Medicinrådet

Baggrund for Medicinrådets anbefaling vedrørende lenvatinib som mulig standardbehandling til hepatocellulært karcinom

Versionsnr.: 1.0

Medicinrådet

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 mulig 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.

De fælles regionale behandlingsvejledninger er vurderinger af, hvilke lægemidler der er mest hensigtsmæssige til behandling af patienter inden for et terapiområde og dermed grundlag for ensartet høj kvalitet for patienterne på tværs af sygehuse og regioner.

Om anbefalingen

Anbefalingen er Medicinrådets vurdering af, om omkostningerne ved behandling lægemidlet er rimelige i forhold til lægemidlets kliniske værdi.

Se Medicinrådets metodehåndbog for yderligere information.

Dokumentoplysninger	
Godkendelsesdato	10. april 2019
Ikrafttrædelsesdato	10. april 2019
Dokumentnummer	44829
Versionsnummer	1.0

Medicinrådet, Dampfærgevej 27-29, 3. th., 2100 København Ø
www.medicinraadet.dk
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Indhold

1 Lægemiddelinformationer

Lægemidlets oplysninger	
Handelsnavn	Lenvima
Generisk navn	Lenvatinib
Firma	Eisai
ATC-kode	L01XE29
Virkningsmekanisme	Lenvatinib er en multireceptortyrosinekinase inhibitor der hæmmer vækstfaktorreceptorerne VEGF 1-3, FGF 1-4, PDGF α og proto-onkogenerne KIT og RET.
Administration/dosis	Lenvatinib administreres oralt som tabletter. Dosis er 8 mg (ved kropsvægt < 60 kg) eller 12 mg (ved kropsvægt ≥ 60 kg) én gang dagligt. Behandlingen fortsættes, så længe klinisk fordel observeres, eller indtil der opstår uacceptable bivirkninger.
EMA-indikation	Lenvatinib er indiceret som monoterapi til behandling af voksne patienter med fremskreden eller ikkeresektabelt hepatocellulært karcinom (HCC), som ikke tidligere har fået systemisk behandling.

2 Medicinrådets anbefaling

Medicinrådet **anbefaler** lenvatinib som mulig standardbehandling til voksne patienter med fremskreden eller ikkeresektabelt hepatocellulært karcinom (HCC), som ikke tidligere har fået systemisk behandling.

Det kliniske spørgsmål, som ligger til grund for anbefalingen, er som følger:

Hvad er den kliniske merværdi af lenvatinib til voksne patienter med fremskredent eller ikkereseptabelt hepatocellulært karcinom, som er kandidater til systemisk behandling, sammenlignet med sorafenib?

3 Formål

Formålet med Baggrund for Medicinrådets anbefaling vedrørende lenvatinib som mulig standardbehandling til hepatocellulært karcinom er at skabe gennemsigtighed om det materiale, der ligger til grund for Medicinrådets anbefaling.

4 Baggrund

Lenvatinib er indiceret til systemisk behandling af patienter med fremskreden eller ikkeresektabelt hepatocellulært karcinom, som ikke tidligere har fået systemisk behandling

Yderligere information findes i "Medicinrådets vurdering af klinisk merværdi for lenvatinib til behandling af hepatocellulært karcinom".

4.1 Sagsbehandlingstid og proces for Medicinrådets vurdering

Medicinrådet modtog den foreløbige ansøgning den 24. maj 2018. Protokollen blev godkendt af Medicinrådet og sendt til ansøger den 11. september 2018.

Det endelige datagrundlag for Medicinrådets vurdering blev modtaget den 14. november 2018. Ansøger udbad sig et clock-stop i processen, som løb fra den 11. december 2018 til den 20. januar 2019.

Medicinrådet traf beslutning om den kliniske merværdi den. 13 marts 2019.

Medicinrådet har gennemført vurderingen af lenvatinib på 15 uger og 2 dage.

5 Medicinrådets vurdering af samlet klinisk merværdi

Medicinrådet vurderer, at lenvatinib til voksne patienter med fremskredent eller inoperabelt hepatocellulært carcinom med performancestatus 0-1 og bevaret leverfunktion svarende til Child-Pugh A og B (7), sammenlignet med sorafenib, giver:

- **Ingen klinisk merværdi** (meget lav evidenskvalitet)

Medicinrådet finder, at lenvatinib og sorafenib kan ligestilles som førstelinjebehandling til patienter med hepatocellulært karcinom.

6 Høring

Ansøger har indgivet høringssvar den 19. marts 2019. Høringssvaret har ikke givet anledning til ændringer i vurderingen af den kliniske merværdi. Høringssvaret er vedlagt som bilag.

7 Resumé af økonomisk beslutningsgrundlag

Amgros vurderer, at behandling med lenvatinib er forbundet med meromkostninger per patient sammenlignet med sorafenib. Meromkostningerne er udelukkende drevet af lægemiddelomkostningerne for lenvatinib. Med den nuværende aftalepris (SAIP) på lenvatinib vurderer Amgros, at omkostningerne ikke er rimelige sammenlignet med den kliniske merværdi, som lægemidlet tilbyder.

8 Overvejelser omkring alvorlighed/forsigtighed

Medicinrådet har ikke fundet anledning til at inddrage forhold vedrørende alvorlighed eller forsigtighed i anbefalingen.

9 Sammensætning af fagudvalg og kontaktinformation til Medicinrådet

Medicinrådets fagudvalg vedrørende leverkræft

Formand	**Indstillet af**
Britta Weber *Afdelingslæge, ph.d.*	Lægevidenskabelige Selskaber
Medlemmer	**Udpeget af**
Gerda Elisabeth Villadsen *Overlæge, ph.d., klinisk lektor*	Region Midtjylland og inviteret af formanden
Merete Krogh *Overlæge*	Region Syddanmark
Kirsten Kjeldgaard Vistisen *Overlæge*	Region Hovedstaden
Lone Galmstrup Madsen *Specialeansvarlig overlæge, ph.d.*	Region Sjælland
Har ikke udpeget	Region Nordjylland
Mette Skalshøi Kjær *Overlæge, klinisk lektor*	Dansk Selskab for Gastroenterologi og Hepatologi
Mette Kudsk Brink *Farmaceut*	Dansk Selskab for Sygehusapoteksledelse
Amy Daugaard Asmussen *Kvalitetskoordinator, sygeplejerske, MHH*	Inviteret af formanden
Niels Jessen *Professor, overlæge*	Dansk Selskab for Klinisk Farmakologi
Tóra Haraldsen *Patient/patientrepræsentant*	Danske Patienter

Medicinrådets sekretariat

Medicinrådet Dampfærgevej 27-29, 3. th. 2100 København Ø + 45 70 10 36 00 medicinraadet@medicinraadet.dk
Sekretariatets arbejdsgruppe Gedske Thomsen (projekt- og metodeansvarlig) Thea Christensen (sundhedsvidenskabelig konsulent) Anette Pultera Nielsen (fagudvalgskoordinator) Annemette Anker Nielsen (teamleder)

10 Versionslog

Version	Dato	Ændring
1.0	10.04.2019	Godkendt af Medicinrådet.

