangements or fusions, other FGF/FGFR alterations or who were negative for any FGF/FGFR alterations, who have progressed on at least 1 line of prior systemic therapy.[125]

[redacted]Subjects underwent regular safety assessments during treatment as well as regular efficacy assessments. Subjects were allowed to continue administration in 21-day cycles until documented disease progression or unacceptable toxicity was reported. See Figure 14 for overall study design.

[redacted]

[redacted]

[redacted]

[redacted]

Pemazyre was self-administered as a once daily oral treatment on a 14 days on/7 days off therapy schedule.[125] The starting dose in this study was 13.5 mg. One cycle was defined as 21 days.

[redacted]

9.4.3 Study endpoints

9.4.3.1 Primary endpoint

The primary endpoint of this study was to determine the overall response rate (ORR) of Pemazyre in subjects with FGFR2 rearrangements or fusions based on the central genomics laboratory results who had progressed on at least 1 previous treatment (Cohort A).[125] ORR was defined as the proportion of subjects who achieved a CR; disappearance of all target lesions) or a partial response (PR; ≥30% decrease in the sum of the longest diameters of target lesions) based on RECIST version 1.1.[125] Clinical response was determined by an independent radiological review committee (IRC).

9.4.3.2 Secondary endpoints

Secondary endpoints were ORR in subjects with FGF/FGFR alterations other than FGFR2 translocations (Cohort B), ORR in all subjects with FGF/FGFR alterations (Cohorts A and B), ORR in subjects negative for FGF/FGFR alterations (Cohort C [US only]), progression free survival (PFS, first dose to progressive disease (PD) or death; all cohorts),

duration of response (DOR, time from the date of CR or PR until PD; all cohorts), disease control rate (DCR, CR+PR + SD; all cohorts), overall survival (OS, first dose to death of any cause; all cohorts), population pharmacokinetics (all cohorts). Safety and tolerability was assessed by evaluating the frequency, duration and severity of AEs; through a review of findings of physical examinations, changes in vital signs and electrocardiograms; and through clinical laboratory blood and urine sample evaluations (all cohorts), X

[redacted]

[redacted]

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9.4.4 Results

9.4.4.1 Study population

[redacted]The efficacy evaluable population included 145 participants who were assigned to cohorts based on tumor FGF/FGFR status [redacted]107 participants with FGFR2 rearrangements or fusions (assigned to Cohort A), 20 participants with other FGF/FGFR alterations (assigned to Cohort B), and 18 participants with tumors that are negative for FGF/FGFR alterations (assigned to Cohort C). As of the data cut-off date, 31 participants, all in Cohort A, remained on Pemazyre treatment. Across all cohorts, the most common reason for Pemazyre discontinuation was progressive disease (58.2%). Sixty-three participants remained in the study as of the data cut-off date, with 32 participants no longer receiving Pemazyre but who are continuing on study. The most common reason for study withdrawal was death (47.3%).[125]

9.4.4.2 Baseline Disease Characteristics, Demographics and Disease History

The majority of participants were under 65 years of age (68.5%), white (71.2%), and had ECOG PS of 0 (40.4%) or 1 (52.1%; see Table 12.[124] Cohort A included higher proportions of females and participants who were under 65 years of age compared with Cohorts B and C. These differences are consistent with previous reports showing the predominance of younger, female patients with FGFR2-genetically altered CCA.[8, 14]

Overall, 89.0% of participants, including 98.1% of Cohort A participants, had iCCA (Table 12).[124] All participants had received at least 1 line of prior systemic therapy, and 39.0% of participants had received 2 or more lines of prior systemic therapy for advanced/metastatic disease.

In addition to prior systemic therapy, 24.7% of participants had received locoregional therapy, including targeted radiotherapy, transarterial radioembolization, or transarterial chemoembolization, [redacted]

[redacted]

Table 12. Summary of Demographics and Baseline Characteristics

	FGFR2 fusions or rearrangements (n=107)	Other FGF/FGFR alterations (n=20)	No FGF/FGFR alterations (n=18)	All patients (N=146)*
Age, median (range), years	56 (26 to 77)	63 (45 to 78)	65 (31 to 78)	59 (26 to 78)
<65	82 (77%)	10 (50%)	7 (39%)	100 (68%)
65 to <75	20 (19%)	7 (35%)	8 (44%)	35 (24%)
≥75	5 (5%)	3 (15%)	3 (17%)	11 (8%)
Sex				
Male	42 (39%)	9 (45%)	10 (56%)	62 (42%)
Female	65 (61%)	11 (55%)	8 (44%)	84 (58%)
Region				
North America	64 (60%)	6 (30%)	18 (100%)	89 (61%)
Western Europe	32 (30%)	3 (15%)	0	35 (24%)
Rest of world†	11 (10%)	11 (55%)	0	22 (15%)
Race				
White	79 (74%)	9 (45%)	15 (83%)	104 (71%)
Asian	11 (10%)	11 (55%)	0	22 (15%)
Black or African American	7 (7%)	0	1 (1%)	8 (6%)
American Indian or Alaska Native	0	0	1 (1%)	1 (1%)
Other or data missing	10 (9%)	0	1 (1%)	11 (8%)
ECOG performance status				
0	45 (42%)	7 (35%)	7 (39%)	59 (40%)
1	57 (53%)	10 (50%)	8 (44%)	76 (52%)
2	5 (5%)	3 (15%)	3 (17%)	11 (8%)
Metastatic disease				
Yes	88 (82%)	20 (100%)	16 (89%)	125 (86%)
No	16 (15%)	0	2 (11%)	18 (12%)
Missing or not evaluable	3 (3%)	0		3 (2%)
Number of previous systemic therapies for advanced mtetastatic disease‡				
1	65 (61%)	12 (60%)	12 (67%)	89 (61%)
2	29 (27%)	7 (35%)	2 (11%)	38 (26%)
≥3	13 (12%)	1 (5%)	4 (22%)	19 (13%)
Previous cancer surgery	38 (36%)	6 (30%)	4 (22%)	48 (33%)
Previous radiotherapy	28 (26%)	3 (15%)	5 (28%)	36 (25%)
Cholangiocarcinoma location◊				
Intrahepatic	105 (98%)	13 (65%)	11 (61%)	130 (89%)
Extrahepatic	1 (1%)	4 (20%)	7 (39%)	12 (8%)
Other or data missing	1 (1%)	3 (15%)ϕ	0	4 (3%)
History of hepatitis				
Hepatitis B	4 (4%)	1 (5%)	0	5 (3%)
Hepatitis C	1 (1%)	1 (5%)	0	2 (1%)
Sites of disease				
Liver	101 (94%)	17 (85%)	18 (100%)	136 (93%)
Lymph nodes	57 (53%)	11 (55%)	10 (56%)	78 (52%)
Lung	58 (54%)	9 (45%)	10 (56%)	77 (52%)
Bone	21 (20%)	4 (20%)	2 (11%)	27 (18%)
Ascites	8 (7%)	5 (25%)	2 (11%)	15 (10%)
Pancreas	7 (7%)	1 (5%)	2 (11%)	10 (7%)
Pleural effusion	4 (4%)	2 (10%)	0	6 (4%)
Skin or subcutaneous tissue	2 (2%)	0	0	2 (1%)
Bladder	0	1 (5%)	0	1 (1%)
Colon	1 (1%)	0	0	1 (1%)
Other	31 (29%)	7 (35%)	12 (67%)	51 (35%)

* The total includes one patient who did not have confirmed FGF/FGFR status by central laboratory and was not assigned to any cohort.

† Rest of world consists of Israel, South Korea, Taiwan, Thailand, and Japan.

‡ Maximum number of five therapies in patients with FGFR2 fusions or rearrangements and three in the other patient cohorts.

◊ Cholangiocarcinoma location was initially missing for one patient at the data cutoff date; however, this patient was later assessed as having intrahepatic cholangiocarcinoma after the data cutoff date.

ϕ The other locations were the gallbladder (n=2) and ampulla of Vater (n=1).

[redacted]

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9.4.4.5 Clinical efficacy

Efficacy results are presented for the 107 participants in Cohort A (tumors that have FGFR2 rearrangements or fusions, referred to as "FGFR2 rearrangements" in efficacy tables), 20 participants in Cohort B (tumors that have other FGF/FGFR alterations), and 18 participants in Cohort C (tumors that are negative for FGF/FGFR alteration). [redacted]

[redacted]

In Cohort A, ORR based on IRC-assessed, confirmed tumor responses was 35.5% (95% CI: 26.50, 45.35), including 3 CRs (2.8%) and 35 PRs (32.7%; see Table 14).[125] [redacted]

Table 14. Primary and Secondary Efficacy Outcomes based on IRC Assessment According to RECIST v1.1 (Cohort A, Efficacy Evaluable and Per Protocol Populations) [124]

	FGFR2 fusions or rearrangements (n=107)	Other FGF/FGFR alterations (n=20)	No FGF/FGFR alterations (n=18)
Proportion of patients with an objective response	35.5% (26.5 to 45.5)	0	0
Best overall response*			
Complete response	3 (2.8%)	0	0
Partial response	35 (32.7%)	0	0
Stable disease	50 (46.7%)	8 (40.0%)	4 (22.2%)
Progressive disease	16 (14.9%)	7 (35.0%)	11 (61.1%)
Not evaluated	3 (2.8%)	5 (25.0%)	3 (16.7%)
Duration of response			
Patient with events	21/38 (55%)	0	0
Patients censored	17/38 (45%)	0	0
Median duration of response, months	7.5 (5.7 to 14.5)	..	..
Kaplan-Meier estimated probability of retaining a response			
At 6 months	68% (49 to 82)	..	..
At 12 months	37% (19 to 56)	..	..
Proportion of patients with disease control	82% (74 to 89)	40% (19 to 64)	22% (6 to 48)
Progression-free survival			
Patients with events	71 (66%)	17 (85%)	16 (89%)
Patients censored	36 (34%)	3 (15%)	2 (11%)
Median, months	6.9 (6.2 to 9.6)	2.1 (1.2 to 4.9)	1.7 (1.3 to 1.8)
Kaplan-Meier estimates of progression-free survival			
At 6 months	62% (52 to 70)	25% (8 to 47)	6% (<1 to 25)
At 12 months	29% (19 to 40)	0	0
Overall survival†			
Patients with events	40 (37%)	16 (80%)	14 (78%)
Patients censored	67 (63%)	4 (20%)	4 (22%)
Median overall survival, months	21.1 (14.8 to not estimable)	6.7 (2.1 to 10.6)	4.0 (2.3 to 6.5)
Kaplan-Meier estimates of overall survival			

At 6 months	89% (81 to 93)	51% (26 to 71)	31% (11 to 54)
At 12 months	68% (56 to 76)	23% (7 to 43)	11% (2 to 33)

Data are % (95% CI), n (%), or months (95% CI). FGFR=fibroblast growth factor receptor.

* Assessed and response confirmed by independent reviewer (95% CIs not available for individual response values).

† Overall survival data were not mature at data cutoff.

The majority, 91 (88%) of 103 of participants in Cohort A with post-baseline target lesion measurements, had IRC-assessed best percentage reductions in target lesion diameters from baseline

median DOR was 7.5 months (95% CI: 5.7, 14.5;

Estimated probabilities of maintaining IRC-assessed, confirmed tumor response for at 12 months 37.4% (95% CI: 18.6, 56.2)

[redacted]

[redacted]

9.4.4.8 Progression-Free Survival Based on IRC Assessment

In Cohort A, median PFS based on IRC assessment was 6.9 months (95% CI: 6.2, 9.6; [redacted] In Cohort A, Kaplan-Meier estimates of PFS at [redacted] 12 months [redacted] 29.2%, [redacted]

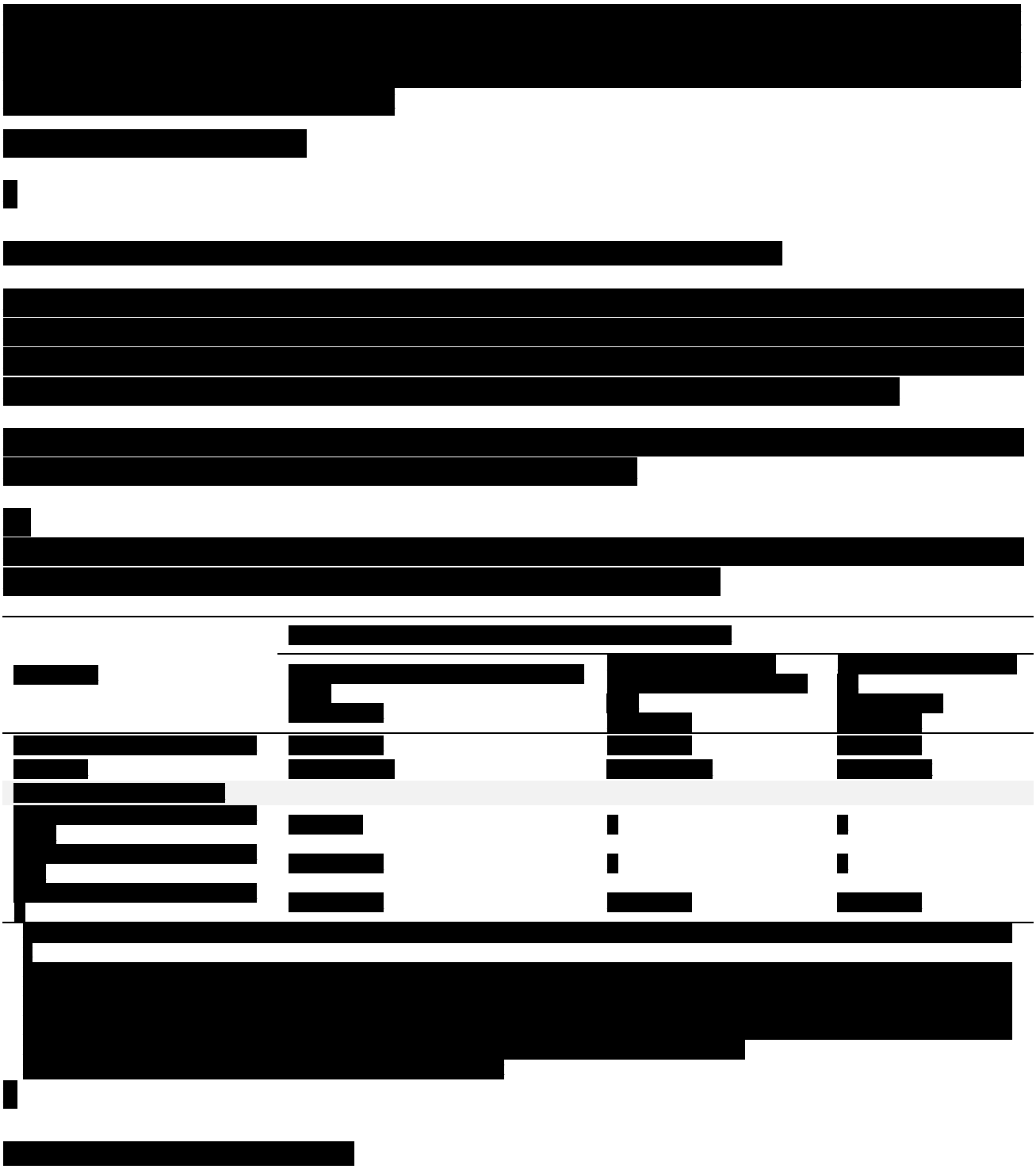
In Cohorts B and C, median PFS (2.1 and 1.7 months, respectively) [redacted]

[redacted]

[redacted]

[redacted]

[redacted]



In Cohort A, as of the data cut-off, 67 participants (62.6%) were alive [redacted] Median OS was 21.1 months (95% CI: 14.8, NE). Kaplan-Meier estimates of 6-month and 12-month OS were 88.6% (95% CI: 80.8, 93.4) and 67.5% (95% CI: 56.4, 76.3), respectively.