11 Bilag

Bilagsliste:

- Amgros' beslutningsgrundlag
- Amgros' sundhedsøkonomiske analyse
- Høringssvar fra ansøger
- Vurdering af den kliniske merværdi af lenvatinib
- Ansøgers endelige ansøgning
- Protokol for vurdering af den kliniske merværdi af lenvatinib

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Beslutningsgrundlag til Medicinrådet

Dette dokument er Amgros' vurdering af lenvatinib (Lenvima) som mulig standardbehandling til patienter med ubehandlet, avanceret, inoperabel HCC i voksne med fremskreden stadie (BCLC stadie C) med leverfunktion svarende til Child-Pugh A eller B. Vurderingen er baseret på lægemidlets gennemsnitlige inkrementelle omkostninger (baseret på SAIP) sammenholdt med Medicinrådets vurdering af den kliniske merværdi.

Dato for Medicinrådsbeslutning	10-04-2019
Firma	Eisai (ansøger)
Lægemiddel	Lenvatinib (Lenvima)
Indikation	Patienter med ubehandlet, avanceret, inoperabel HCC i voksne med fremskreden stadie (BCLC stadie C) med leverfunktion svarende til Child-Pugh A eller B

Amgros' vurdering

- Amgros vurderer at der ***ikke*** er et rimeligt forhold mellem meromkostningerne og den kliniske merværdi for lenvatinib (Lenvima) som mulig standardbehandling til patienter med ubehandlet, avanceret, inoperabel HCC i voksne med fremskreden stadie (BCLC stadie C) med leverfunktion svarende til Child-Pugh A eller B

Overordnet konklusion

Medicinrådet har vurderet, at lenvatinib (Lenvima) sammenlignet med sorafenib (Nexavar) giver **ingen klinisk merværdi.**

Behandling med lenvatinib (Lenvima) er forbundet med meromkostninger sammenlignet med sorafenib (Nexavar) til nævnte indikation. Amgros vurderer, at der **ikke** er rimeligt forhold mellem den kliniske merværdi for lenvatinib (Lenvima), sammenlignet med behandling med sorafenib (Nexavar). Meromkostninger drives af prisen på lenvatinib (Lenvima) og komparator.

Andre overvejelser

Amgros har indgået en aftale med Eisai om indkøb af lenvatinib (Lenvima) til en SAIP, som er lavere end AIP. Konklusionen er baseret på SAIP.

Da lenvatinib (Lenvima) har forskellige dosis alt efter vægt, vil patientens vægt have stor betydning på resultatet. Resultatet af Amgros' analyse baseret på dosis efter vægt resulterer i meromkostninger for lenvatinib (Lenvima) sammenlignet med sorafenib (Nexavar).

Konklusion for populationen

Tabel 1 Merværdi, meromkostninger og Amgros' vurdering (baseret på SAIP)

Population	Komparator	Merværdi	Usikkerhed for klinisk merværdi	Amgros' konklusion om forholdet mellem meromkostninger og merværdi
Voksne patienter med HCC i fremskredent stadie og voksne patienter med inoperabel HCC, som ikke tidligere er behandlet systemisk. Patienterne har performance status 0-1 og bevaret leverfunktion svarende til Child-Pugh A og B	Sorafenib (Nexavar)	Ingen klinisk merværdi	Meget lav evidenskvalitet	Ikke rimeligt

Konklusionen er baseret på at Medicinrådet har valgt sorafenib som komparator for patientpopulationen, og vurderingen af meromkostninger og klinisk værdi beror på denne.

Supplerende informationer (resumé af resultaterne fra afrapporteringen)

Konklusion på omkostnings- og budgetkonsekvensanalyserne

Resultatet fra Amgros' afrapportering på omkostningsanalyserne er gengivet i det følgende. For uddybende gennemgang af analyse og resultater henvises til afrapporteringen på http://www.amgros.dk.

Amgros' afrapportering - Inkrementelle omkostninger per patient

Behandling med lenvatinib (Lenvima) er forbundet med meromkostninger sammenlignet med behandling med komparator.

I tabel 2 ses de inkrementelle omkostninger for lenvatinib (Lenvima) og sorafenib (Nexavar).

Amgros' hovedanalyse resulterer i gennemsnitlige meromkostninger per patient for lenvatinib (Lenvima) sammenlignet med sorafenib (Nexavar) på ca. [redacted] DKK.

Tabel 2: Resultat af Amgros hovedanalyse for lenvatinib (Lenvima) sammenlignet med sorafenib, DKK, SAIP

Omkostningselement	Lenvatinib (Lenvima)	Sorafenib (Nexavar)	Inkrementelle omkostninger (DKK)
Lægemiddelomkostninger	[redacted] DKK	[redacted] DKK	[redacted] DKK
Hospitalsomkostninger	172.070 DKK	169.826 DKK	2.244 DKK
Omkostninger udenfor hospital	13.854 DKK	14.100 DKK	247 DKK
Totale gennemsnitsomkostninger per patient	[redacted] DKK	[redacted] DKK	[redacted] DKK

Hvis analysen udføres på baggrund af AIP, bliver de inkrementelle omkostninger per patient for lenvatinib (Lenvima) sammenlignet med sorafenib (Nexavar) ca. 153.000 DKK. Lægemiddelomkostningerne for lenvatinib (Lenvima) er 290.388 DKK og for sorafenib (Nexavar) er lægemiddelomkostningerne 139.109 DKK i AIP.

Amgros' afrapportering – Budgetkonsekvenser

Amgros vurderer at anbefaling af lenvatinib (Lenvima) som mulig standardbehandling, vil resultere i budgetkonsekvenser på ca. [redacted] DKK per år. Hvis analysen udføres med AIP, vil budgetkonsekvenserne være på ca. 2,4 mio. DKK per år.

LENVATINIB (LENVIMA)

HEPATOCELLULÆRT KARCINOM

AMGROS 27. marts 2019

AMGROS

OPSUMMERING

Baggrund

Lenvatinib (Lenvima) er en multi-receptortyrokinase inhibitor indiceret til behandling af patienter med hepatocellulært karcinom (HCC) i fremskreden stadie, eller patienter med inoperabel HCC, som ikke tidligere er behandlet systemisk. Omkring 400 patienter diagnosticeres årligt, ca. 40 patienter behandles på nuværende tidspunkt med 1. linje systemisk behandling med multi-kinaseinhibitor. Amgros' vurdering tager udgangspunkt i dokumentationen indsendt af Eisai.

Analyse

I analysen estimeres de inkrementelle omkostninger per patient og de samlede budgetkonsekvenser for regionerne forbundet med behandling med lenvatinib (Lenvima) sammenlignet med behandling med sorafenib (Nexavar) til patienter med ubehandlet, avanceret, inoperabel HCC i voksne med fremskreden stadie (BCLC stadie C) med leverfunktion svarende til Child-Pugh A ellller B.

Inkrementelle omkostninger og budgetkonsekvenser

Amgros har vurderet de gennemsnitlige meromkostninger per patient ved brug af lenvatinib (Lenvima) sammenlignet med komparator. De inkrementelle omkostninger er angivet i SAIP.

I det scenarie Amgros vurderer er mest sandsynligt er de gennemsnitlige inkrementelle omkostninger per patient ved brug af lenvatinib (Lenvima) sammenlignet med sorafenib (Nexavar) ca. [redacted] DKK. Hvis analysen udføres med AIP bliver de inkrementelle omkostninger ca. 153.000 DKK.

Amgros vurderer at budgetkonsekvenserne for regionerne per år ved anbefaling lenvatinib (Lenvima) som standardbehandling vil være på ca. [redacted] DKK per år. Hvis analysen udføres med AIP, er budgetkonsekvenserne ca. 2,4 mio. DKK per år.