In Cohort B, as of the data cut-off, [redacted] 125] Median OS was 6.7 months (95% CI: 2.10, 10.55). Kaplan-Meier estimates of 6-month and 12-month OS

were [redacted] (50.5% [95% CI: 26.4, 70.5] and 22.5% [95% CI: 7.0, 43.2], respectively; see Table 14 [redacted]

In Cohort C, [redacted]

Median OS was 4.02 months (95% CI: 2.33, 6.47). Kaplan-Meier estimates of 6-month and 12-month OS were [redacted] (31.3% [95% CI: 11.4, 53.6] and 12.5% [95% CI: 2.1, 32.8], respectively; see Table 14 [redacted]

[redacted]

[redacted]

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[redacted]

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[redacted]

[redacted]

[redacted]

Serious TEAEs occurred in 44.5% of participants [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Treatment-Emergent Adverse Events

Across all three cohorts (n=146), the most common adverse event was hyperphosphatemia occurring in 88 (60%) of 146 patients [redacted]

93 (64%) patients had grade 3 or worse adverse events.[124] The most frequently reported ≥ Grade 3 TEAE (irrespective of cause) was hypophosphatemia (12%), arthralgia (6%), stomatitis (5%), hyponatremia (5%), abdominal pain (5%) and fatigue (5%). [redacted]

[redacted]

[redacted]

[redacted]

Fatal Treatment-Emergent Adverse Events

Six participants (4.1%) had serious TEAEs with a fatal outcome as of the data cut-off date: failure to thrive in 2 participants and bile duct obstruction, cholangitis, sepsis, and pleural effusion in a single participant each.[125] None of the TEAEs with a fatal outcome were considered to be related to Pemazyre by the investigator.

[redacted]

In the overall population, among the 65 participants (44.5%) who had serious adverse events, the most frequently reported serious adverse events (more than three patients) were abdominal painand pyrexia [redacted] and cholangitis and pleural effusion [redacted]

[redacted]

In the overall population, among the 13 participants (8.9%) who discontinued treatment owing to adverse events, the only events that occurred in more than 1 participant were intestinal obstruction and acute kidney injury in 2 participants [redacted] each.

In the overall population, among the 62 participants (42.5%) with TEAEs leading to Pemazyre interruption, the most frequently reported events were stomatitis [redacted] palmar-plantar erythrodysesthesia syndrome [redacted] arthralgia [redacted] and fatigue [redacted]

[redacted]In the overall population, among the 20 participants (13.7%) with TEAEs leading to Pemazyre dose reduction, the most frequently reported events were stomatitis, arthralgia, and palmar-plantar erythrodysesthesia syndrome [redacted](3.4%) [redacted]1.4%) [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]ORR of 35.5% (95% CI: 26.50, 45.35). Tumor responses were durable, with a median DOR of 7.49 months (95% CI: 5.65, 14.49). The safety profile of Pemazyre 13.5 mg QD on a 2-weeks-on/1-week-off schedule is manageable. The benefit/risk ratio for Pemazyre therapy is favorable. Pemazyre provides a novel, targeted, therapeutic approach for previously treated CCA patients with FGFR2 rearrangements or fusions, for whom second-line systemic therapies offer inadequate efficacy.

Cost Analysis of Pemigatinib for Patients with Previously Treated Locally Advanced Or Metastatic Cholangiocarcinoma (CCA) With An FGFR2 Rearrangement Or Fusion

Technical report v 4.0

Prepared For: The Danish Medicines Council

Company: Incyte Biosciences Nordic AB

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Contents

Abbreviations

Abbreviation/acronym	Definition
AE	Adverse event
AIC	Akaike information criterion
ASC	Active symptom control
BIC	Bayesian information criterion
BTC	Biliary tract cancer
CCA	Cholangiocarcinoma
CI	Confidence interval
CT	Computerised tomography
DSU	Decision Support Unit
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal growth factor receptor
ESMO	European Society for Medical Oncology
FGFR	Fibroblast growth factor receptor
FU	Fluorouracil
HR	Hazard ratio
iCCA	Intrahepatic cholangiocarcinoma
IPD	Individual patient-level data
ITC	Indirect treatment comparison
KM	Kaplan–Meier
MAIC	Matching-adjusted indirect comparison
mFOLFOX	Oxaliplatin, L-folinic acid and fluorouracil with active symptom control
MO	Mobility
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
OS	Overall survival
PCR	Polymerase chain reaction
PD	Progressed disease
PF	Progression-free
PFS	Progression-free survival
PH	Proportional hazards
PPS	Post-progression survival
PSM	Parametric survival model
RDI	Relative dose intensity
SD	Standard deviation
TA	Technology appraisal

Abbreviation/acronym	Definition
TOT	Time on treatment
TSD	Technical support document
UA	Usual activities
VAT	Value added tax

1. Introduction

Cholangiocarcinoma (CCA) is a rare form of liver cancer of the biliary tract. It includes both intrahepatic and extrahepatic bile duct cancers and has an incidence of 1.3 per 100,000 in Denmark.[1]

For unresectable CCA, current international guidelines suggest first-line treatment with either cisplatin plus gemcitabine, a fluoropyrimidine-based regimen or other gemcitabine-based chemotherapy regimens.[2,3] Currently, there is no established systemic therapy for patients with CCA who have progressed following first-line treatment. However, the ABC-06 study (a randomized Phase III, multicentre, controlled, open-label clinical trial) has recently published evidence of advanced or metastatic biliary tract cancer patients benefitting from chemotherapy in the second-line setting.[4]

Pemigatinib is a selective fibroblast growth factor receptor (FGFR) inhibitor and was investigated in the Phase II, open-label multi-centre clinical trial FIGHT-202.[5] Pemigatinib has previously been approved by the Food and Drugs Administration (FDA)[6] and received positive opinion from the Committee of Medicinal Products for Human Use (CHMP) on the 28 January 2021.[7]

2. Methods

2.1 Economic analysis

2.1.1 Patient population

The patient population for the economic analysis is the same as the population from Cohort A of FIGHT-202 – patients with previously treated locally advanced or metastatic CCA with an FGFR2 fusion or rearrangement. The age at baseline was 55 years and the proportion male in the patient population was 39%. Incidence is increasing with age and most patients in Denmark are diagnosed with CCA between ages 50-70[8], which is in line with the baseline age of Cohort A in FIGHT-202. The proportion of CCA in men and women in Denmark respectively is in line with the model population. The patient population relevant for this assessment is a subgroup of CCA, which differs somewhat from CCA patients in general. This subgroup of patients presents a slightly lower age and a higher share of women, than in CCA overall.[9]

2.1.2 Model structure

Cohort simulation model

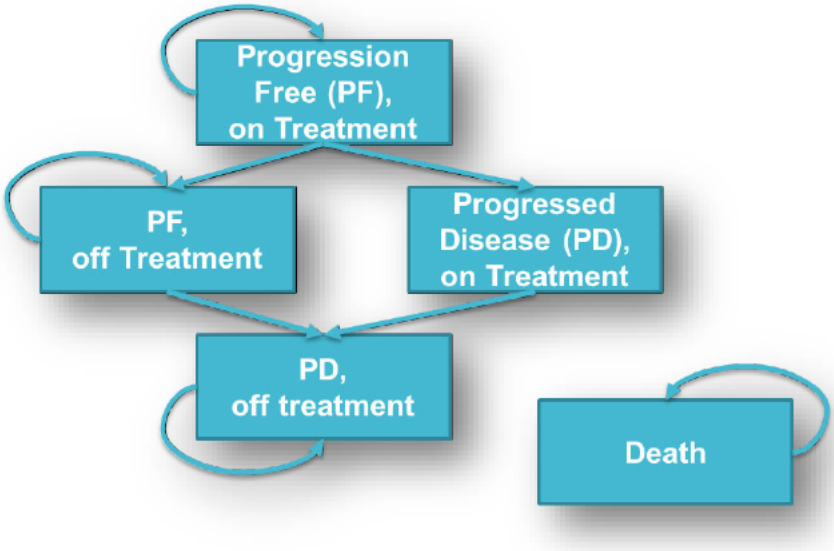
The model uses a five-state partitioned survival approach to estimate the costs of pemigatinib and the comparators. All patients start in the 'progression-free, on treatment' health state. Upon treatment discontinuation, patients move to 'progression-free, off treatment'; upon disease progression, patients move to 'progressed disease, on treatment'; and after both treatment discontinuation and disease progression,

patients move to 'progressed disease, off treatment'. However, in the base case, patients cannot undergo disease progression without also discontinuing their treatment. Once patients have progressed or discontinued treatment, they cannot return to the previous health state. Once patients have died, they remain in the 'death' health state until the end of the model (Figure 1).

The lifetime time horizon in the model is set to 40 years at base case, at which point 99.87% of patients in the pemigatinib arm have died. A longer time horizon of 50 years is considered in the scenario analysis, at which point all patients have died. The model has a cycle length of 1 week, which should be considered sufficiently short and accurate to not require a half-cycle correction.[10]

Patient health state distributions over time are determined by extrapolating overall survival (OS), progression-free survival (PFS) and time on treatment (TOT) data from available clinical trials. Since the model time horizon extends beyond most trial periods, clinical trial data are extrapolated into survival curves across the entire model time horizon. For each clinical outcome (TOT, PFS and OS), parameters are derived for various survival functions, and the most plausible survival models are selected based on visual, statistical and clinical validity.

Figure 1: Model health states



Note: The progressed disease (PD) state is not considered in the base case analysis due to treatment scheduling rules for both the intervention and comparators.

2.1.3 Perspective

The analysis is conducted from a restricted social perspective. The discount rates for costs are 3.5% annually, applied per model cycle. All costs have been adjusted to the latest available prices expressed in Danish kroner (DKK).

The choice of model is in line with NICE guidelines for oncology modelling. Inputs used in the model have been validated both internally and by clinicians and is described in each section where applied.

Intervention

Pemigatinib is an inhibitor of the FGFR types 1, 2 and 3 (FGFR1/2/3). It is administered orally once daily for 14 days, followed by 7 days with no administrations.[5] This 21-day cycle repeats for the duration of treatment. The treatment cycle of 14 administration days per 21 days is modelled as an average weekly number of administrations of 14/3. During each administration, a dosage of 13.5 mg is applied.

Table 1. Intervention

Intervention	Clinical documentation (including source)	Used in the model (number/value including source)	Expected Danish clinical practice (including source if known)
Posology	Oral administration of 13.5 mg once daily for 14 days, followed by 7 days with no administration (FIGHT-202[9]).	Oral administration of 13.5 mg once daily for 14 days, followed by 7 days with no administration (FIGHT-202[9]).	Oral administration of 13.5 mg once daily for 14 days, followed by 7 days with no administration (Assumed use as suggested by evidence of FIGHT-202[9]).
Length of treatment (time on treatment) (mean/median)	Treat to progression (FIGHT-202[9])	Treat to progression (FIGHT-202[9])	Treat to progression (Assumed use as examined in FIGHT-202[9])
The pharmaceutical's position in Danish clinical practice	2nd line treatment for patients with previously treated locally advanced or metastatic cholangiocarcinoma (CCA) with an FGFR rearrangement or fusion (FIGHT-202[9])	2nd line treatment for patients with previously treated locally advanced or metastatic cholangiocarcinoma (CCA) with an FGFR rearrangement or fusion (FIGHT-202[9])	2nd line treatment for patients with previously treated locally advanced or metastatic cholangiocarcinoma (CCA) with an FGFR rearrangement or fusion (Assumed positioning as suggested by indication and examined in FIGHT-202[9])

2.1.4 Comparator

No well-established standard of care is currently available in Denmark for the patient population. Since cholangiocarcinoma has a low prevalence, there remains a lack of data in the literature. A majority of patients with refractory cholangiocarcinoma are likely too vulnerable to be treated with chemotherapy, and so the most relevant comparator is active symptom control (ASC), for which trial data are available from the recent ABC-06 study.[11] ABC-06 is a randomized Phase III, multicentre, open-label study of active symptom control (ASC) alone or ASC with oxaliplatin/5-FU chemotherapy (mFOLFOX) for patients with locally advanced/metastatic biliary tract cancers previously treated with cisplatin/gemcitabine chemotherapy. mFOLFOX is not included as a comparator in the model, as the patient population relevant for this assessment is likely too weak to be treated with chemotherapy. However, as PFS is not available for the ASC arm of the

ABC-06 trial, PFS for ASC is assumed to be equal to that of the mFOLFOX+ASC arm. This is likely a conservative assumption, as the effect of mFOLFOX+ASC has proven more effective than that for ASC. The ABC-06 trial was based on a UK population and while this related disease area does not exactly match the patient population of interest for the cost model (ABC-06 investigates all biliary tract cancers [BTCs], whereas FIGHT-202 only includes those who have FGFR2 rearrangements or fusions and intrahepatic cholangiocarcinomas), the ABC-06 study provides the strongest and most relevant available data to compare against.

Patients receiving ASC alone may receive biliary drainage, antibiotics, analgesia, steroids, anti-emetics, etc. as well as palliative radiotherapy and blood transfusions. The costs for these drugs and procedures are not explicitly included in the model since they would be expected to apply to both arms equally and are thus not expected to significantly impact the outcomes.

2.2 Clinical parameters and variables

Since FIGHT-202 was a single-arm trial, additional statistical methods are required to calculate a relative treatment effect between trials. The following section details the alternative survival modelling approaches that are built into the cost model. These include: extrapolating survival data from clinical trials and comparing these naïvely, extrapolating using Kaplan–Meier (KM) data that have been adjusted for patient characteristics of comparator trials using matched-adjusted indirect treatment comparison (MAIC), or applying hazard ratios (HRs) for relative treatment effects to the pemigatinib extrapolation (either naïve or MAIC).

In the base case, the MAIC analysis (using patient characteristics from the ASC arm) is used. KM data were taken from the relevant trials. Several curve functions recommended by the NICE Decision Support Unit (DSU) Technical Support Document (TSD) 14 were fitted to these data.[12] The most appropriate curve was then selected based on visual, statistical and clinical validity within and beyond the trial period. Statistical validity was assessed through the Akaike information criterion (AIC) and Bayesian information criterion (BIC).

2.2.1 Overall survival

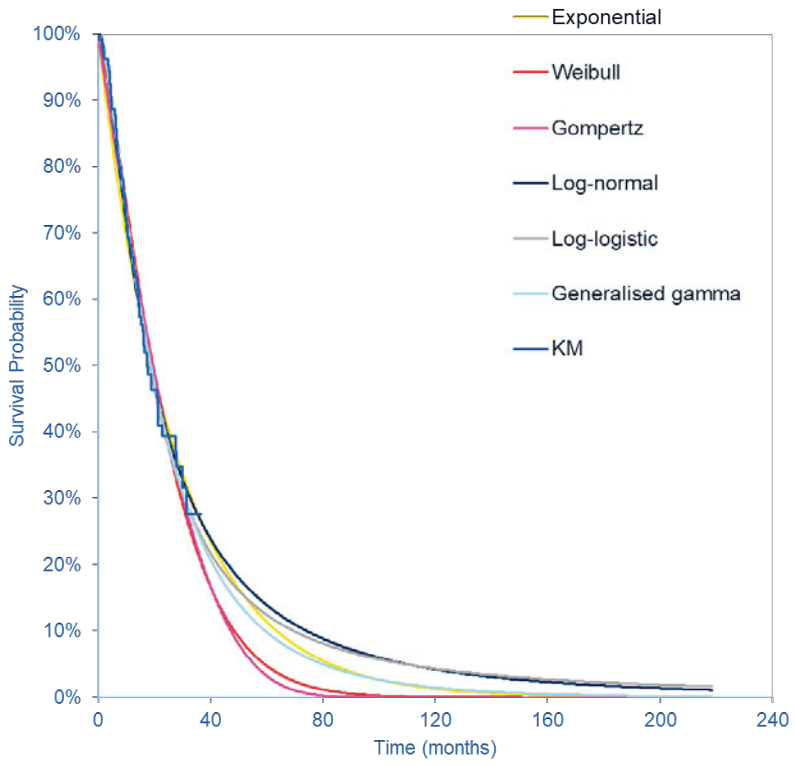
OS curves were extrapolated from relevant trial data across the model time horizon. For clinical validity, the survival rates were limited in any cycle where they provided relative survival greater than those reported for the age-matched general population of Denmark.

The same survival model has been selected across the treatment arms in the base case to ensure a consistent approach, as recommended by the NICE DSU TSD 14. Based on the results reported in the following sections, the log-logistic model was selected as the base case for both treatment arms. Alternative model fits are tested in scenario analysis.

Intervention

OS for the pemigatinib treatment arm was extrapolated from the FIGHT-202 OS KM data for Cohort A patients (participants with FGFR2 rearrangements or fusions), using a MAIC to adjust and match for patient characteristics from the ASC arm of ABC-06 (Figure 4). The Gompertz, Weibull and generalized gamma curves provide a relatively conservative OS estimate, whereas the log-logistic, log-normal and exponential curves produce more optimistic survival projections. The AIC and BIC scores (Table 3) suggest the Weibull, Gompertz and log-logistic curves are the best statistical fit. When validating the extrapolations of pemigatinib OS, both interviewed clinicians struggled to choose the most feasible curve but suggested that they may expect to observe 5% of patients alive at 5 years. Neither the log-logistic (10%), the Weibull (1%) or the Gompertz (0%) curves had 5-year survival estimates close enough to the clinicians' estimates to be considered better than the other. Therefore, the log-logistic curve was selected for the base case due to it being a better fit to comparator data (for which there are more complete data), as shown in Table 3. Since the Weibull curve was also a good fit, this was explored as an option in scenario analysis. The mean OS for the base case model (log-logistic) was 34.3 months.

Figure 2: Pemigatinib OS KM data and models



Key: KM, Kaplan–Meier; OS, overall survival.

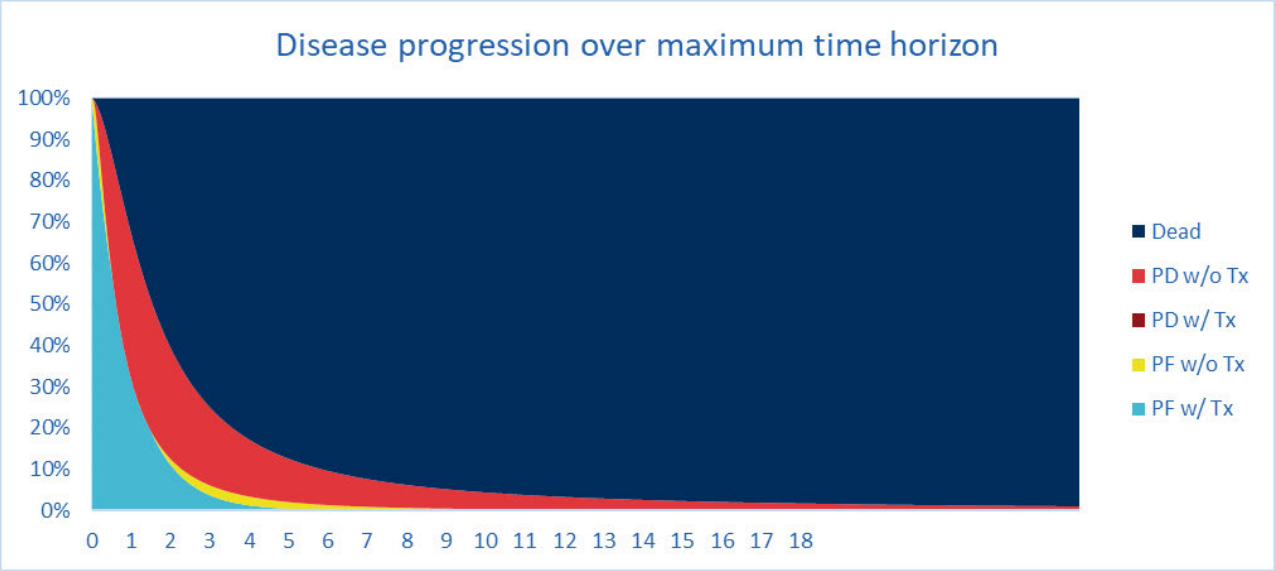
Table 2: Pemigatinib OS AIC and BIC scores

Model	AIC	BIC
Exponential	546.39	549.07
Generalized gamma	542.89	550.94
Gompertz	546.56	551.93
Log-logistic	540.42	545.79
Log-normal	541.89	547.25
Weibull	542.91	548.27

Key: AIC, Akaike information criterion; BIC, Bayesian information criterion; OS, overall survival.

The patient flow for the pemigatinib treatment arm, showing the distribution of patients among health states at each time point, is presented in Figure 3.

Figure 3: Patient flow for pemigatinib

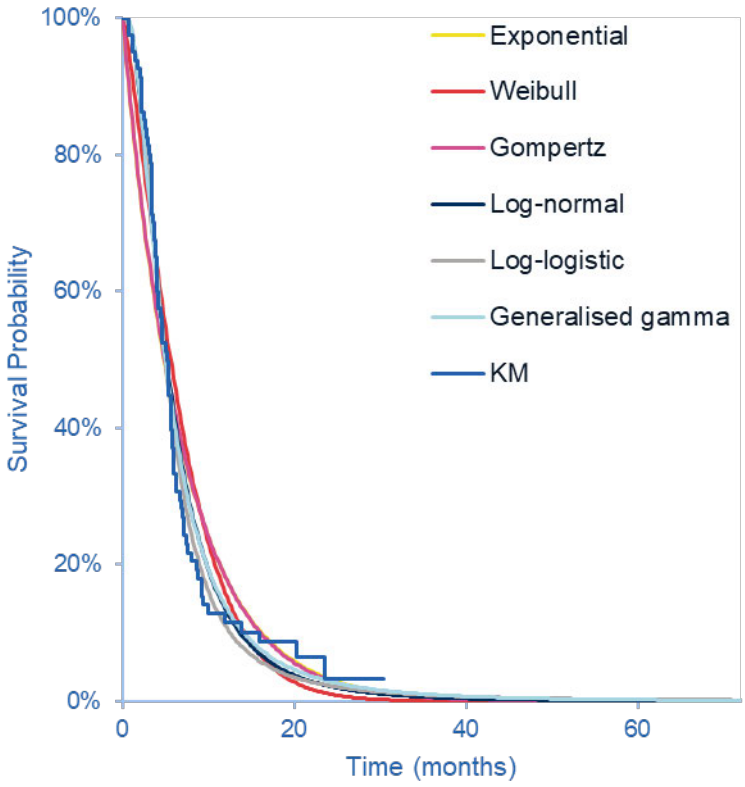


Key: PD, progressed disease; PF, progression-free; Tx, treatment; w/, with; w/o, without.

Active symptom control

OS for the ASC treatment arm was extrapolated from the ABC-06[4] OS KM data. Due to the high data maturity, all curves drop below 1% at similar time points, except for the Weibull curve (Figure 4). The AIC and BIC scores (Table 3) favour the log-logistic and log-normal curves. To align curve choice across model arms, log-logistic was chosen in the base case. The mean OS for the base case model (log-logistic) was 6.9 months.

Figure 4: ASC OS KM data and models



Key: ASC, active symptom control; KM, Kaplan–Meier; OS, overall survival.

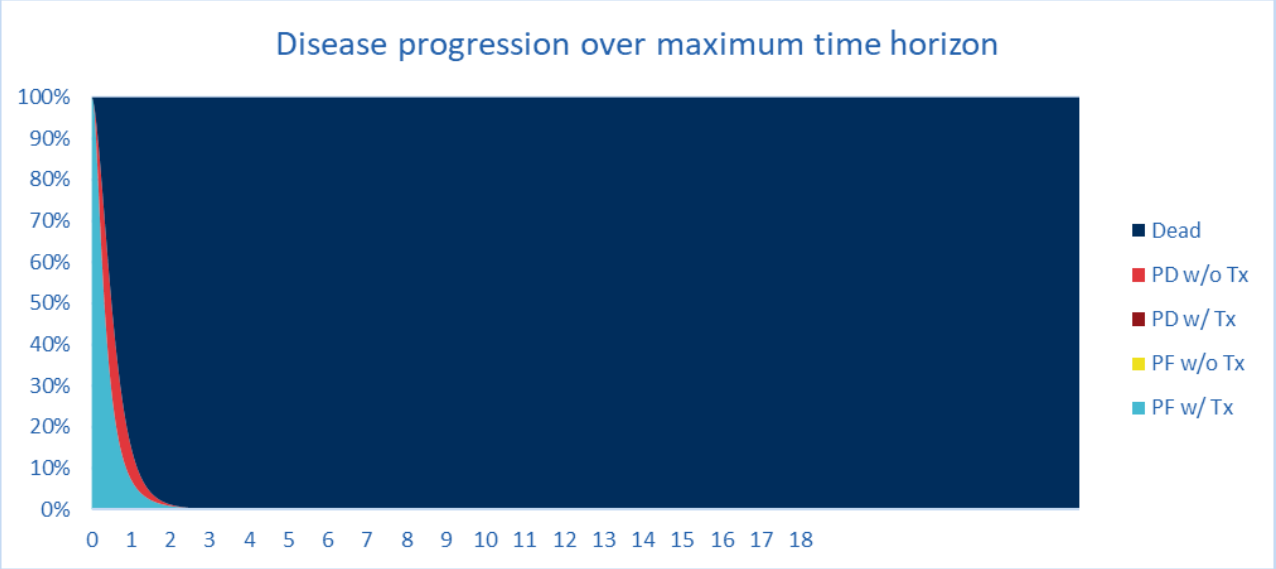
Table 3: ASC OS AIC and BIC scores

Model	AIC	BIC
Exponential	438.89	441.28
Generalized gamma	415.48	422.66
Gompertz	440.86	445.65
Log-logistic	**409.56**	**414.35**
Log-normal	**414.16**	**418.95**
Weibull	433.01	437.80

Key: AIC, Akaike information criterion; ASC, active symptom control; BIC, Bayesian information criterion; OS, overall survival.

The patient flow for the ASC treatment arm, showing the distribution of patients among health states at each time point, is presented in Figure 5.

Figure 5: Patient flow for ASC



Key: PD, progressed disease; PF, progression-free; Tx, treatment; w/, with; w/o, without.

MAIC

Since FIGHT 202 is a single-arm trial, alternative methods to estimate relative treatment effects between pemigatinib and relevant comparators were considered. In this instance, MAIC has been chosen since it allows the calculation of adjusted relative treatment effect estimates (e.g. HRs) in one direct step and a set of weights can be derived; the same set of weights can be used for all relevant outcome models (e.g. OS and PFS).

Prognostic variables and treatment effect modifiers were identified for use as covariates in the matching process based on those that were reported in existing publications. These baseline characteristics had to be available in the individual patient-level data (IPD) of FIGHT-202 and reported for the comparator trials.

The available variables included in the matching included:

- Age (continuous)
- Sex (binary)
- ECOG status (binary, proportion 0–1)
- Albumin (binary, proportion <35)

Details of the matching and weighting process for these variables are provided in the Appendix.

After the matching procedure was conducted and the weights were derived, efficacy outcomes were compared between balanced treatment groups using analyses that incorporate the derived weights. Parametric survival models (PSMs) of the re-weighted pemigatinib data were then fitted and compared to the PSM curve fits of the digitized comparators. The Cox proportional HRs were also calculated between the weighted and comparator data.

While using PSMs allows more flexibility to model survival, this method generates individual pemigatinib curves for each comparator that reflect the population of each comparator trial for the re-weighted pemigatinib data. The alternative approach is to use weighted HRs that can be applied to the unweighted pemigatinib data. This method results in only one curve for pemigatinib in the FIGHT-202 data population, but there is less flexibility for the fits, and it relies on the proportional hazards (PH) assumption. Log-cumulative hazard plots were used to test the PH assumption and showed that this assumption is met since the lines are relatively straight and parallel (Figure 12, 13 and 14 in appendix). Both options (PSMs and HRs) are implemented in the economic model and tested in scenario analyses. For the PSMs, uncertainty is captured using the multivariate normal distribution and the variance-covariance from each PSM.

The unweighted and MAIC-weighted HRs for OS are presented in Table 4. In general, the relative effect was larger for the weighted analysis compared to the unweighted analysis. When these are applied in the cost model, they are applied for 2 years (the approximate length of follow-up in the FIGHT-202 trial data), after which the hazard ratio is assumed to be equal to 1 to reflect the lack of treatment effect expected once a patient has discontinued treatment.[13]

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FGFR2+/iCCA prognostic factor

There is some evidence suggesting that FGFR2 fusions and rearrangements may confer a survival advantage to patients with BTC and CCA.[14,15] Discussions with clinical and health economic experts in validation meetings have suggested that this potential prognostic factor may be conflated with a higher proportion of iCCA, female or younger patients.[13] Unfortunately, FGFR mutation status is not reported in the aforementioned comparator clinical trials, and only iCCA patients were captured in FIGHT-202; therefore, these variables cannot be included in any matching analysis. In an attempt to address this, the [redacted]

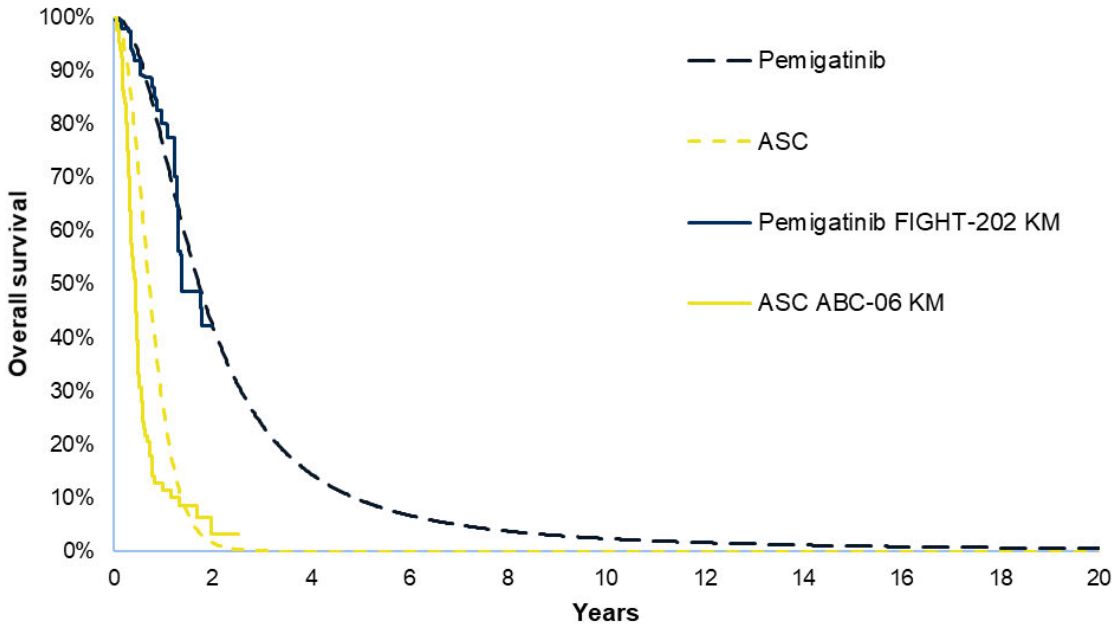
[redacted]

[redacted]. For the proportion of wild-type FGFR2 patients in the cost model, the cycle probability of survival from the extrapolations is weighted using the FGFR2+ HR. Although this could be driven by iCCA, this is referred to as an FGFR2 prognostic factor due to the published evidence used to inform this hazard ratio.