Konklusion

Amgros kan konkludere, at behandling med lenvatinib (Lenvima) er forbundet med meromkostninger sammenlignet med komparator. Meromkostningerne er i denne analyse udelukkende drevet af lægemiddelomkostninger for lenvatinib (Lenvima) og sorafenib (Nexavar).

Liste over forkortelser

AIP	Apotekernes indkøbspris
DKK	Danske kroner
DRG	Diagnose Relaterede Grupper
HCC	Hepatocellulært karcinom
SPC	Summary of Product Characteristics

INDHOLD

LOG

Ansøgning	
Lægemiddelfirma:	Eisai
Handelsnavn:	Lenvima
Generisk navn:	Lenvatinib
Indikation:	Behandling til hepatocellulært karcinom
ATC-kode:	L01XE29

Proces	
Ansøgning modtaget hos Amgros:	14-11-2018
Endelig rapport færdig:	27-03-2019
Sagsbehandlingstid fra endelig ansøgning:	133 dage
Arbejdsgruppe:	**Louise Greve Dal** Line Brøns Jensen Lianna Christensen Mark Friborg Pernille Winther Johansen

Priser
Denne rapport bygger på analyser udført på baggrund sygehusapotekernes indkøbspriser (SAIP). Enkelte steder er analysens resultat yderligere angivet på baggrund af listepriser (AIP).

1 BAGGRUND

Lenvatinib (Lenvima) er en multi-receptortyrokinase inhibitor indiceret til behandling af patienter med hepatocellulært karcinom (HCC) i fremskreden stadie, eller patienter med inoperabel HCC, som ikke tidligere er behandlet systemisk. Eisai (herefter omtalt som ansøger) er markedsføringstilladelsesindehaver af lenvatinib (Lenvima) og har den 14.11.2018 indsendt en ansøgning til Medicinrådet om anbefaling af lenvatinib (Lenvima) som standardbehandling på danske sygehuse af den nævnte indikation. Som et led i denne ansøgning vurderer Amgros, på vegne af Medicinrådet de økonomiske analyser, ansøger har sendt som en del af den samlede ansøgning til Medicinrådet. Denne rapport er Amgros' vurdering af de fremsendte økonomiske analyser (herefter omtalt som analysen).

1.1 Problemstilling

Formålet med analysen er at estimere de inkrementelle omkostninger forbundet med behandling af hepatocellulært karcinom (HCC) i fremskreden stadie, eller patienter med inoperabel HCC, som ikke tidligere er behandlet systemisk, i form af de gennemsnitlige inkrementelle omkostninger per patient og de samlede budgetkonsekvenser for regionerne ved anbefaling af lenvatinib (Lenvima) som standardbehandling på danske sygehuse af den nævnte indikation. I analyserne sammenlignes behandling med lenvatinib (Lenvima) med behandling med sorafenib (Nexavar) der er defineret i Medicinrådets protokol som nuværende standardbehandling.

1.2 Patientpopulation

HCC er en mindre hyppigt forekommende kræftform i Danmark. Incidensen er for perioden 2011-2015 429 nye tilfælde per år(1). I Danmark havde 652 patienter HCC i 2015, hvilket afspejler en lav overlevelse for denne patientgruppe. Etårsoverlevelsen er 37% for mænd og 40% for kvinder, mens femårsoverlevelsen kun er 9% for mænd og 11% for kvinder(1).

Udvikling af HCC forekommer oftest i patienter der har levercirrose. Leverfunktionen hos patienter med leversygdomme opdeles efter hvor god leverfunktionen er, og benævnes i kategorierne Child-Pugh A, B og C, fra bedst til værst leverfunktion(1).

1.3 Behandling med lenvatinib (Lenvima)

HCC udgør et sygdomskontinuum, hvor Barcelona Clinic Liver Cancer (BCLC) stadiesystemet ofte bruges til stadieinddeling og ligeledes beslutte, hvilken behandling patienten har gavn af. Stadierne går fra A til C. I det fremskredne stadie (BCLC C) har patienter stadig leverfunktion svarende til Child-Pugh A eller B men kandiderer ikke længere til lokal behandling, og vurderes med henblik på 1. linje systemisk behandling(1).

Indikation

Lenvatinib (Lenvima) er indiceret til behandling af voksne patienter med HCC i fremskredent stadie og voksne patienter med inoperabel HCC, som ikke tidligere er behandlet systemisk. Patienterne har performance status 0-1 og bevaret leverfunktion svarende til Child-Pugh A og B(1).

Lenvatinib (Lenvima) er i forvejen indiceret som monoterapi til behandling af voksne patienter med differentieret thyreoideakarcinom refraktært over for radioaktivt jod og i kombination med everolimus til behandling af voksne patienter med fremskredet nyrecellekarcinom efter én forudgående behandling rettet mod vaskulær endothelvækstfaktor(1).

Virkningsmekanisme

Lenvatinib (Lenvima) er en multi-receptortyrosinkinase inhibitor, der hæmmer vækstfaktorreceptorer VEGF receptor 1-3, FGF receptor 1-4 og PDGF receptor α samt proto-onkogenerne RET og KIT(1).

Dosering

Lenvatinib (Lenvima) administreres peroralt som tabletter:

- 8 mg ved kropsvægt <60 kg
- 12 mg ved kropsvægt ≥60 kg

1.3.1 Komparator

Medicinrådet har defineret komparator som:

- 400 mg sorafenib (Nexavar) to gange dagligt så længe klinisk fordel observeres eller indtil der opstår uacceptable bivirkninger. Sorafenib (Nexavar) administreres peroralt som tabletter af 200 mg (2 tabletter 2 gange dagligt)

Tabel 1: Definerede population og komparator

Population	Komparator
Voksne patienter med HCC i fremskredent stadie og voksne patienter med inoperabel HCC, som ikke tidligere er behandlet systemisk. Patienterne har performance status 0-1 og bevaret leverfunktion svarende til Child-Pugh A og B	Sorafenib (Nexavar)

1.4 Medicinrådets kliniske spørgsmål

Medicinrådet har vurderet den kliniske merværdi af behandling med lenvatinib (Lenvima) sammenlignet med sorafenib (Nexavar) ud fra følgende kliniske spørgsmål.

- Hvad er den kliniske merværdi af lenvatinib (Lenvima) til voksne patienter med fremskredent eller inoperabelt hepatocellulært karcinom, som er kandidater til systemisk behandling, sammenlignet med sorafenib (Nexavar)?

2 VURDERING AF INDSENDT ØKONOMISK ANALYSE

I analysen af gennemsnitlige behandlingsomkostninger per patient sammenlignes behandling med lenvatinib (Lenvima) med behandling med sorafenib (Nexavar) til voksne patienter med HCC i fremskredent stadie og voksne patienter med inoperabel HCC, som ikke tidligere er behandlet systemisk.

Amgros havde flere indvendinger mod den initiale model, som ansøger indsendte. Det er kun den seneste indsendte model, som præsenteres herunder.

2.1 Model, metode og forudsætninger

2.1.1 Modelbeskrivelse

Ansøger har indsendt en partitioned survival model for behandling af patienter i den nævnte population. Modellen estimerer andelen af patienter i hvert stadie baseret på parametriske funktioner. Stadierne består af Progressionsfri overlevelse (PFS), Progression af sygdom (PD) og Overlevelse (OS). Til hvert sygdomsstadie er beregnet den tid patienten befinder sig i stadiet og de behandlingsrelaterede omkostninger. De gennemsnitlige omkostninger per patient relaterer sig derfor til et givent sygdomsstadie og den tid patienten befinder sig i dette.