Base case

For the base case, the MAIC-adjusted survival curves (using the patient characteristics from the ASC arm of ABC-06) from FIGHT-202 are used to inform pemigatinib efficacy. For the comparator arm so that assumptions regarding PH and treatment effect cut-offs are not required to be made, efficacy is estimated based on the survival curve extrapolation from the published KM data. For all treatment arms, the mortality rate is replaced with that of the general population of Denmark if the modelled mortality rate is lower than this for any model cycle. Figure 6 presents OS estimates and extrapolations for a selection of treatment regimens, including the base case OS estimates for pemigatinib and for ASC. The use of HRs rather than independently extrapolated survival curves is tested in scenario analysis.

Figure 6: Overall survival



Key: ASC, active symptom control; OS, overall survival.

2.2.2 Progression-free survival

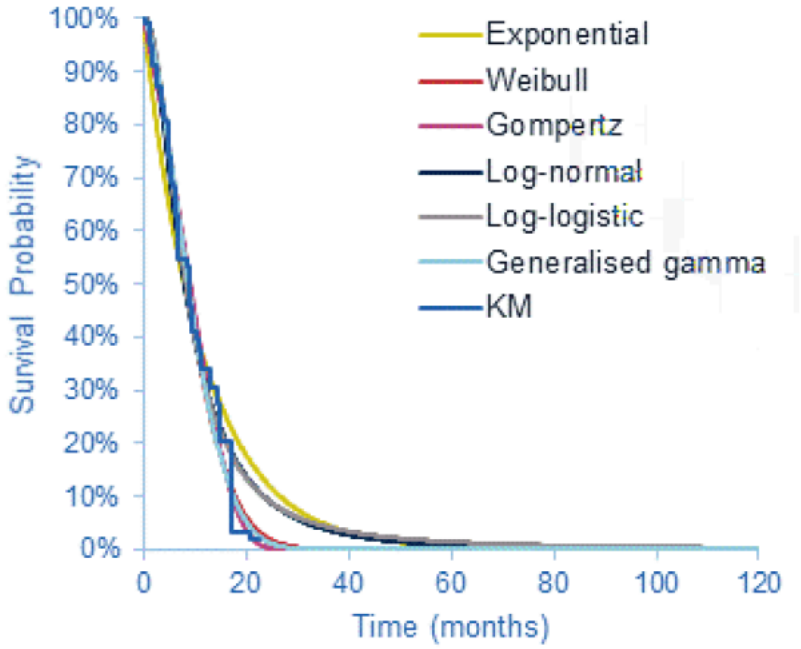
PFS values were taken from the same data sources as OS, where possible. As with OS, the same model is used across the treatment arms in the base case to ensure a consistent approach. Based on the results reported in the following sections, the log-normal model was selected for all treatment arms. Alternative model fits are tested in scenario analyses.

Intervention

PFS for the pemigatinib treatment arm was extrapolated from the FIGHT-202 KM data using a MAIC to adjust and match for patient characteristics from the mFOLFOX+ASC arm of ABC-06 (Figure 7). The reason for using the mFOLFOX+ASC arm for the MAIC is that PFS data is not available for the ASC arm in the ABC-06 trial. For

this reason, the MAIC assumes that PFS of ASC is equal to that of mFOLFOX+ASC, see section 2.1.4. The Weibull and Gompertz curves form the best fit of the tail end of the KM data. The AIC and BIC scores (Table 5) point favourably towards the Gompertz and Weibull curves. According to interviewed clinicians, approximately 10% of patients are expected to be progression-free 2 years after entering the model. This is aligned with the 2-year PFS estimate generated using the log-normal and log-logistic curves (9%). As log-normal was a better statistical fit for comparator data, this was selected as the base case. The mean PFS for the base case model (log-normal) was 12.6 months.

Figure 7: Pemigatinib MAIC-adjusted (using ABC-06 mFOLFOX+ASC) PFS KM data and models



Key: KM, Kaplan–Meier; PFS, progression-free survival.

Table 4: Pemigatinib MAIC-adjusted (using ABC-06 mFOLFOX+ASC) PFS AIC and BIC scores and 2-year PFS estimates

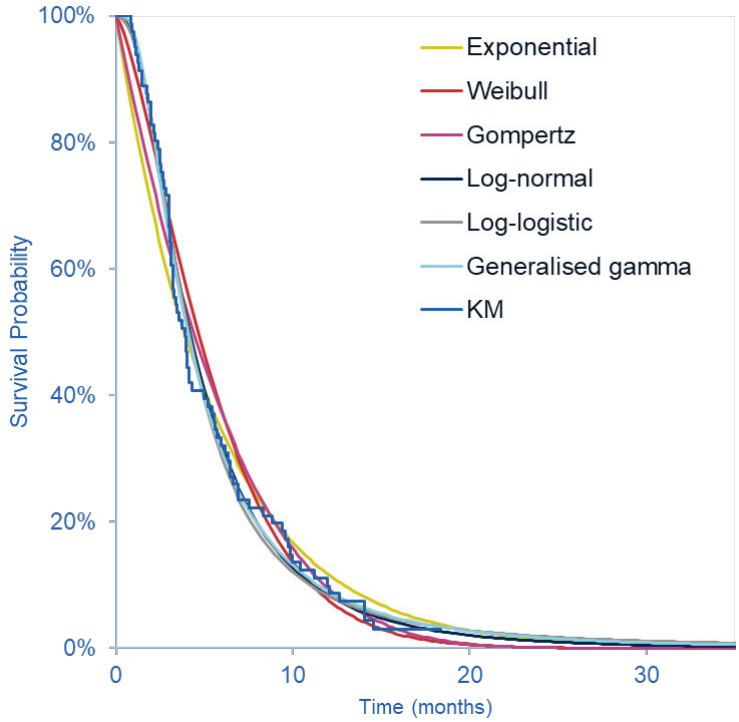
Model	AIC	BIC	2-year PFS estimates
Exponential	286.93	289.51	12%
Generalized gamma	277.11	284.86	2%
Gompertz	**276.75**	**281.92**	**0%**
Log-logistic	279.19	284.36	9%
Log-normal	279.62	284.79	9%
Weibull	**275.18**	**280.35**	**2%**

Key: AIC, Akaike information criterion; BIC, Bayesian information criterion; PFS, progression-free survival.

Active symptom control

In the absence of any PFS data reported for ASC in the ABC-06 publication[4], PFS for the ASC arm was assumed to be equal to that of the mFOLFOX+ASC arm. This is a conservative assumption, as the effect of mFOLFOX+ASC has been to be better than that for ASC alone. For mFOLFOX+ASC, PFS was extrapolated from the ABC-06 KM data.[4] The log-normal curve has a good fit (Figure 8) and very favourable AIC and BIC scores for the generalized gamma and log-logistic models (Table 6). For this reason and to align with the choice for the intervention, log-normal was selected as the base case for ASC. The mean PFS for the base case model (log-normal) was 5.9 months.

Figure 8: ASC (mFOLFOX+ASC) PFS KM data and models



Key: KM, Kaplan–Meier; mFOLFOX+ASC, oxaliplatin, L-folinic acid and fluorouracil; PFS, progression-free survival.

Table 5: ASC (mFOLFOX+ASC) PFS AIC and BIC scores

Model	AIC	BIC
Exponential	426.60	428.99
Generalized gamma	**406.41**	**413.59**
Gompertz	425.29	430.08
Log-logistic	**407.06**	**411.84**
Log-normal	**404.87**	**409.65**
Weibull	416.72	421.51

Key: AIC, Akaike information criterion; BIC, Bayesian information criterion; mFOLFOX+ASC, oxaliplatin, L-folinic acid and fluorouracil; PFS, progression-free survival.

MAIC

As discussed in Section 2.2.1, both MAIC options (PSMs and HRs) are implemented in the economic model for PFS and OS, and they are tested in scenario analyses. The unweighted and MAIC-weighted HRs for PFS are presented in Table 7. In general, the relative effect was larger for the weighted analysis compared to the unweighted analysis. As with OS, when applied in the model, the HR is applied for 2 years, after which the hazard ratio is expected to be 1. PFS for ASC is assumed to be equal to that of mFOLFOX+ASC in the ABC-06 trial. For this reason, the unweighted and MAIC weighted PFS hazard ratios for pemigatinib vs. ASC are assumed to be equal to those of pemigatinib vs. mFOLFOX+ASC.

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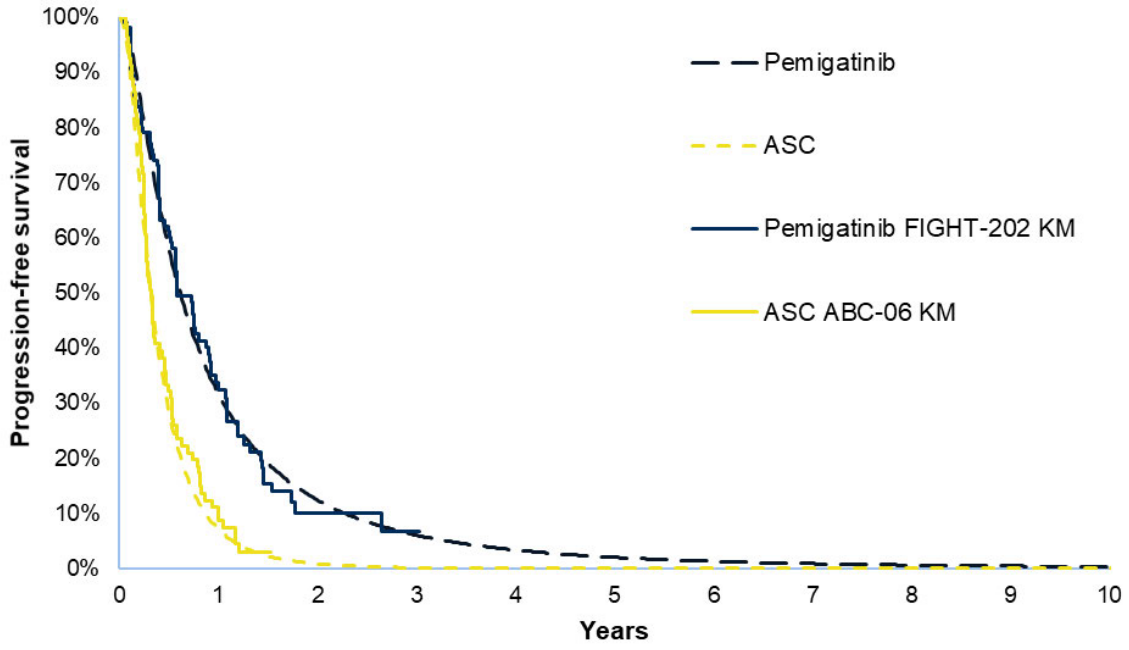
FGFR2+ translocation prognostic factor

Given that there is no evidence for a significant prognostic effect of FGFR2 fusions or rearrangements (or iCCA) on PFS[15], FGFR2+ prognostic factor HR is not applied to PFS in the base case. However, it is applied in a scenario analysis.

Base case

For the base case, aligned with the rationale for OS, the MAIC-adjusted survival curves (using the ABC-06 trial ASC arm patient characteristics) are used for extrapolation of pemigatinib PFS, while independently fitted survival curves are used for the comparator arms. For each treatment arm, the PFS is then set equal to OS in any cycle in which the PFS exceeds OS. Figure 9 presents PFS estimates and extrapolations for a selection of treatment regimens, including the base case PFS estimates for pemigatinib and for ASC.

Figure 9 Progression-free survival



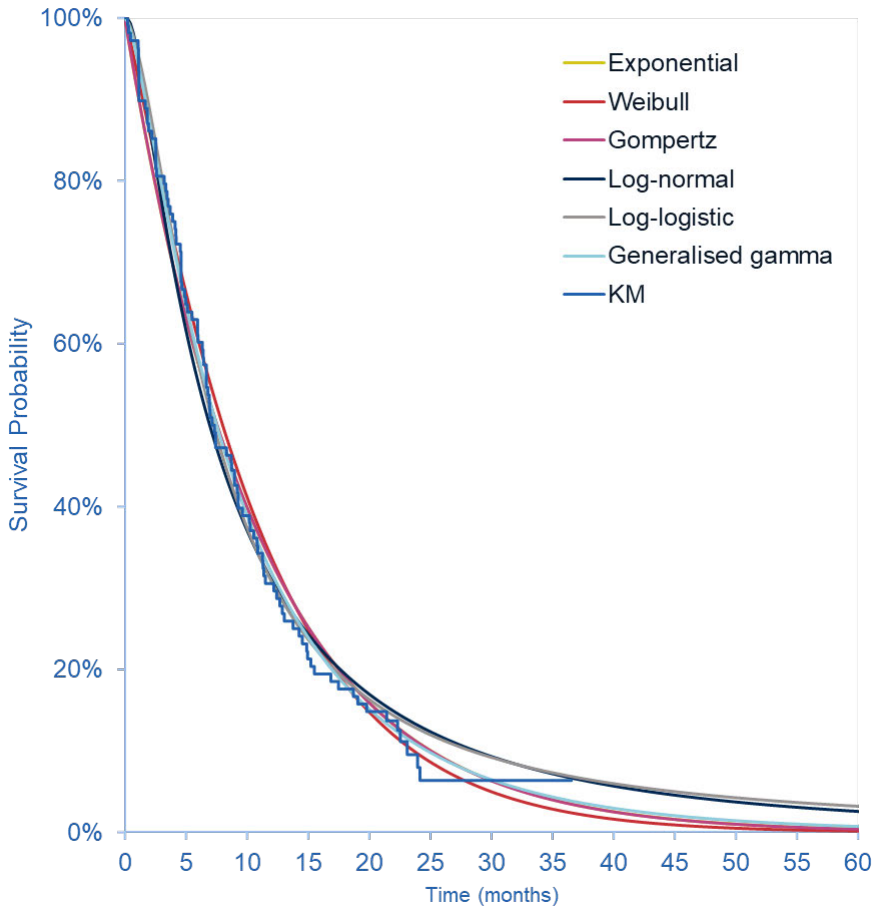
Key: ASC, active symptom control; PFS, progression-free survival.