Ansøger har ekstrapoleret ud fra data givet fra studiet *kudo et al (2018)*(2). Ansøger har valgt distribution log-normal for både de ekstrapolerede OS og ekstrapolerede PFS data, der viste bedste fit. Ansøger har ligeledes argumenteret for den kliniske plausibilitet.
Lenvatinib (Lenvima) er forbundet med senere progression sammenlignet med sorafenib (Nexavar), men ens overlevelse. Der kan være usikkerheder forbundet med dette som kan skyldes ubalance mellem baseline karakteristika i behandlingsarmene.

Analysen estimerer de gennemsnitlige samlede omkostninger forbundet med behandlingerne med en tidshorisont på 25 år og inkluderer omkostninger for lægemidler, monitorering og bivirkninger.

Amgros' vurdering

Amgros accepterer ansøgers valg af distributioner, da der er valgt de distributioner med bedste fit.

Amgros vurderer, at den overordnede modeltilgang er acceptabel.

2.1.2 Analyseperspektiv

Analysen anvender et begrænset samfundsperspektiv. Tidshorisonten i analysen er 25 år. Omkostningerne er diskonteret med en faktor på 4%.

Amgros' vurdering

Analysens perspektiv og diskonteringsraten er i tråd med Amgros' retningslinjer, Jf. Amgros Metodevejledning om, hvad der må inkluderes i en økonomisk analyse.

Amgros vurderer, at tidshorisonten er tilstrækkelig lang til at opfange betydelige relevante forskelle mellem de sammenlignede interventioner i analysen, eftersom få patienter er i live efter 25 år.

Amgros godtager analysens perspektiv og tidshorisonten.

2.1.3 Omkostninger

Indsendt dokumentation

Det følgende afsnit om omkostninger redegør for hvordan og hvilke omkostninger ansøger har inkluderet i analysen

Lægemiddelomkostninger

Alle anvendte lægemiddelpriser er på SAIP-niveau.

Tabel 2 illustrerer de lægemiddelpriser, som anvendes i analysen.

Tabel 2: Anvendte lægemiddelpriser, SAIP (marts 2019)

Lægemiddel	Styrke	Pakningsstørrelse	Pris pr pakning (DKK)	Kilde
Lenvitinib (Lenvima)	4 mg 10 mg	30 stk. (blister)	[redacted]	Amgros
Sorafinib	200 mg	112 stk. (blister)	[redacted]	Amgros

Ansøger har i deres analyse anvendt estimater baseret på medianer, for dosis per dag per patient for henholdsvis lenvatinib (Lenvima) og sorafenib (Nexavar).

Ansøger har i den indsendte model gjort det muligt at til- og fravælge spild ifm. behandling med lenvatinib (Lenvima). Antallet af dage med spild under behandling er valgt til 7 dage. Ansøgers argumentation for kun at inkludere 7 dages spild beror på, at det har begrænsede betydning for omkostningerne. Den begrænsede betydning er bekræftet af kliniske eksperter i NICE evalueringen af lenvatinib (Lenvima). De 7 dage med spild er vurderet til at være klinisk plausibel og er valideret af en kliniker. Ansøger har i deres hovedanalyse valgt at ekskludere spild.

Øvrige omkostninger før og efter progression

Omkostninger til øvrig behandling er de omkostninger, der er specifik forbundet med enten et progressionsfrit sygdomsstadie (PFS-stadie) eller sygdomsstadie (PD-stadie). Omkostningerne er dermed ikke knyttet til enten behandling med lenvatinib (Lenvima) eller sorafenib (Nexavar), men til den gennemsnitlige tid en patient befinder sig i det givne stadie, hvilket relaterer sig til hvilken behandling patienten modtager.

Ansøger har estimeret ressourceforbruget med behandling i PFS og PD gennem spørgeskemaer indsamlet om ressourceforbruget for sorafenib (Nexavar). Ansøger har efterfølgende fået valideret estimaterne af en dansk kliniker.

Ansøger har estimeret forbrug af antal ambulatorisk besøg hos onkolog, AFP test, leverfunktionstest, INR, komplet blodcelletal, biokemiske test, endoskopi, CT scanning, MRI scanning, hospitalisering, sygeplejerske og hjemmepleje. Værdisætningen af ressourceforbruget er sket ud fra danske laboratoriemedicinske vejledninger, DRG- og DAGS-takster 2018 og Amgros' katalog for enhedsomkostninger.

Ansøger antager at INR tages for 50% af patienterne der befinder sig i PFS-stadiet, og at 0% får taget INR i PD-stadiet. Ansøger antager også at patienter i PFS-stadiet får lavet komplet blodcelletal og lavet endoskopi 25% oftere end patienter i PD-stadiet.

Ansøger antager at 46% af patienterne indlægges 0,16 gang per måned i PFS-stadiet og at 48% af patienterne indlægges 0,4 gang per måned i PD-stadiet. Derudover antager ansøger at frekvensen for hjemmehjælp og sygeplejerskehjælp er 0,5 i PFS-stadiet og 1 i PD-stadiet for alle patienter.

Tabel 3 illustrerer ressourceforbrug, andel patienter der oplever ressourceforbruget og frekvensen per måned for henholdsvis PFS-stadiet og det PD-stadie.

Tabel 3: ressourceforbrug og andel patienter der oplever ressourceforbruget

	PFS-stadie		PD-stadie	
	% af patienter	Frekvens pr. måned	% af patienter	Frekvens pr. måned
Ambulatorisk besøg	100%	1	100%	1
AFP	100%	0,5	100%	0,5
Leverfunktion	100%	1	100%	1
INR	50%	0,67	0%	0
Komplet blodcelletal	75%	1	50%	1
Biokemi	50%	1	25%	1
Endoskopi	25%	0,33	0%	0
CT scanning	100%	0,5	100%	0,5
MRI af abdomen	28%	0,1	28%	0,1
Indlæggelse	46%	0,16	48%	0,4
Sygeplejerske	100%	0,5	100%	1
Hjemmepleje	100%	0,5	100%	1

Tabel 4 illustrerer værdisætningen af ressourceforbruget fra tabel 3.

Tabel 4: Værdisætningen af ressourceforbruget

	Kr.	Reference
Ambulatorisk besøg	2.269,20	Ambulant DAGS takster: BG50A+DG30L (Sundhedsdatastyrelsen, 2017)
AFP	30,00	Region Sjælland Laboratoriemedicinske vejledninger: Klinisk Biokemi; AFP (Region Sjælland, 2018)
Leverfunktion	40,00	Region Sjælland Laboratoriemedicinske vejledninger: Klinisk Biokemi; Albumin; ALAT+ASAT+Bilirubiner;P+Protein (Region Sjælland, 2018)
INR	30,00	Region Sjælland Laboratoriemedicinske vejledninger: Klinisk Biokemi; Koagulationsfaktor II+VII+X (Region Sjælland, 2018)
Komplet blodcelletal	40,00	Region Sjælland Laboratoriemedicinske vejledninger: Klinisk Biokemi; DIFF; maskinel+Hæmoglobin;B+Trombocytter;B (Region Sjælland, 2018)
Biokemi	80,00	Region Sjælland Laboratoriemedicinske vejledninger: Klinisk Biokemi; Gamma-Glutamyltransferase;P+eatinkinase MB;P (Region Sjælland, 2018)
Endoskopi	4.275,00	DRG-takster 2018: PG05F (Sundhedsdatastyrelsen, 2018b)
CT scanning	1.785,00	DRG-takster 2018: PG14G (Sundhedsdatastyrelsen, 2018b)
MRI af abdomen	2.288,00	DRG-takster 2018: PG14C (Sundhedsdatastyrelsen, 2018b)
Indlæggelse	34.663,00	DRG-takster 2018: 0719 (Sundhedsdatastyrelsen, 2018b)
Sygeplejerske	523,00	Amgroskatalog: Nurse (AMGROS, 2018)
Hjemmepleje	355,00	Amgroskatalog: Social and healthcare staff, untrained (AMGROS, 2018)

Tabel 5 illustrerer samlede omkostninger for ressourceforbruget stadierne PFS og PD.