2.2.3 Time on treatment

Intervention

TOT for the pemigatinib treatment arm was extrapolated from the FIGHT-202 KM data (Figure 10). Only curves unadjusted to the comparator arms are available due to the similarity of PFS and TOT and the similarity of unadjusted and adjusted FIGHT-202 PFS KM data. All models fit the KM data well. Towards the end of the extrapolations, the log-normal and log-logistic curves form relatively optimistic extrapolations beyond the KM data compared to the other models (Table 8). The AIC and BIC scores show the exponential and log-logistic models providing the best statistical fit. Since exponential is the simplest model and provides estimates closer to the expected values of interviewed clinicians (10% at 2 years estimated by clinicians – aligned with PFS[13]; 12% for exponential and 15% for log-logistic), this is selected in the base case. The mean TOT for the base case model (exponential) was 11.0 months.

Figure 10: Pemigatinib unadjusted TOT KM data and models



Key: KM, Kaplan–Meier; TOT, time on treatment.

Table 6: Pemigatinib unadjusted TOT AIC and BIC scores

Model	AIC	BIC	2-year TOT estimates
Exponential	**1043.70**	**1046.37**	**12%**
Generalized gamma	1044.63	1052.65	12%
Gompertz	1045.61	1050.95	11%
Log-logistic	**1042.84**	**1048.18**	**15%**
Log-normal	1044.70	1050.05	16%
Weibull	1044.24	1049.59	10%

Key: AIC, Akaike information criterion; BIC, Bayesian information criterion; TOT, time on treatment.

Comparator

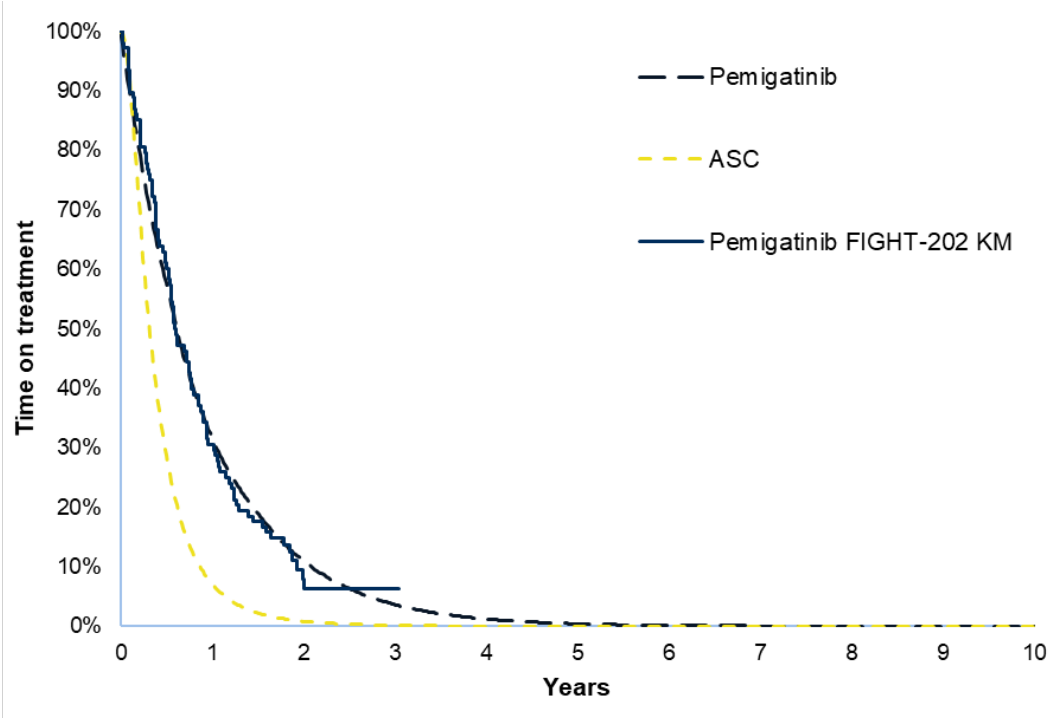
Due to the absence of TOT KM data for the comparator trial[4], it is assumed that patients discontinue treatment at the time of treatment progression or after a fixed number of weeks, depending on the treatment regimen

(Section 2.3.2).[4] Due to the lack of TOT data for ASC, TOT is assumed to be equal to PFS. Therefore, mean TOT for ASC in the base case model (log-normal) was 5.9 months.

Base case

For each treatment arm, as treatment with pemigatinib should not be continued beyond progression[16], the TOT is set equal to PFS in any cycle in which the TOT exceeds PFS. The resulting TOT for each treatment arm is presented in Figure 11.

Figure 11: base case time on treatment



Key: ASC, active symptom control; TOT, time on treatment.

2.2.4 Safety

Adverse events (AEs) affect the costs for each arm during the modelled time in which treatments are administered. To limit the number of AEs to those that are most likely to impact the model costs, AEs were only included if they were Grade 3 or higher or if they are known to have a significant clinical impact. For each arm, AE occurrences were divided by the total patient years in which they were recorded to derive an annual AE rate (Table 9). AEs are realized in the model as costs (Section 2.3.5). All-cause AEs are used since treatment-related AEs were not reported in comparator publications.

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2.3 Costs

2.3.1 Drug costs

. No acquisition costs apply for ASC, as they are expected to affect both treatment arms equally and thus have no impact on the results.

The unit costs are multiplied by the planned dosing regimens and corrected for any observed deviations from the planned dose (using the relative dose intensity).

No wastage is assumed in the model. This is because, for the main comparator, ASC, no acquisition cost is assumed in the model. Given the assumed packaging for pemigatinib, it will include 14 tablets for a 21-day cycle; therefore, wastage is expected to be minimal.

Table 7: Weekly drug costs

Treatment	Drug	Cost per mg	Admin dose	Relative dose intensity	Weekly dose intensity	Weekly dose	Weekly cost	Source	Active weekly total cost
[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ASC		0.00 DKK/mg			0 mg/m^2	0 mg	0.00	Lamarca et al.2019[4]	0.00 DKK

Key: ASC, active symptom control.

Note: [a], calculated using average daily dose (from Table 10 of the FIGHT-202 clinical study report) divided by the planned daily dose.

2.3.2 Administration costs

Since pemigatinib is administered orally, no administration cost is assumed. ASC is also assumed to incur no administration costs, as these costs are assumed to be equal across arms (Section 2.1.4).

2.3.3 Monitoring costs

According to the European Society for Medical Oncology (ESMO) guidelines for biliary cancer follow-up, major centres currently employ a monitoring strategy using a combination of clinical examination, computed tomography scans and blood tests.[2] These are used in the cost model and, using DRG reference costs[17] 2021 and Laboratoriemedicinske Vejledninger (LMV)[18] 2020, are costed as 10,429.56 DKK (clinical exam, DRG: 07MA98), 8,019.97 DKK (CT scan, DRG: 30PR06) and 1,118.88 DKK (Blood tests[1]), annually. The guidelines suggest follow-up visits once every 3 months during the first 2 years after therapy[2] – this frequency is assumed for all patients in the model, with patients incurring each test cost once every 3 months, irrespective of progression status for clinical examinations and blood tests. However, CT scans are assumed to be performed once every 12 months for progressed patients, as clinician feedback suggested these scans would be performed less frequently after progression.[13] Patients receiving treatment with pemigatinib have an annual probability of developing visual symptoms of 1.95. For this reason, additional monitoring is applied as one ophtalmological examination once every 2 months for the first 6 months of treatment and thereafter every 3 months. Costs associated with visual symptoms are only applied for the pemigatinib arm. Monitoring costs are presented in Table 11.

Table 8: Monitoring costs

Resource	Unit cost (DKK)	Annual patient cost (DKK)	Reference
Clinical exam	2,610.00	10,429,56	DRG-takster 2021, Assumption: One visit to physician ["MDC07 1-dagsgruppe, pat. mindst 7 år", 07MA98]
CT scan	2,007.00	8,019.97	DRG-takster 2021, CT scan ["CT-scanning, kompliceret", 30PR06]
Blood tests	280.00	1,118.88	LMV 2020, sum of several tests[1]
Opthtalmological exam	1,028.00	4,626.00	DRG-takster 2021, Ophtalmological exam

[1] Calculation, sum of tests and cost for test taking (LMV): NPU02319, "Hæmoglobin;B" & NPU01961, "Erytrocytter,vol.fr.;B" & NPU02593, "Leukocytter;B" & NPU19748, "C-reaktivt protein (CRP) " & NPU19674, "Albumin;Plv", & NPU03688, "Urat; P" & NPU02725, "Methæmoglobin;HB(B)" & NPU03568, "Trombocytter; B" & NPU08694, "Reticulocytter; B" & NPU04998, "Kreatinin;P"

			["Øjenundersøgelse, mindre", 02PR01]

2.3.4 End-of-life costs

End-of-life costs were based on the DRG-takster 2021[17] and included in the model at a cost of 88,471.00 DKK [26MP45].

2.3.5 Adverse event costs

The cost associated with each AE was taken from the DRG-takster for 2021[17]. A large number of AEs reported in FIGHT-202 and ABC-06 were not reported explicitly in the reference costs and are thus informed using assumptions instead. All modelled event costs are reported in Table 12.

Table 9: Adverse event costs

Event	Unit cost	Assumption/ Code
Abdominal pain	2,610 DKK	One visit to physician ["MDC07 1-dagsgruppe, pat. mindst 7 år", 07MA98]
Alanine aminotransferase increased	2,610 DKK	One visit to physician ["MDC07 1-dagsgruppe, pat. mindst 7 år", 07MA98]
Anaemia	3,114 DKK	One visit to physician ["MDC16 1-dagsgruppe, pat. mindst 7 år", 16MA98]
Anorexia	2,610 DKK	One visit to physician ["MDC07 1-dagsgruppe, pat. mindst 7 år", 07MA98]
Arthralgia	2,610 DKK	One visit to physician ["MDC07 1-dagsgruppe, pat. mindst 7 år", 07MA98]
Aspartate aminotransferase increased	2,610 DKK	One visit to physician ["MDC07 1-dagsgruppe, pat. mindst 7 år", 07MA98]
Biliary event	2,610 DKK	One visit to physician ["MDC07 1-dagsgruppe, pat. mindst 7 år", 07MA98]
Cholangitis	18,694 DKK	Biliary tract disease ["Sygdomme i galdeveje, u. kompl. bidiag.", 07MA13]
Decreased serum albumin level	2,610 DKK	One visit to physician ["MDC07 1-dagsgruppe, pat. mindst 7 år", 07MA98]
Fatigue	2,610 DKK	One visit to physician ["MDC07 1-dagsgruppe, pat. mindst 7 år", 07MA98]
Hypophosphataemia	2,610 DKK	One visit to physician ["MDC07 1-dagsgruppe, pat. mindst 7 år", 07MA98]
Infection (lung/urinary/fever/not specified)	2,610 DKK	One visit to physician ["MDC07 1-dagsgruppe, pat. mindst 7 år", 07MA98]
Stomatitis	2,610 DKK	One visit to physician ["MDC07 1-dagsgruppe, pat. mindst 7 år", 07MA98]
Neutropenia	2,610 DKK	One visit to physician ["MDC07 1-dagsgruppe, pat. mindst 7 år", 07MA98]
Palmar-plantar erythrodysaesthesia syndrome	2,610 DKK	One visit to physician ["MDC07 1-dagsgruppe, pat. mindst 7 år", 07MA98]
Thromboembolic events	18,295 DKK	Acute stroke ["Akut myokardieinfarkt med ST-segment elevation", 05MA01]
Hyperphosphataemia (Grade 2+)	2,610 DKK	One visit to physician ["MDC07 1-dagsgruppe, pat. mindst 7 år", 07MA98]
Source: DRG-takster 2021[17]		

2.3.6 FGFR testing costs

The patient population for this cost model is previously treated patients with CCA including FGFR2+ fusions and rearrangements. Since FGFR2 testing is not part of standard clinical practice in Denmark, a cost for FGFR2 testing may need to be realised within the cost model for patients in the intervention arm. This cost is only applied to the intervention arm because, in current clinical practice, patients would not need to be tested for FGFR2 fusions or rearrangements before receiving current standard of care. Additionally, since not everyone tested would be positive for FGFR2 translocations, more than one person may need to be tested to treat one person with pemigatinib. To calculate the number of patients that must be tested before one pemigatinib-eligible patient is identified, an FGFR2+ translocation frequency of 8.6% was used.[19] This results in approximately eight tests being conducted per patient treated with pemigatinib. The total cost per test used in the model is 9,947.00 DKK ("Sammedagspakke: Klinisk genetisk udredning, omfattende, med svar", [31SP02]).

2.3.7 Patient costs

Patient costs are included in the model as transportation cost and time consumption cost. As mentioned in section 2.3.2, no administration costs or related visits are applied to neither the intervention nor comparator. Resource use is most pronounced in terms of monitoring, for which patients have a hospital visit once every three months. Resource use associated with monitoring are assumed to occur during the same hospital visit, for which reason a transport cost is only applied once per monitoring occasion. As CT scan is performed annually following disease progression, the time cost for CT scan is applied every fourth visit during progressed disease. Opthalmological examinations are assumed to incur visits and associated patient costs independently from general monitoring, the time consumption is assumed to correspond to that of a clinical exam. The FGFR test is a one-off resource use that is assumed to be applied during the first hospital visit and at the same time as the regular blood test. For this reason, the FGFR test is assumed to not incur any additional patient cost. Patient costs and assumptions informing time costs are summarized in Tables 13 and 14.

Table 10: Patient costs

Input	Unit cost	Reference
Transportation cost	100 DKK	Roundtrip to hospital, in line with guidelines[20]
Patient time cost	179 DKK	Mean wage per hour, in line with guidelines[20]

Table 11: Patient time inputs

Associated resource	Time consumption (Hours)	Assumption
Adverse events	3.0	Assumption: Time spent on average hospital visit linked to AEs (including transportation)
Clinical exam	0.5	Assumption: Time spent on average clinical exam (including transportation)

CT scan	2.0	Assumption: Time spent on average CT scan
Blood test	0.5	Assumption: Time spent on average blood test
FGFR test	0.0	Assumption: No additional time cost as FGFR test is conducted at the first blood test

2.4 Sensitivity analysis

The base case outcomes are based on deterministic inputs and assumptions. To explore the representativeness of the base case, alternative scenarios are explored.

2.5 Summary of base-case analysis inputs and assumptions

2.5.1 Summary of base-case analysis inputs

A summary of the key base-case analysis inputs is presented in Table 15, along with the distribution used for sensitivity analysis. Fixed-value inputs have not been included in the sensitivity analysis. A full summary of all base-case parameters can be found in Appendix.

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2.5.2 Model assumptions

A summary of all the model assumptions is provided in Table 16, complete with a short description of the justification.