Tabel 5: Samlede omkostninger for ressourceforbruget PFS og PD

	Progressionsfri-stadie (PFS)	Progredierede-stadie (PD)
Hospitalsomkostninger	5.762,53 kr.	9.176,40 kr.
Kommunale omkostninger	403,81 kr.	807,62 kr.
Total	**6.166,35 kr.**	**9.984,02 kr.**

Omkostninger til bivirkninger

Ansøger har inkluderet bivirkningsomkostninger for begge lægemidler. Bivirkningsomkostninger er beregnet udfra en engangsomkostning for henholdsvis lenvatinib (Lenvima) og sorafenib (Nexavar) i pre-progressions-stadiet, når patienten skifter til PD-stadie. Frekvensen af bivirkninger er taget fra studiet *kudo et al. (2018)*, og inkluderer grad 3 og 4 bivirkninger hvor ≥ 5% af patienterne oplever dem i hver behandlingsarm.(2) Bivirkninger af grad 3 og 4 der sker i ≤ 5% af patienterne, blev inkluderet hvis dette vurderes klinisk relevant. Bivirkninger af grad 3 og 4 der er sket i ≤ 5% af patienterne, og som blev vurderet klinisk relevant er diarré, asteni og træthed. Ansøger antager at alle bivirkninger behandles ambulant og værdisættes ud fra DAGS-taksten 2017, Ambulant besøg, Pat. Mindst 7 år, på 672 kr. Tabel 6 illustrerer bivirkningerne og frekvensen af bivirkninger for henholdsvis lenvatinib (Lenvima) og sorafenib (Nexavar).

Tabel 6: % af patienter og antal event per patient for henholdsvis lenvatinib og sorafenib (Nexavar), 3-4 grad bivirkninger

Grad 3- og 4 bivirkninger	% af patienterne		Antal event pr. patient ≥1 event	
	Lenvatinib	Sorafenib	Lenvatinib	Sorafenib
Forhøjet aspartatamino-transferase	5,04	8,00	1,04	1,11
Asteni	2,94	2,32	1,07	1,00
Forhøjet Bilirubin	6,51	4,84	1,10	1,04
Diarré	4,20	4,21	1,20	1,20
Træthed	3,78	3,58	1,00	1,00
Forhøjet gamma-glutamattranseferase	5,46	4,00	1,04	1,05
Hypertension	23,32	14,32	1,12	1,09
Palmar-plantar erythrodysaesthesia	2,94	11,37	1,07	1,17
MRI af abdomen	5,46	3,37	1,12	1,00
Indlæggelse	5,67	1,68	1,04	1,00
Sygeplejerske	7,56	2,95	1,03	1,00

Patientomkostninger

Patientomkostninger er ikke inkluderet i modellen. Ansøger antager, at der ingen forskel er i patientomkostninger.

Amgros' vurdering

Ansøgers estimater af dosis per dag per patient adskiller sig fra protokollen, hvor Medicinrådet vurderer at størstedelen af patienter vejer over 60 kg, og dermed skal have 12 mg/dag. Amgros mener at ansøgers valg af median estimater for dosis per patient for henholdsvis lenvatinib (Lenvima) og sorafenib (Nexavar) underestimerer de reelle omkostninger. De valgte dosis for lægemidlerne afspejler at størstedelen af patienterne vejer under 60 kg. Amgros udarbejder sin egen hovedanalyse hvor de gennemsnitlige estimater af dosis per patient per dag anvendes. Dette vurderer Amgros er mere plausibelt i henhold til klinisk praksis.

Amgros' vurderer, ligeledes at omkostninger for spild har begrænset betydning for analysen. Amgros' inkluderer dog spild i deres egen hovedanalysen, da 7 dages spild virker plausibelt.

Amgros vurderer, at estimeringen af monitoreringsomkostningerne skal forbeholdes med en vis usikkerhed, da ressourceestimaterne kun er valideret af én dansk onkolog.

Amgros vurderer, at estimeringen af bivirkningsrelaterede omkostninger er acceptabel.

Amgros accepterer at ansøger ikke har inkluderet patientomkostninger, da lægemidlerne gives oralt.

Amgros har valgt gennemsnitsestimater som værdi for dosis per patient per dag, som er højere end ansøgers estimerede værdi. Amgros udarbejder en ny hovedanalyse på baggrund af dette.

Amgros inkluderer spild af 7 dage i hovedanalysen.

2.2 Følsomhedsanalyser

Ansøger har udarbejdet følsomhedsanalyser og præsenteret det i et tornadodiagram. Der er ændret på en parameter af gangen. Ud fra følsomhedsanalyserne ses at ændring af den inkrementelle omkostning per patient med behandling med lenvatinib (Lenvima) sammenlignet med behandling med sorafenib (Nexavar), er mest følsom overfor lægemiddelprisen.

Ansøger har yderligere udarbejdet tre scenarieanalyser:

1. 2. linjebehandling inkluderes
2. Spild inkluderes
3. Kaplan-Meier data er anvendt uden at blive ekstrapoleret

Amgros' vurdering

Amgros mener at de indsendte følsomhedsanalyser, belyser usikkerheden af resultatet. Amgros mener at en følsomhedsanalyse med ændring af dosis per patient per dag er en vigtig usikkerhed at belyse, og udarbejder en følsomhedsanalyse hvor dosis per patient per dag varierer -+20%.

Amgros vurderer, at scenarie analysen med 2. linjebehandling ikke er relevant, da der inkluderes behandling som ikke anvendes i Danmark. Denne analyse kan derfor ikke anvendes til at være plausibel i dansk klinisk praksis.

Amgros mener at scenariet med spild bør være inkluderet i hovedanalysen.

Amgros mener ikke at scenarieanalysen med data, der kun baserer sig fra Kaplan-Meier estimater er relevant, da denne analyse belyser en tidshorisont der ikke inkluderer alle inkrementelle omkostninger af klinisk relevans.

Amgros har udarbejdet sin egen analyse hvor spild er inkluderet i hovedanalysen

Amgros udarbejder en følsomhedsanalyse der belyser usikkerheden af dosis per patient per dag.