Table 12: Summary of base-case assumptions,

Subject	Base-case assumption	Justification
Model settings		
Model type	Partitioned survival model	In line with NICE guidelines for oncology modelling
Time horizon	40 years	Because of a high age at baseline, a majority of patients will have died after 40 years. A longer time horizon is tested in scenario analyses.
Discount rate	3.5%	Base case in compliance with DMC guidelines
Included costs	Treatment costs Adverse event costs Patient costs	Treatment costs and adverse event costs are included in the model, as stated in the DMC guidelines. Patient costs are not included for the intervention or comparator, as the intervention is administered orally at no cost for the patient and the comparator costs is assumed to affect both treatment arms equally.
Treatment line	2nd line	In line with indication.
Include wastage	No	No acquisition cost is assumed for the comparator, as costs are assumed to apply to both treatment arms. Given the assumed packaging for pemigatinib, it will include 14 tablets for a 21-day cycle; therefore, wastage is expected to be minimal.
Perspective	Restricted societal	Base case in compliance with DMC guidelines
Discounting of outcomes	Applied per cycle rather than per year	Maximum level of detail
Efficacy		
Survival hazard rate for FGFR2+ mutation	None	Available data is not conclusive; we cannot accurately estimate the prognostic value of FGFR2 rearrangement or fusions
Apply HR to PFS?	No	No significant difference in PFS from Jain et al.[15]

Prevent TOT from exceeding PFS?	Yes	As per licence (treatment should continue until disease progression or unacceptable toxicity)[16]
Comparator efficacy	Weighted HRs	Relative efficacy using the MAIC
Pemigatinib		
Use MAIC survival analysis	Unadjusted	All survival functions converge; comparator efficacy for the survival analysis is informed using the MAIC
Days on treatment model	Exponential	Statistically and visually, this is one of the best fitting models to the FIGHT-202 data and met clinician expectations for the proportion on treatment at two years[13]
PFS model	Log-normal	Statistically and visually, this is one of the best fitting models across all treatments, and met clinician expectations for the proportion of progression-free patients at two years[13]
Overall survival model	Log-logistic	Statistically and visually, this is one of the best fitting models across all treatments
Assume TOT equal to PFS	No	TOT data available
ASC		
PFS model	Assume equal to PFS of mFOLFOX+ASC	No PFS data are available for ASC in ABC-06
Overall survival model	Log-logistic	Statistically and visually, this is one of the best fitting models across all treatments. The same distribution as other treatments is used, aligning with NICE guidance[12]
Assume TOT equal to PFS	Yes	No TOT data available
Costs		
Apply FGFR testing costs for pemigatinib	Yes	Part of treatment pathway
Apply FGFR testing costs for ASC	No	Not a part of the treatment pathway
Treatment acquisition costs	Uses the mean rather than the minimum unit cost	More reflective of the spread of costs across packages and regions

Key: AE, adverse event; ASC, active symptom control; FGFR, fibroblast growth factor receptor; FGFR2+, fibroblast growth factor receptor 2-positive; MAIC, matching-adjusted indirect comparison; NICE, National Institute for Health and Care Excellence; PFS, progression-free survival; PPS, post-progression survival; TOT, time on treatment.

3. Results

3.1 Deterministic results

The incremental cost of treatment with pemigatinib compared to ASC is 1,035,275 DKK (Table 17). The impact of modelling decisions on the outcome is explored in the scenario analysis (Section 3.2).

Table 13: Incremental analysis

	Total		Incremental (pemigatinib vs.)
	Pemigatinib	ASC	ASC
Costs (DKK)	1,136,189	100,913	1,035,275

A full breakdown of the costs as well as the incremental results of ASC versus pemigatinib, are presented in Table 18.

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3.2 Scenario analysis

To assess the impact of key model assumptions, a selection of scenario analyses were run to determine the incremental costs under different assumptions (Table 19). Incremental costs compared to ASC range from 919,613 DKK when excluding the cost of genetic testing for the pemigatinib arm to 1,142,688 DKK when using the log-logistic model to extrapolate the TOT for pemigatinib.

Table 14: Scenario analysis

	Scenario	Incremental costs of pemigatinib vs ASC	Rationale
1	**Base case**	**1,035,275 DKK**	
2	A longer time horizon of 50 years	1,035,315 DKK	Exploration of the impact of longer model duration
3	Costs and benefits are not discounted	1,073,694 DKK	Undiscounted results
4	A higher discounting rate of 6% is assumed	1,011,601 DKK	Explore impact of alternative higher discount rate
9	Assume FGFR2+ HR adjustment for comparators (all stages Cox model)	1,032,728 DKK	Explore structural assumptions relating to potential prognostic effect of FGFR2
10	Assume FGFR2+ HR adjustment for comparators (all stages Cox model) using prevalence from source (Jain et al)	968,163 DKK	Explore structural assumptions relating to potential prognostic effect of FGFR2, varying the prevalence of FGFR2 GA
11	Comparator efficacy informed by naïve HRs	1,034,514 DKK	Test estimates of treatment effect unadjusted for prognostic factors
12	Comparator efficacy informed by MAIC HRs, using a Weibull extrapolation for pemigatinib OS	1,028,009 DKK	Explore impact on results of using MAIC HRs with alternative more pessimistic extrapolation of pemigatinib OS (Weibull)
13	Comparator efficacy informed by independent PSMs fitted to unadjusted KM	1,035,154 DKK	Explore impact on results of using independent curve fits to unadjusted comparator survival data
14	Survival informed by independent curve fits. Pemigatinib PSMs fitted to KM function unadjusted	1,031,807 DKK	Same as scenario 13, but using pemigatinib survival adjusted to match ASC arm of ABC-06 study
15	Survival informed by independent curve fits. Pemigatinib PSMs fitted to KM function unadjusted	1,032,412 DKK	Same as scenario 13, but using pemigatinib survival adjusted to match mFOLFOX arm of ABC-06 study
16	Extrapolate PFS for all treatments using Weibull (unadjusted KM)	995,326 DKK	Test alternative parameterisations of the PFS curves
17	Extrapolate OS for all treatments using Weibull (unadjusted KM)	1,027,907 DKK	Test alternative parameterisations of the OS curves
18	Extrapolate TOT for pemigatinib using log-logistic	1,142,688 DKK	Test alternative parameterisations of the pemigatinib ToT curve

	Scenario	Incremental costs of pemigatinib vs ASC	Rationale
19	Exclude genetic testing (including FGFR2) only for pemigatinib	919,613 DKK	Explore impact of including FGFR testing costs only for patients treated with pemigatinib

Key: ASC, active symptom control; FGFR2+, fibroblast growth factor receptor 2-positive; HR, hazard ratio; MAIC, matching-adjusted indirect comparison; OS, overall survival; PFS, progression-free survival; TOT, time on treatment.

4. Budget impact analysis

The estimated incidence of cholangiocarcinoma in Denmark is estimated to approximately 1.3 per 100,000. Of all patients with CCA, 86% are assumed to be diagnosed with iCCA. If iCCA is discovered at an early stage and the tumour is in a favourable position, patients can undergo resectable surgery. Of the remaining 70%, it is assumed that 8.6% of patients have an FGFR translocation. This results in a very limited patient population relevant for treatment with pemigatinib. The assumption of the proportion of CCA patients that are iCCA is based on the patient population of CCA in England. This is a conservative assumption, as it results in a larger (yet limited) patient population in Denmark than what would otherwise be expected. The increase in the market share for pemigatinib over the five-year period results in less than one additional patient per year.

4.1 Number of patients

Table 15: Number of patients expected to be treated over the next five-year period - if the pharmaceutical is introduced

Pemigatinib Diagnosis year	Year 1	Year 2	Year 3	Year 4	Year 5
1	0.8	0.8	0.8	0.8	0.8
2		1.2	1.2	1.2	1.2
3			1.6	1.6	1.6
4				2.0	2.0
5					2.4

ASC Diagnosis year	Year 1	Year 2	Year 3	Year 4	Year 5
1	3.2	3.2	3.2	3.2	3.2
2		2.8	2.8	2.8	2.8
3			2.4	2.4	2.4
4				2.0	2.0
5					1.6

Table 16: Number of patients expected to be treated over the next five-year period - if the pharmaceutical is NOT introduced

ASC Diagnosis year	Year 1	Year 2	Year 3	Year 4	Year 5
1	4.0	4.0	4.0	4.0	4.0
2		4.0	4.0	4.0	4.0
3			4.0	4.0	4.0
4				4.0	4.0
5					4.0

4.2 Market share

Table 17: Market share that is expected over the next five-year period - if the pharmaceutical is recommended

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

Table 18: Market share that is expected over the next five-year period - if the pharmaceutical is NOT recommended

	Year 1	Year 2	Year 3	Year 4	Year 5
Pemigatinib	0.00%	0.00%	0.00%	0.00%	0.00%
ASC	100.00%	100.00%	100.00%	100.00%	100.00%

4.3 Expenditure per patient per year

The outline of the tables are structured such that each row shows the type of expenditure related to treatment of one patient in years 1-5. Costs are decreasing over time due to the poor survival prognostics of the disease; the patient(s) either die or can no longer be treated during the course of the five-year period. Drug expenditure per patient per treatment year is presented in Table 24 and Table 25 for pemigatinib and ASC, respectively.

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Table 19: Expenditure per patient per treatment year, ASC

	Year 1	Year 2	Year 3	Year 4	Year 5
Drug	0 DKK	0 DKK	0 DKK	0 DKK	0 DKK
Administration	0 DKK	0 DKK	0 DKK	0 DKK	0 DKK
AEs	1,561 DKK	106 DKK	15 DKK	2 DKK	0 DKK
Resource use	85,056 DKK	13,111 DKK	1,016 DKK	111 DKK	18 DKK
Total	**86,618 DKK**	**13,217 DKK**	**1,031 DKK**	**114 DKK**	**18 DKK**

4.4 Expenditure per year

Expenditures are presented for the full patient population over five years. The tables are structured such that the total cost for the market share of the patient population diagnosed in year 1-5 in the budget impact years 1-5 are presented.

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ASC Diagnosis year	Year 1	Year 2	Year 3	Year 4	Year 5
1	277,176 DKK	42,295 DKK	3,300 DKK	364 DKK	58 DKK
2		242,529 DKK	37,008 DKK	2,888 DKK	319 DKK
3			207,882 DKK	31,721 DKK	2,475 DKK
4				173,235 DKK	26,434 DKK
5					138,588 DKK
Total	**277,176 DKK**	**284,824 DKK**	**248,191 DKK**	**208,208 DKK**	**167,874 DKK**

Table 20: Expenditure per year - if the pharmaceutical is NOT introduced

ASC Diagnosis year	Year 1	Year 2	Year 3	Year 4	Year 5
1	346,470 DKK	52,869 DKK	4,125 DKK	455 DKK	72 DKK
2		346,470 DKK	52,869 DKK	4,125 DKK	455 DKK
3			346,470 DKK	52,869 DKK	4,125 DKK
4				346,470 DKK	52,869 DKK
5					346,470 DKK
Total	**346,470 DKK**	**399,339 DKK**	**403,464 DKK**	**403,919 DKK**	**403,992 DKK**

4.5 Budget impact

Table 21: Expected budget impact of recommending the pharmaceutical for the current indication

	Year 1	Year 2	Year 3	Year 4	Year 5
The pharmaceutical under consideration is recommended	907,015 DKK	1,409,115 DKK	1,846,109 DKK	2,270,270 DKK	2,692,354 DKK

Minus: The pharmaceutical under consideration is NOT recommended	346,470 DKK	399,339 DKK	403,464 DKK	403,919 DKK	403,992 DKK
Budget impact of the recommendation	**560,545 DKK**	**1,009,776 DKK**	**1,442,644 DKK**	**1,866,351 DKK**	**2,288,362 DKK**

The budget impact of including pemigatinib in the reimbursement scheme ranges from 560,545 DKK in year 1 to 2,288,362 DKK in year 5. The patient population used for the assessment is based on conservative assumptions.

5. Discussion

In the phase II trial FIGHT-202, which provides the efficacy inputs for the pemigatinib arm, pemigatinib was shown to confer significant benefits in PFS and OS for the treatment of patients with previously treated locally advanced or metastatic CCA with an FGFR2 rearrangement or fusion.

The partitioned survival model presented in this report evaluates the cost of pemigatinib in the treatment of patients with previously treated locally advanced or metastatic CCA with an FGFR2 rearrangement or fusion. The cost was evaluated compared with ASC, using the best available clinical and economic evidence. Because the Danish Medicines Agency (DMC) have no specific guidelines for survival extrapolations, these were conducted in accordance with NICE guidelines along with clinician input, while regression analyses were internally and externally validated. Although only limited literature is available for this indication, the current standard of care has been validated with clinicians, thus informing the key model comparator as well as costs associated with resource use and the monitoring of patients.

The results of the cost analysis are consistent with findings from the clinical trial. The health gains associated with pemigatinib came with a higher lifetime cost compared to ASC where the primary cost driver was treatment duration.

In the base case analysis, the Incremental cost was 1,035,275 DKK compared to ASC. Scenario analysis has been explored to test the impact of altering elements in the model structure. The analyses indicated that the results were most sensitive to changes in the parameters contributing to resource use in the pemigatinib arm as well as the choice of curve for extrapolating TOT for pemigatinib.

The budget impact of including pemigatinib in the reimbursement scheme ranges from 560,545 DKK in year 1 to 2,288,362 DKK in year 5.

6. Conclusion

The results of the cost analysis suggest that pemigatinib is a relevant treatment option compared to ASC in the treatment of patients with previously treated locally advanced or metastatic CCA with FGFR2 rearrangement or fusion. In regard to the severity of the disease, the limited patient population and the lack of treatment options, pemigatinib should be considered as a relevant treatment.

7. References

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Medicinrådet

Medicinrådets protokol for vurdering vedrørende pemigatinib til behandling af lokalavanceret eller metastatisk cholangiokarcinom

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 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 sin endelige ansøgning. Til hvert spørgsmål knytter sig en definition af patientgruppen, det lægemiddel, Medicinrådet undersøger, den behandling, Medicinrådet 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 vedr. nye lægemidler og indikationsudvidelser*, 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 den ansøgende virksomhed få besked.

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1. Begreber og forkortelser

BSC: *Best supportive care*

CCA: Cholangiokarcinom *(cholangiocarcinom)*

CrCl: Kreatinin-clearance (*Creatinine Clearance)*

eCCA: Ekstrahepatisk cholangiokarcinom

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

EPAR: *European Public Assessment Report*

EUnetHTA: *European Network for Health Technology Assessment*

FDA: *The Food and Drug Administration*

FGFR2: *Fibroblast growth factor receptor 2*

FINOSE: Finland, Norge og Sveriges samarbejde om medicinske teknologivurderinger

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

HTA: Medicinsk teknologivurdering (*Health Technology Assessment)*

IQWIG: *The Institute for Quality and Efficiency in Healthcare*

iCCA: Intrahepatisk cholangiokarcinom

ITT: *Intention-to-treat*

MKRF: Mindste klinisk relevante forskel

NICE: *The National Institute for Health and Care Excellence*

PICO: Population, intervention, komparator og effektmål (*Population, Intervention, Comparison and Outcome)*

PS: *Performance status*

PP: *Per protocol*

PSC: Primær skleroserende cholangitis

RR: Relativ risiko

SMD: *Standardized Mean Difference*

TNM: *Tumor, node, metastases*

ULN: *Upper limit of normal*

2. Introduktion

Protokollen er udarbejdet, fordi Medicinrådet har modtaget en foreløbig ansøgning fra Incyte, som ønsker, at Medicinrådet vurderer pemigatinib til patienter med lokalavanceret eller metastatisk cholangiokarcinom (CCA), som enten har haft tilbagefald af sygdom eller udviser refraktær sygdom efter mindst én linje systemisk behandling. Medicinrådet modtog den foreløbige ansøgning den 20. november 2020.

2.1 Cholangiokarcinom

Cholangiokarcinom er den næsthyppigste form for primær leverkræft efter hepatocellulært carcinom, med cirka 200 nye tilfælde i Danmark om året, og udgør omkring 3 % af alle gastrointestinale tumorer. Diagnosen er vanskelig at stille, og CCA er ofte asymptomatisk i tidlige stadier, hvilket medfører, at sygdommen ofte er dødelig, da diagnosen stilles sent. 1-års overlevelsen er ca. 50 %, og 5-års overlevelsen omkring 15 % [1]. Medianoverlevelsen for patienter, der modtager systemisk behandling, er under 1 år [2,3]. Det er svært at finde studier af medianoverlevelsen for patienter med CCA, der er kandidater til 2. linje behandling, men i et studie (publiceret i form af et abstract) af CCA og galdeblærekræft samlet var median OS i 2. linje 6,2 måneder [4].

Ved udgangen af 2016 havde 478 danske patienter CCA, hvilket afspejler den lave overlevelse for denne patientgruppe. Patienter med CCA er oftest ældre (medianalderen er 71 år), og sygdommen er lidt hyppigere hos mænd end hos kvinder.

CCA opstår i slimhinden i galdevejene. Hyppigst uden for leveren (ekstrahepatisk CCA, eCCA), men kan også findes inde i leveren (intrahepatisk CCA, iCCA). For iCCA er incidens og mortalitet dog steget inden for de seneste år, mens det modsatte er tilfældet for eCCA [2,5]. En del af stigningen i iCCA skyldes sandsynligvis, at mange af de patienter, som tidligere blev diagnosticeret med ukendt primær tumor, nu bliver diagnosticeret med iCCA[6]. Ekstrahepatisk CCA opdeles yderligere i perihilar CCA (pCCA) og distal CCA (dCCA). På trods af at der findes en række veletablerede risikofaktorer for at udvikle CCA, hvoraf den mest betydende er primær skleroserende cholangitis (PSC) med eller uden samtidig inflammatorisk tarmsygdom, kan risikofaktorer forklare under 30 % af alle tilfælde, hvilket indikerer, at CCA oftest opstår sporadisk [3]. Andre mindre veletablerede risikofaktorer omfatter cirrose samt kronisk viral hepatitis B- eller C-infektion. Symptomer på CCA vil typisk være icterus (gulsot), kolestatisk hudkløe, træthed, vægttab og mavesmerter og kan bl.a. medføre risiko for cholangitis med behov for stentning af galdeveje, galdedræning [7].

TNM (tumor, node, metastases)-klassifikationen bruges til stadieinddeling og er specifik for hver undertype af CCA (iCCA, eCCA) [8]. Stadieinddelingen baseres på antallet af tumorer, vaskulær indvækst og lymfeknudemetastaser, mens tumorstørrelse ikke lader til at være afgørende for prognosen [3,5]. Dog er det eksisterende stadiesystem for iCCA utilstrækkeligt til at prædiktere langsigtet prognose samt til at planlægge behandling [3].

2.2 Pemigatinib

Pemigatinib (handelsnavn: Pemazyre) er indikeret til 2. linje behandling af patienter med lokalavanceret eller metastatisk CCA med en *fibroblast growth factor receptor 2* (FGFR2)-fusion eller andet rearrangement, som enten har haft tilbagefald af sygdom eller udviser refraktær sygdom efter mindst én linje systemisk behandling. Pemigatinib er formuleret som en tablet og gives i en dosis af 13,5 mg én gang dagligt i 14 dage efterfulgt af 7 dages pause. Denne cyklus gentages, indtil sygdomsprogression eller uacceptable bivirkninger.

Pemigatinib virker ved at blokere enzymer (proteinkinaser), som er del af de receptorer, der kaldes *fibroblast growth factor receptorer* (FGFR). Disse receptorer findes på ydersiden af kræftcellerne og er involveret i vækst og spredning af kræftcellerne. Pemigatinib virker ved at hæmme denne proces.

For at være kandidat til behandling med pemigatinib skal patienterne have en *fibroblast growth factor receptor 2* (FGFR2)-fusion, hvilket næsten udelukkende ses hos patienter med intrahepatisk CCA [9]. Derudover indebærer inklusionskriterierne i registreringsstudiet, at patienterne skal have tilstrækkelig lever- og nyrefunktion samt en performance status (PS) fra 0-2 på Eastern Cooperative Oncology Group (ECOG)-skalaen [9]. ECOCG PS-skalaen har 6 niveauer fra 0-5, hvoraf 0 er det bedste, og 5 det værste [10].

Tilstrækkelig leverfunktion defineres som total bilirubin < 1,5 x øvre grænse for normalen (upper limit of normal) eller < 2,5 x øvre grænse for normalen hos patienter med metastatisk sygdom involverende leveren; aminotransferase ≤ 2,5 x øvre grænse for normalen. Tilstrækkelig nyrefunktion defineres som kreatinin-clearance (CrCl) > 30 mL/min. Pemigatinib anslås at kunne tilbydes til 3-8 patienter om året i Danmark.

I registreringsstudiet anvendes en test for FGFR2-fusion kaldet FoundationOne. Denne test skelner mellem FGFR fusion, rearrangement og andre forandringer. Testen er ikke standard i Danmark, men udføres på alle de patienter der indgår i eksperimentel behandling med tocolizumab, hvilket tilbydes alle patienter med god PS samt god nyre- og leverfunktion. Den eksperimentelle behandling kører på Herlev hospital, og Aarhus er tilbudt at deltage.

Pemigatinib er et *orphan drug*. Pemigatinib vurderes ikke i en accelereret proces hos EMA. Incyte modtog en positive opinion fra det Europæiske Lægemiddelagentur (European Medicines Agency, Committee for Medical Products for Human use (EMA CMPH)) den 28. januar 2021 og forventer at få en betinget (conditional) markedsføringstilladelse, hvor betingelsen er at indsamle mere data på pemigatinib. Pemigatinib er et nyt lægemiddel og har dermed ikke andre godkendte indikationer.

2.3 Nuværende behandling

Patienter med sygdom på et meget tidligt stadie tilbydes kirurgisk fjernelse af tumor med helbredende sigte. Dette er dog kun muligt hos omkring 30 % af patienter diagnosticeret med CCA (ca. 60 patienter årligt i Danmark), og risikoen for tilbagefald er høj [9].

For patienter med ikke-resektabel eller metastatisk sygdom (ca. 140 patienter årligt i Danmark) er standardbehandlingen i 1. linje livsforlængende behandling i form af systemisk kemoterapi med gemcitabin og cisplatin, med det sigte at opnå sygdomskontrol og bevare livskvalitet. Der er p.t. ingen veletableret standardbehandling for 2. linje behandling, og patienter vil dermed tilbydes best supportive care (BSC) [3] eller, ved god almen status, eksperimentel behandling. BSC indebærer månedlige kliniske undersøgelser, symptomkontrol inklusive galdedræning og stentning af galdeveje efter behov, antibiotika, smerte- og kvalmestillende lægemidler, steroider, palliativ stråleterapi og blodtransfusioner samt anden palliativ behandling for symptomer som gulsot og hudkløe.

3. Kliniske spørgsmål

3.1 Klinisk spørgsmål 1

Hvilken værdi har pemigatinib sammenlignet med best supportive care for patienter med lokalavanceret eller metastatisk CCA med en *fibroblast growth factor receptor 2* (FGFR2)-fusion eller andet rearrangement, som har haft tilbagefald af sygdom eller udviser refraktær sygdom efter mindst én linje systemisk behandling?

Population
Patienter med lokalavanceret eller metastatisk CCA med en FGFR2-fusion eller andet rearrangement, som enten har haft tilbagefald af sygdom eller udviser refraktær sygdom efter mindst én linje systemisk behandling, og som har en ECOG-performance status ≤ 2 og tilstrækkelig lever- og nyrefunktion (se afsnit 2.3).

Intervention
Pemigatinib administreres i cyklusser af 13,5 mg per oral tablet én gang dagligt i 14 dage, efterfulgt af 7 dages pause.

Komparator
Best supportive care.

Effektmål
De valgte effektmål fremgår af tabel 1.

3.2 Effektmål

Medicinrådet mener, at vurderingen af lægemidlets værdi bliver bedst understøttet af de effektmål, der er nævnt i tabel 1. For hvert effektmål har Medicinrådet fastsat en mindste klinisk relevant forskel (MKRF). Den mindste klinisk relevante forskel er den forskel mellem intervention og komparator, der som minimum skal opnås for at effektforskellen vurderes at være klinisk relevant. I det følgende afsnit argumenterer Medicinrådet for valget af effektmål og MKRF.

Tabel 1. Oversigt over valgte effektmål. For hvert effektmål er angivet deres vigtighed, måleenhed og mindste klinisk relevante forskel samt indplacering i de tre effektsmålsgrupper (1) dødelighed/overlevelse, 2) livskvalitet, alvorlige symptomer og bivirkninger, 3) ikke-alvorlige symptomer og bivirkninger).

Effektmål*	Vigtighed	Effektmålsgruppe**	Måleenhed	Mindste klinisk relevante forskel
Overlevelse	Kritisk	Dødelighed/overlevelse	Median overlevelse i antal måneder	3 måneder
			Overlevelsesrate efter 6 måneder	10 %-point
			Median Progressionsfri overlevelse (PFS) i antal måneder ***	3 måneder
Objektiv responsrate (ORR)	Kritisk	Livskvalitet, alvorlige symptomer og bivirkninger	Andel patienter, som opnår objektiv respons	30 %-point
Livskvalitet	Kritisk	Livskvalitet, alvorlige symptomer og bivirkninger	EORTC QLQ-C30	≥ 10 point
Uønskede hændelser	Vigtig	Livskvalitet, alvorlige symptomer og bivirkninger	Andel patienter med grad 3-4 uønskede hændelser	5 %-point
			Kvalitativ gennemgang af uønskede hændelser med henblik på at vurdere alvorlighed, håndterbarhed og hyppighed af uønskede hændelser	Narrativ vurdering

*For alle effektmål ønsker Medicinrådet data med længst mulig opfølgningstid, medmindre andet er angivet.
**Effektmålsgruppe refererer til de væsentlighedskriterier, som Medicinrådet lægger til grund for kategoriseringen af de relative forskelle i effekt, bivirkninger eller livskvalitet.
***Hvis ansøger ikke kan levere data på OS, ønsker fagudvalget effektmålet opgjort på PFS.

3.2.1 Kritiske effektmål

Overlevelse

Overlevelse er højeste standard for at demonstrere klinisk effekt i onkologiske studier, herunder CCA. Det er et patientrelevant effektmål, der belyser patienternes levetid. Overlevelse defineres som tiden fra randomisering i det kliniske studie til død uanset årsag. Fagudvalget ønsker overlevelse opgjort som median overlevelse samt overlevelsesrate efter 6 måneders behandling. Fagudvalget vurderer overlevelse som et kritisk effektmål for vurderingen af pemigatinib.

Medianoverlevelse

Baseret på populationens forventede korte levetid vurderer fagudvalget, at 3 måneder er den mindste klinisk relevante forskel. Medianoverlevelsen er under et år for 1. linje behandling og derved endnu kortere for 2. linje behandling. I et studie af CCA og galdeblærekræft samlet var median OS i 2. linje 6,2 mdr.[4]

Overlevelsesrate

Fagudvalget vurderer, at overlevelsesraten ved 6 måneder er klinisk relevant og kan bruges trods eventuel kort opfølgningstid i de kliniske studier. På baggrund af at medianoverlevelsen i 2. linje er 6,2 måneder, antager fagudvalget, at overlevelsesraten efter 6 måneder er ca. 50 %. På den baggrund vurderer fagudvalget, at 10 %-point forskel i overlevelsesrate er den mindste klinisk relevante forskel.

Progressionsfri overlevelse (PFS)

Hvis ansøger ikke kan levere modne data på OS, ønsker fagudvalget i stedet for data for PFS. Progressionsfri overlevelse defineres som tiden fra randomisering til radiologisk progression (vurderet i henhold til RECIST v1.1 [11]), klinisk progression eller død.

Fagudvalget har kendskab til et studie af et lægemiddel til CCA, hvor Kaplan-Meier-kurverne for OS og recurrence-free survival havde nogenlunde tilsvarende forløb [12]. Usikkerheden om korrelationen vil give sig til udtryk i en ændring af effektmålets vigtighed fra kritisk til vigtig, såfremt vurderingen kommer til at bero på PFS- og ikke OS-data.

Pemigatinib er indiceret til lokalavanceret eller metastatisk CCA, når øvrige acceptable behandlingsmuligheder er udtømte. Derfor vurderer fagudvalget, at patientgruppen generelt vil have relativt kort tid til sygdomsprogression. På den baggrund vurderer fagudvalget, at 3 måneder er den mindste klinisk relevante forskel.

Objektiv respons rate (ORR)

ORR anvendes til belysning af behandlingsrespons og afspejler interventionens effekt på tumorstørrelse. Ved vurdering af ORR kategoriserer man ændringer af tumors størrelse efter påbegyndt behandling, jævnfør standardiserede guidelines (Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1) [11]. Fagudvalget vurderer, at et væsentligt tumorsvind ofte vil bevirke en reduktion i patientens sygdomsbyrde. Selv en mindre reduktion af tumorbyrden i galdeveje vil lindre icterus (gulsot), kolestatisk hudkløe, reducere behov for stentning af galdeveje og mindske risiko for cholangitis.

Fagudvalget forventer, at patienter, som ikke modtager aktiv behandling, vil have en objektiv responsrate tæt på 0 %. ORR underinddeles i følgende kategorier:

- Komplet respons (CR): Radiologisk kræftfri. Alle tumorlæsioner er væk, og ingen nye er fremkommet.
- Partielt respons (PR): Mindst 30 % reduktion af tumorlæsioner sammenlignet med baseline.

Objektiv respons (OR) opnås for en patient, hvis vedkommende er klassificeret som havende CR eller PR, og objektiv responsrate defineres som CR + PR delt med det samlede patientantal. Fagudvalget vil vurdere den samlede andel af patienter, som opnår OR. Fagudvalget vurderer, at 30 %-point forskel i andelen af patienter, som opnår ORR, er den mindste klinisk relevante forskel.

Helbredsrelateret livskvalitet
Helbredsrelateret livskvalitet har stor betydning for den enkelte patient og er derfor et patientnært effektmål, der her vurderes at være af kritisk betydning, fordi behandlingen er livsforlængende og ikke kurativ. Ligeledes forventes dette effektmål også at kunne give en indikation af, om bivirkningerne påvirker patienternes livskvalitet. Fagudvalget ønsker at belyse helbredsrelateret livskvalitet med spørgeskemaet European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQC30) [13].

EORTC QLQ-C30 er udviklet til at måle livskvaliteten hos patienter med kræft. EORTC QLQ-C30 er et spørgeskema med 30 spørgsmål opdelt på følgende domæner: fem funktionsskalaer, tre symptomskalaer, seks enkeltstående symptomer/omstændigheder og en global livskvalitetsskala [13]. Der anvendes en scoringsskala fra 0-100, hvor høj score indikerer højere niveau af livskvalitet.