3 RESULTATER

3.1 Ansøgers hovedanalyse

3.1.1 Antagelser i ansøgers hovedanalyse

- *Tidshorisonten er 25 år i analysen for lenvatinib (Lenvima) og sorafenib (Nexavar)*
- *Det antages at estimater for dosis per patient per dag er baseret på medianer.*
- *Der inkluderes ikke spild*

3.1.2 Resultat af ansøgers hovedanalyse

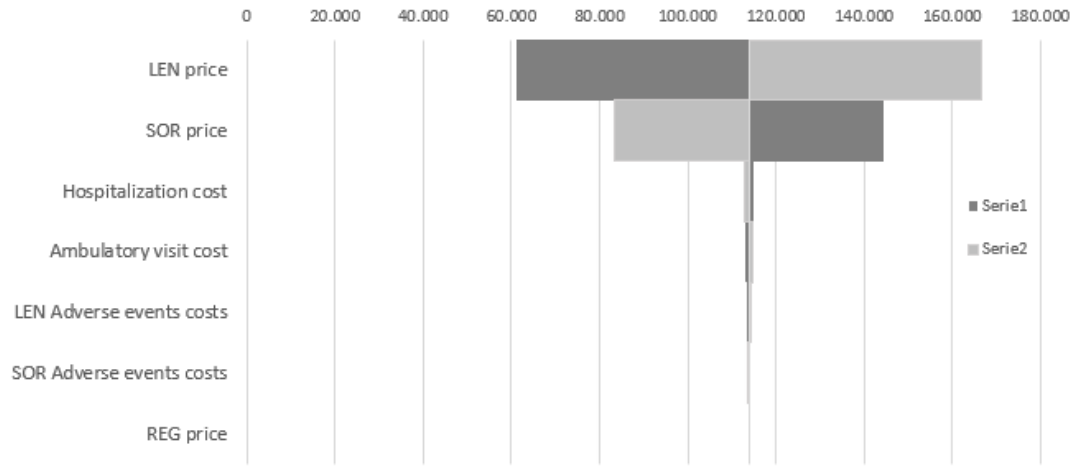
Ansøgers resultater er præsenteret i tabel 7.

Tabel 7: Resultat af ansøgers hovedanalyse for lenvatinib (Lenvima) sammenlignet med sorafenib (Nexavar), DKK, SAIP

Omkostningselement	Lenvatinib (Lenvima)	Sorafenib (Nexavar)	Inkrementelle omkostninger (DKK)
Lægemiddelomkostninger	[redacted] DKK	[redacted] DKK	[redacted] DKK
Hospitalsomkostninger	168.828 DKK	166.636 DKK	2.192 DKK
Omkostninger udenfor hospital	13.589 DKK	13.831 DKK	- 243 DKK
Totale gennemsnitsomkostninger per patient	[redacted] DKK	[redacted] DKK	[redacted] DKK

3.2 Ansøgers følsomhedsanalyser

Figur 1 illustrerer ansøgers følsomhedsanalyser i et tornadodiagram. Diagrammet viser vertikalt kategoriseret, de parametre, hvor ændring har størst betydning for resultatet.



Tabel 8 illustrerer ansøgers scenarieanalyser hvor inkludering af 2. linje behandling og spild er belyst og et scenarie hvor kun Kaplain-Meier data er benyttet.

Tabel 8: Resultat af ansøgers scenarieanalyse, DKK, SAIP

Scenarie	Lenvatinib (Lenvima)	Sorafenib (Nexavar)	Inkrementelle omkostninger (DKK)
2. linjebehandling inkluderet	[redacted] DKK	[redacted] DKK	[redacted] DKK
Spild inkluderet	[redacted] DKK	[redacted] DKK	[redacted] DKK
Kaplan-Meier data brugt	[redacted] DKK	[redacted] DKK	[redacted] DKK

3.3 Amgros' hovedanalyse

3.3.1 Antagelser i Amgros hovedanalyse

Amgros anvender ansøgers hovedanalyse, men med følgende justeringer:

- *Amgros anvender gennemsnitsværdier for estimaterne af dosis per patient per dag for henholdsvis lenatinib (Lenvima) og sorafenib (Nexavar)*
- *Amgros inkluderer spild*

3.3.2 Resultat af Amgros hovedanalyse

Som beskrevet i afsnit 2.1.3, mener Amgros, at analysen er forbundet med estimater for dosisdispensering per patient, der ikke virker plausibelt set i henhold til dansk klinisk praksis.
Justeringen af estimaterne for dosisdispensering per dag har betydning for analysens resultater, da behandling med lenvatinib (Lenvima) efter justeringerne bliver forbundet med højere meromkostninger.

Tabel 9: Resultat af Amgros hovedanalyse for lenvatinib (Lenvima) sammenlignet med sorafenib, DKK, SAIP

Omkostningselement	Lenvatinib (Lenvima)	Sorafenib (Nexavar)	Inkrementelle omkostninger (DKK)
Lægemiddelomkostninger	[redacted] DKK	[redacted] DKK	[redacted] DKK
Hospitalsomkostninger	172.070 DKK	169.826 DKK	2.244 DKK
Omkostninger udenfor hospital	13.854 DKK	14.100 DKK	247 DKK
Totale gennemsnitsomkostninger per patient	[redacted] DKK	[redacted] DKK	[redacted] DKK

De inkrementelle omkostninger for lenvatinib (Lenvima) sammenlignet med sorafenib (Nexavar) er ca. [redacted] DKK. Laves analysen med AIP bliver de inkrementelle omkostninger ca. 153.000 DKK.

3.4 Amgros' følsomhedsanalyse

3.4.1. Resultat af Amgros' følsomhedsanalyse

Som tidligere nævnt anvender ansøger median dosisdispensering som et estimat for den gennemsnitlige patient. Denne tilgang kan underestimere den reelle dosis, der ikke er i tråd med medicinrådets vurdering af en gennemsnitlig patient i Danmark. Da der er stor usikkerhed ved fordelingen af hvilken vægt patienterne har (over eller under 60 kg) udarbejder Amgros en følsomhedsanalyse der justerer mg/dag for en patient ≤ 60 kg og ≥ 60 kg.

Tabel 10: Resultat af Amgros følsomhedsanalyse med dosis fordelt på en patient ≤ 60 kg og ≥ 60 kg per dag, DKK, SAIP

Analyse	Lenvatinib (Lenvima)	Sorafenib	Inkrementelle omkostninger (DKK)
Amgros' hovedanalyse (basecase)	[redacted] DKK	[redacted] DKK	[redacted] DKK
≤ 60 kg	[redacted] DKK	[redacted] DKK	[redacted] DKK
≥ 60 kg	[redacted] DKK	[redacted] DKK	[redacted] DKK

Ud fra Amgros' følsomhedsanalyse ses at de inkrementelle meromkostninger per patient, har stor betydning for om patienten er ≤ 60 kg og ≥ 60 kg.

4 BUDGETKONSEKVENSER

Budgetkonsekvenserne er baseret på antagelsen om, at lægemidlet vil blive anbefalet som standardbehandling. Analysen tager derfor udgangspunkt i to scenarier:

A. Lægemidlet bliver anbefalet som standardbehandling af Medicinrådet til indikationen, som denne analyse omhandler

B. Lægemidler bliver ikke anbefalet som standardbehandling

Budgetkonsekvenser er differencen mellem budgetkonsekvenserne i de to scenarier.

Patientpopulation

Ansøger har estimeret at såfremt lenvatinib (Lenvima) anbefales, vil 15 patienter blive behandlet med lenvatinib (Lenvima). Dette baseres på incidensen af HCC på 429 patienter årligt i Danmark og at ca. 40 patienter behandles med nuværende 1. linjebehandling af HCC(1,3). Ansøger antager, at hvis lenvatinib (Lenvima) ikke anbefales vil 0 patienter blive behandlet med lenvatinib (Lenvima).
Ansøger har indsendt budgetkonsekvenser for 1 år, da ansøger antager ens markedsoptag per år. Budgetkonsekvenserne er estimeret til at være det samme alle år.

Ansøger har yderligere lavet en scenarieanalyse af budgetkonsekvenserne, hvor et optag på 10-20 patienter per år estimeres.

Amgros' vurdering af estimeret patientpopulation

Ansøger har argumenterer for populationsstørrelsen ud fra incidensen og nuværende antal patienter behandlet med sorafenib (Nexavar), som er defineret i Medicinrådets protokol. Amgros mener at optaget af patienter virker plausibelt og accepterer ligeledes ansøgers scenarieanalyse af budgetkonsekvenserne.

4.1 Resultater af budgetkonsekvensanalysen

Resultatet af budgetkonsekvenserne justeret ud fra resultatet af Amgros' hovedanalyse.

Tabel 11: Resultat af budgetkonsekvensanalyse, DKK, SAIP

	Anbefales som standardbehandling	Anbefales ikke som standardbehandling
Lenvatinib (Lenvima)	[redacted] DKK	0 DKK

Anbefales lenvatinib (Lenvima) vil det resultere i budgetkonsekvenser på ca. [redacted] DKK per år. Hvis analysen udføres med AIP, er budgetkonsekvenserne ca. 2,4 mio. DKK per år.

4.2 Scenarieanalyse

I nedenstående tabel præsenteres scenarieanalysen af henholdsvis lavt og højt patientantal hvis lenvatinib (Lenvima) anbefales.

Tabel 12 illustrerer resultatet af scenarieanalysen for budgetkonsekvenserne.

Tabel 12: Resultat af scenarie budgetkonsekvensanalyse, DKK, SAIP

	Anbefales som standardbehandling	Anbefales ikke som standardbehandling
Lavt patientantal (8 patienter)	[redacted] DKK	0 DKK
Højt patientantal (20 patienter)	[redacted] DKK	0 DKK

Antages det at kun 8 patienter vil blive behandlet med lenvatinib (Lenvima) hvis lægemidlet anbefales, ses budgetkonsekvenser på [redacted] DKK per år.
Antages det at 20 patienter vil modtage behandling med lenvatinib (Lenvima) hvis det anbefales, ses budgetkonsekvenser på [redacted] DKK per år.

5 DISKUSSION

Behandling med lenvatinib (Lenvima) er forbundet med betydelige meromkostninger sammenlignet med behandling med sorafenib (Nexavar). Analysens resultater påvirkes i høj grad af prisen på lenvatinib (Lenvima). Hospitalsomkostninger og tværsektorielle omkostninger har lille betydning for resultatet.

Amgros vurderer, at estimeringen af behandlingsomkostningerne er meget følsom overfor dosisjustering, som er afhængig af vægten, og derfor er forbundet med en vis usikkerhed. Der er forbundet stor usikkerhed med det estimerede antal patienter der vil blive behandlet per år, hvis lenvatinib (Lenvima) anbefales, og dermed stor usikkerhed omkring budgetkonsekvenserne.

6 REFERENCER

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Comments in response to the Medical Council's assessment of clinical added value for lenvatinib for the treatment of hepatocellular carcinoma 19/03/2019

Eisai would like to thank the Medical Council for considering the additional evidence and clarification of the REFLECT trial in the previous response, and amending its "assessment of overall clinical added value and overall evidence level". This amendment will allow Danish patients to be treated with the most appropriate treatment option as early as possible and in line with their tolerance profile. Please find below Eisai's comments in relation to the clinical value assessment report of lenvatinib in hepatocellular carcinoma (HCC) received on 13 03 19.

1. **Review of studies (section 6.1.1 of report)**

Baseline characteristics

"*No significant difference in baseline characteristics between lenvatinib and sorafenib in the REFLECT study, however, notes that hepatitis C aetiology is unevenly distributed. The academic committee does not expect that the imbalance between the study arms will have a significant impact on the impact estimates*"

Comment

There were notable differences in baseline characteristics which may have favoured sorafenib (as discussed in Section 4.2 of the original submission and in the response document).

- The proportion of patients with AFP levels ≥200 ng/mL, a marker of poor HCC prognosis, was higher in the lenvatinib arm (46.4%) than the sorafenib arm (39.3%)
- The proportion of patients with aetiology of HCV was lower in the lenvatinib arm (19%) than in the sorafenib arm (26.5%). Evidence suggests that patients with HCV aetiology may derive more clinical benefit from sorafenib than patients with other aetiologies, particularly HBV

2. **Results and assessment (section 6.1.2 of report)**

Overall survival

"*lenvatinib is placed in the category of no clinical added value"*

Comment

It is notable that after adjustment for the baseline imbalance in AFP levels, the HR favoured lenvatinib when OS was adjusted for the baseline imbalance in AFP levels. Lenvatinib was nominally superior to sorafenib, HR was 0.856 with upper limit of the 95% CI <1 (95% CI: 0.736, 0.995], p=0.0342). Analyses that adjust for imbalances in baseline characteristics that are considered prognostic of outcome, are likely to be the least biased and most applicable to patients, as stated in the EMA "Guideline on the evaluation of anticancer medicinal products in man". In addition the HR also favoured lenvatinib when OS was adjusted for the baseline imbalance in HCC aetiologies (HR 0.855, 95% CI: 0.721 to 1.013).

These results confirm that the direction of imbalance between groups is likely to have biased OS in favour of sorafenib.

Post-progression therapies

"*The Committee notes that there is not much difference in the proportion of patients who after the study received other medical treatment for their cancer disease between the lenvatinib and sorafenib (33% and 39%, respectively). Since the absolute and relative efficacy estimates do not detect statistically significant or clinically significant differences in survival for lenvatinib compared to sorafenib, the expert estimates that lenvatinib does not offer any clinical added value to the survival target*"

Comment

There was a notable imbalance between the treatment arms regarding the proportion of patients who received post-treatment anti-cancer therapy (including procedures and medications) during survival follow-up.

A higher proportion of subjects in the sorafenib than in the lenvatinib arm received post-treatment anticancer therapy: **51.1%** (243/476) versus **43.1%** (206/478) respectively)[1]. Further, a higher proportion of subjects in the sorafenib arm rather than in the lenvatinib arm (**9.5%** vs **3.1%)** received post-treatment anticancer therapy with investigational drugs, including regorafenib, mostly within clinical trials. Additionally, **121** of the **156** patients that received an anticancer medication post-progression on lenvatinib received sorafenib[2]. This imbalance in treatment with new agents is an artifact of clinical trial design rather than reflective of clinical practice.

- In the overall population, the HR (95% CI) for lenvatinib versus sorafenib was 0.87 (0.75, 1.01) in the adjusted analysis (post-hoc analysis of OS results adjusted by use of post-treatment anti-cancer therapy) compared with 0.92 (0.79, 1.06) in the unadjusted analysis

- Furthermore, as per the exploratory analysis provided in the response document[3], lenvatinib first-line followed by any subsequent anti-cancer medication demonstrated a longer OS than sorafenib followed by any subsequent anti-cancer medication. Patients who received any subsequent medication had a 4-month OS benefit if they began on lenvatinib vs sorafenib (21 vs 17 months)

These results also confirm that the direction of imbalance in subsequent therapies is likely to have biased OS in favour of sorafenib.