En lille ændring er defineret som en ændring på 5-10 point, en moderat ændring er 10-20 point, og en stor ændring er > 20 point [14]. Medicinrådet betragter mindste klinisk relevante forskel som ≥ 10 point.

3.2.2 Vigtige effektmål

Uønskede hændelser
Bivirkninger har betydning for den enkelte patients livskvalitet og compliance. Da patienterne, som er kandidater til 2. linje behandling, har en dårlig prognose og mange symptomer, betragtes effektmålet som vigtigt og ikke kritisk, da fagudvalget forventer, at patienterne vil tolerere et vist niveau af bivirkninger.
Fagudvalget ønsker uønskede hændelser ved pemigatinib belyst ved antallet af uønskede hændelser grad 3-4 defineret ved CTCAE [15]. Baggrunden for, at fagudvalget ønsker en opgørelse over uønskede hændelser og ikke bivirkninger, er, at lægemidlet og dermed bivirkningsprofilen endnu kun er undersøgt i få studier. Dernæst ønsker fagudvalget også at foretage en kvalitativ vurdering af profilerne for uønskede hændelser. Beskrivelser af de enkelte effektmål følger nedenfor.

Andel patienter med grad 3-4 uønskede hændelser

Forekomst af uønskede hændelser grad 3-4 kan være et udtryk for alvorlig toksicitet af lægemidlet, og disse kan have væsentlig indvirkning på patienternes velbefindende. Da pemigatinib skal anvendes til behandling af uhelbredeligt syge patienter med kort forventet overlevelse, vurderes det, at uønskede hændelser er et vigtigt effektmål. Medicinrådet ønsker dette opgjort som andelen af patienter, der oplever en eller flere grad 3-4 uønskede hændelser. Den mindste klinisk relevante forskel vurderes at være 5 %-point.

Kvalitativ gennemgang af uønskede hændelser

Medicinrådet vil desuden foretage en kvalitativ gennemgang af typerne af uønskede hændelser for at vurdere, om der er betydende forskel i profilerne for uønskede hændelser mht. alvorlighed, håndterbarhed og hyppighed. Ansøger bedes derfor bidrage med produktresuméet for lægemidlet samt indsende en opgørelse af frekvensen af alle uønskede hændelser fra kliniske studier af pemigatinib til patienter med cholangiokarcinom. Opgørelsen af uønskede hændelser ønskes suppleret med en opgørelse over bivirkninger, da de kan være årsag til dosisreduktioner.

4. Litteratursøgning

Medicinrådets vurdering af lægemidlets værdi vil i udgangspunktet være baseret på data fra fuldtekstartikler publiceret i videnskabelige, fagfællebedømte (peer-reviewed) tidsskrifter og data fra Det Europæiske Lægemiddelagenturs (EMAs) European Public Assessment Reports (EPAR). Herudover kan data fra Food and Drug Administration (FDA) og internationalt anerkendte HTA-agenturer (f.eks. NICE, EUnetHTA, FINOSE og IQWiG) indgå i vurderingen. Hvis disse data er tilstrækkelige til at kunne vurdere lægemidlet, vil Medicinrådet som hovedregel ikke anvende andre data[1]. Data skal derudover stemme overens med protokollens beskrivelser. Hvis ansøger har kendskab til upublicerede data, der kan belyse eventuelle angivne mangler, kan de indgå/indsendes, jf. Medicinrådets princippapir[1].

Medicinrådet er i den foreløbige ansøgning blevet orienteret om, at der ikke findes studier, hvor pemigatinib er sammenlignet direkte med best supportive care. Derfor skal ansøger søge efter studier til en indirekte sammenligning. Det betyder, at der både skal søges efter primærstudier af effekten af pemigatinib og efter primærstudier af effekten af BSC for patientpopulationen. Ansøger skal først søge efter randomiserede, kontrollerede kliniske studier. Hvis der ikke findes sådanne studier, som kan inkluderes i ansøgningen, skal ansøger søge efter observationelle studier. Ansøger forventes at begrunde udvælgelse af studier detaljeret samt redegøre for, hvor direkte de inkluderede studier, interventioner (for komparator) og populationer svarer til, hvad der forventes i dansk klinisk praksis.

[1] For yderligere detaljer se Medicinrådets nye principper for anvendelse af upublicerede data godkendt (medicinraadet.dk)

Søgestrengene fremgår af bilag 1. Derudover skal ansøger konsultere EMAs EPAR for både det aktuelle lægemiddel og dets komparator(er).

Ansøger skal ekskludere artikler med andre populationer end de, der er specificeret i protokollen, og artikler, der ikke rapporterer mindst ét af de kritiske eller vigtige effektmål.

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

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

Den ansøgende virksomhed skal ved screening af artikler først ekskludere på titel- og abstractniveau, dernæst ved gennemlæsning af fuldtekstartikler. Artikler, der ekskluderes ved fuldtekstlæsning, skal fremgå af en eksklusionsliste, hvor eksklusionen begrundes kort. Den samlede udvælgelsesproces skal afrapporteres ved brug af et flowdiagram som beskrevet i PRISMA-Statement.

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

5. Den endelige ansøgning

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 (population, intervention, komparator og effektmål) 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 (jf. 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 (jf. 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'-modeller 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.

Sundhedsøkonomiske analyser
En sundhedsøkonomisk ansøgning består af en sammenhængende, dynamisk sundhedsøkonomisk model og et teknisk dokument, hvor modellen og de antagelser, der er bygget ind i modellen, beskrives, og hvor ansøgers sundhedsøkonomiske analyse fremgår. Ved dynamisk forstås, at en variabel kun skal ændres ét sted for at være gennemgående for hele modellen. Anvend eventuelt Medicinrådets metodevejledning og tjekliste til sundhedsøkonomiske modeller til at teste modellens dynamik, og at modellen overholder formelle krav.

En sundhedsøkonomisk analyse er ikke et resultat, men er en bred analyse af modellens dynamik, hvilke parametre der har indflydelse på resultaterne, samt hvorfor og hvordan disse parametre indgår. Derfor skal det tekniske dokument som minimum indeholde følgende:

- Beskriv den valgte modelstruktur grundigt.
- Beskriv, hvis der er anvendt en indirekte analyse, hvordan den vil blive håndteret i den sundhedsøkonomiske analyse.
- Begrund og beskriv samtlige antagelser i modellen, og lad specifikke analysevalg fremgå tydeligt.
- Beskriv alle de inkluderede studier, argumentér for deres relevans, og beskriv, hvor og hvordan data anvendes i modellen.
- Begrund både de inkluderede og ekskluderede omkostninger.
- Beskriv, hvad der driver modellen, f.eks. behandlingslængde eller lægemiddelomkostninger.

- Ekstrapoleret data skal beskrives.
- Udfør følsomhedsanalyser, som belyser, hvilke parametre i modellen der har størst indflydelse på resultatet.
- Argumentér for eventuelle afvigelser fra protokollen og den kliniske ansøgning.
- Budgetkonsekvensanalysen skal være dynamisk med omkostningsanalysen, uden diskontering og patientomkostninger.

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 man kan have tiltro til den evidens, Medicinrådet baserer vurderingen af lægemidlets værdi på.

7. Andre overvejelser

Medicinrådet ønsker, at ansøger gør rede for, hvilken metode man anvender ved test for FGFR2-fusion, og om den stemmer overens med metoden i det kliniske studie. Endvidere ønsker Medicinrådet, at ansøger gør rede for omkostningerne ved en test og kommer med et estimat for antallet af patienter, der skal testes, for at finde én patient med FGFR2-fusionen. Medicinrådet ønsker, at ansøger redegør for disse forhold, idet omkostninger til implementering af lægemidlet skal indgå som del af den sundhedsøkonomiske analyse.

Medicinrådet ønsker, at ansøger gør rede for eventuelle dosisreduktioner ved behandling med pemigatinib.

Medicinrådet ønsker, at ansøger beskriver, hvorvidt CCA-patienter med FGFR2-fusion har en bedre prognose end CCA-patienter uden FGFR2-fusion og redegør for den eventuelle betydning af dette for de forskellige effektmål [16]. Herunder skal ansøger redegøre for fordelingen af patienter med og uden FGFR2-fusion i litteraturen, som beskriver effekten af komparator.

Medicinrådet ønsker, at ansøger redegør for behandling af patienter med PS2.

Medicinrådet skønner, at datagrundlaget for vurderingen kan være begrænset grundet den diagnostiske indikation med FGFR2 fusion og designet af det studie, der ligger til grund for EMAs vurdering af pemigatinib. Medicinrådet ønsker en opgørelse, som sammenligner PFS og ORR-data for den behandling, patienterne modtog i første linje umiddelbart inden pemigatinib, med behandlingen med pemigatinib.
Medicinrådet ønsker også en opgørelse over varigheden af responset (duration of response).

8. Relation til behandlingsvejledning

Der findes ikke en relevant behandlingsvejledning.

9. Referencer

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10. Sammensætning af fagudvalg og kontaktinformation til Medicinrådet

Medicinrådets fagudvalg vedrørende leverkræft

Sammensætning af fagudvalg	
Formand	**Indstillet af**
Britta Weber *Afdelingslæge*	Lægevidenskabelige Selskaber
Medlemmer	**Udpeget af**
Kan ikke udpege en kandidat, der opfylder Medicinrådets habilitetskrav	Region Nordjylland
Gerda Elisabeth Villadsen *Overlæge, klinisk lektor*	Region Midtjylland
Merete Krogh *Overlæge*	Region Syddanmark
Lone Galmstrup Madsen *Overlæge*	Region Sjælland
Kirsten Kjeldgaard Vistisen *Overlæge*	Region Hovedstaden
Sidsel Marcussen *Farmaceut*	Dansk Selskab for Sygehusapoteksledelse
Amy Daugaard Asmussen *Kvalitetskoordinator, sygeplejerske, MHH*	Inviteret af formanden
Niels Jessen *Professor, overlæge*	Dansk Selskab for Klinisk Farmakologi
Finn Ole Larsen *Overlæge*	Inviteret af formanden
Rozeta Abazi *Overlæge*	Dansk Selskab for Gastroenterologi og Hepatologi
Tóra Haraldsen Dahl *Patient/patientrepræsentant*	Danske Patienter
Marijanne Nord Madsen *Patient/patientrepræsentant*	Danske Patienter

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

11. Versionslog

Versionslog		
Version	**Dato**	**Ændring**
1.0	10. marts 2021	Godkendt af Medicinrådet

12. Bilag

Bilag 1: Søgestrenge

Klinisk spørgsmål 1

Søgestreng til PubMed:

#	Søgestreng	Kommentar
#1	Biliary Tract Neoplasms[majr]	Søgning population
#2	Bile Duct Neoplasms[majr]	
#3	Cholangiocarcinoma[majr:noexp]	
#4	cholangiocarcinoma*[ti] OR biliary cancer[ti]	
#5	(bile duct*[ti] OR biliary tract[ti] OR gall bladder[ti]) AND (carcinoma*[ti] OR cancer[ti] OR cancers[ti] OR tumor*[ti] OR tumour*[ti])	
#6	#1 OR #2 OR #3 OR #4 OR #5	
#7	advanced[tiab] OR metasta*[tw] OR unresectable[tiab] OR un-resectable[tiab] OR non-resectable[tiab] OR inoperable[tiab]	
#8	#6 AND #7	
#9	untreated[ti] OR non-treated[ti] OR nontreated[ti] OR treatment-naive[ti] OR resectable[ti] OR resected[ti] OR neoadjuvant[ti] OR adjuvant[ti]	
#10	#8 not #9	
#11	pemigatinib[nm] OR pemigatinib[tiab] OR Pemazyre*[tiab] OR INCB054828[tiab]	Søgning intervention
#12	best supportive care[tiab] OR active supportive care[tiab] OR BSC[tiab]	Søgning komparator
#13	(relief[tiab] OR reliev*[tiab] OR alleviat*[tiab]) AND (pain[tiab] OR symptom*[tiab])	
#14	symptom control[tiab] OR symptoms control[tiab] OR symptomatic control[tiab]	
#15	Palliative Care[mh] OR palliation[tiab] OR palliative[tiab]	
#16	#11 OR #12 OR #13 OR #14 OR #15	
#17	#10 AND #17	Population + intervention/komparator

#18	Case Reports[pt] OR Comment[pt] OR Editorial[pt] OR Guideline[pt] OR Letter[pt] OR News[pt] OR Review[pt] OR case report[ti]	Eksklusion af irrelevante publikationstyper
#19	#17 NOT #18	
#20	("Randomized Controlled Trial"[pt] OR "Controlled Clinical Trial"[pt] OR randomized[tiab] OR randomised[tiab] OR placebo[tiab] OR "Clinical Trials as Topic"[mh:noexp] OR randomly[tiab] OR trial[ti]) NOT ("Animals"[mh] NOT "Humans"[mh])	Filter til identifikation af randomiserede studier.
#21	**#19 AND #20**	Endelig søgning RCT
#22	Multicenter Study[pt] OR Comparative Study[pt] OR Cohort Studies[mh] OR Observational Study[pt]	Filter til identifikation af observationelle studier.
#23	(observational[tiab] OR cohort[tiab] OR retrospective*[tiab]) AND (study[tiab] OR studies[tiab] OR analy*[tiab])	
#24	Registries[mh] OR registry[tiab] OR nation-wide[tiab] OR nationwide[tiab] OR population-based[tiab] OR real-worl[tiab]	
#25	#22 OR #23 OR #24	
#26	**(#19 AND #25) NOT #21**	Endelig søgning på observationelle studier med eksklusion af tidl. screenede RCT'er.

Søgestreng til CENTRAL:

#	Søgestreng	Kommentar
#1	(("bile duct" or "biliary tract" or "gall bladder") near/2 (carcinoma* or cancer or cancers or tumor* or tumour*)):ti,kw	Søgning population
#2	cholangiocarcinoma*:ti	
#3	(biliary next cancer):ti	
#4	#1 or #2 or #3	
#5	(advanced or metasta* or unresectable or un-resectable or non-resectable or inoperable):ti,ab,kw	
#6	(untreated or non-treated or nontreated or treatment-naive or resectable or resected or neoadjuvant or adjuvant):ti	
#7	(#4 and #5) not #6	
#8	(pemigatinib or Pemazyre* or INCB054828 or INCB-054828 or incb54828 or incb-54828):ti,ab,kw	Søgning intervention
#9	((relief or reliev* or alleviat*) near/5 (pain or symptom*)):ti,ab	Søgning komparator
#10	(symptom* next control*):ti,ab	
#11	("best supportive care" or "active supportive care" or BSC):ti,ab	
#12	(palliation or palliative):ti,ab,kw	
#13	#8 or #9 or #10 or #11 or #12	
#14	#7 and #13	Population + intervention/komparator
#15	(clinicaltrials.gov or trialsearch):so	Eksklusion af irrelevante publikationstyper
#16	("conference abstract" or review):pt	
#17	(abstract or conference or meeting or proceeding*):so	
#18	NCT*:au	
#19	#15 or #16 or #17 or #18	
#20	#14 not #19	
#21	**#20 not pubmed:an in Trials**	Endelig søgning, fratrukket referencer fra Pubmed