Adverse events

"*Overall, the committee considers that there are no significant differences in the adverse reaction profiles, which mean that a product is preferred over the other*"

Comment

Lenvatinib and sorafenib have safety profiles that are consistent with other VEGF/VEGFR-targeted therapies; however, the nature and extent of adverse events (AEs) differed between the two agents based on their different mechanisms of action. The mechanism of action of sorafenib has been

[1] European Medicines Agency Assessment report, section 2.4.2, 28 June 2018, Available at https://www.ema.europa.eu/en/medicines/human/EPAR/lenvima

[2] Alsina A, Kudo M, Vogel A, et al. Subsequent anticancer medication following first-line lenvatinib: A posthoc responder analysis from the phase 3 REFLECT study in unresectable hepatocellular carcinoma: Journal of Clinical Oncology. Conference: Americal Society of Clinical Oncology: Gastrointestinal Cancers Symposium. San Francisco, CA, USA. 37(no. 4_suppl):371. Date of Publication: February 1, 2019.

[3] Alsina A, Kudo M, Vogel A, et al. Subsequent anticancer medication following first-line lenvatinib: A posthoc responder analysis from the phase 3 REFLECT study in unresectable hepatocellular carcinoma: Journal of Clinical Oncology. Conference: Americal Society of Clinical Oncology: Gastrointestinal Cancers Symposium. San Francisco, CA, USA. 37(no. 4_suppl):371. Date of Publication: February 1, 2019.

thought to play a role in exacerbating PPE (hand foot syndrome)[4]. Specifically, the sorafenib inhibition of EGF receptors, which are abundantly expressed on epithelial cells of skin, results in an immune reaction leading to skin inflammation, folliculitis, and rash[5,6].

The qualitative difference in adverse event profiles between sorafenib and lenvatinib allows for a personalised approach, providing physicians with the opportunity to choose the most appropriate treatment according to patient profile.

PFS

"*The committee concludes that the two analyses provide consistent results. Since the smallest clinically relevant difference is achieved, the efficacy target is assigned an important clinical added value*"

Comment

Eisai would like to thank the scientific committee for considering the additional evidence.

Quality of life

Comment

All published data has been provided as part of the response document submitted on December 19, 2018. The QoL impact of lenvatinib and sorafenib was broadly equivalent across the majority of function and symptom areas; however it is notable that there was a statistically significant and clinically meaningful delay in worsening for lenvatinib compared with sorafenib across several domains including diarrhoea, nutrition and pain.

Medical Council's assessment of clinical added value for lenvatinib for the treatment of hepatocellular carcinoma

"*The Medicines Council finds that lenvatinib and sorafenib can be treated as first line therapy in patients with HCC*"

Comment

Eisai would like to thank the Medicines Council for considering the evidence and providing Danish patients access to a treatment alternative in first line therapy for HCC.

Conclusion

The REFLECT trial is the first study in 10 years to demonstrate a proven overall survival benefit by statistical confirmation of non-inferiority when compared with sorafenib, and as such represents an advancement in HCC therapy.

The clinical benefits of Lenvatinib were demonstrated in the REFLECT trial, a randomized, multicenter, head-to-head, open-label Phase III study comparing lenvatinib to sorafenib, which showed:

- Non-inferiority of OS: 13.6-month median OS (95% CI: 12.1-14.9) vs 12.3 months (95% CI: 10.4-13.9) (HR: 0.92 [95% CI: 0.79-1.06])
- A statistically significant and clinically meaningful improvement across all secondary efficacy endpoints:

[4] Harandi A, Zaidi AS, Stocker AM, Laber DA. Clinical Efficacy and Toxicity of Anti-EGFR Therapy in Common Cancers. J Oncol 2009;2009:567486.
[5] Akinyemiju T, Abera S, Ahmed M, et al. The burden of primary liver cancer and underlying etiologies from 1990 to 2015 at the global, regional, and national level: results from the Global Burden of Disease Study 2015. JAMA oncology 2017;3:1683-91.
[6] Pastore S, Mascia F, Mariani V, Girolomoni G. The epidermal growth factor receptor system in skin repair and inflammation. J Invest Dermatol 2008;128:1365-74.

    - A 34% improvement in PFS (median 7.4 vs 3.7 months, respectively; HR, 0.66; 95% CI, 0.57–0.77; P <0.0001)
    - A 37% improvement in TTP (median 8.9 vs 3.7 months, respectively; HR, 0.63; 95% CI, 0.53–0.73; P <0.0001)
    - A 2.6-fold increase in the proportion of patients with an ORR (24.1% vs 9.2%, respectively; odds ratio [OR] 3.13; 95% CI 2.15–4.56; P <0.0001)
        - Meaningful tumour shrinkage is an important management tool for HCC. The promising ORR results observed with lenvatinib in the REFLECT trial may potentially enable tumour downstaging, and thereby, allow patients with unresectable tumours, or those that cannot receive other local interventions (such as transplantation, radiofrequency ablation, percutaneous ethanol injection, TACE), to become eligible for these types of treatments. While this was not an option in REFLECT, based on the design of the trial, it is conceivable and would be appealing in clinical practice.
- A clinically meaningful delay in deterioration of health-related quality of life outcomes for multiple domains
- A consistent and manageable safety profile relative to sorafenib, without the increased risk of developing PPE
- Tailoring of starting doses based on weight for all lenvatinib patients to help deliver the optimal efficacy and tolerability balance

Lenvatinib offers a valuable treatment alternative to a patient population with poor survival rates. Patients should be given the opportunity for the best treatment option as early as possible and in line with their tolerance profile.

Medicinrådet

Medicinrådets vurdering af klinisk merværdi for lenvatinib til behandling af hepatocellulært carcinom

Medicinrådets konklusion vedrørende klinisk merværdi

Medicinrådet vurderer, at lenvatinib til hepatocellulært carcinom giver **ingen klinisk merværdi** sammenlignet med sorafenib. Evidensens kvalitet vurderes at være meget lav.

Handelsnavn	Lenvima
Generisk navn	Lenvatinib
Firma	Eisai
ATC-kode	L01XE29
Virkningsmekanisme	Lenvatinib er en multireceptortyrosinekinase inhibitor der hæmmer vækstfaktorreceptorerne VEGF 1-3, FGF 1-4, PDGF α og proto-onkogenerne KIT og RET.
Administration/dosis	Lenvatinib administreres oralt som tabletter. Dosis er 8 mg (ved kropsvægt < 60 kg) eller 12 mg (ved kropsvægt ≥ 60 kg) én gang dagligt. Behandlingen fortsættes, så længe klinisk fordel observeres, eller indtil der opstår uacceptable bivirkninger.
EMA-indikation	Lenvatinib er indiceret som monoterapi til behandling af voksne patienter med fremskreden eller ikkeresektabelt hepatocellulært carcinom (HCC), som ikke tidligere har fået systemisk behandling.
Godkendelsesdato Offentliggørelsesdato Dokumentnummer Versionsnummer	13. marts 2019 13. marts 2019 45297 1.0

Definition af klinisk merværdi:

Medicinrådet kategoriserer lægemidlets kliniske merværdi i en af følgende kategorier:

Kategori 1. Stor merværdi: Vedvarende og stor forbedring i effektforhold der ikke tidligere er opnået med et relevant behandlingsalternativ. Eksempler herpå er sygdomsremission, markant stigning i overlevelsestid, langvarigt fravær af alvorlige sygdomssymptomer eller udtalt fravær af alvorlige bivirkninger.

Kategori 2. Vigtig merværdi: Markant forbedring, eksempelvis lindring af sygdomstilstand, moderat stigning i overlevelsestid, lindring af alvorlige symptomer, fravær af alvorlige bivirkninger og væsentligt fravær af andre bivirkninger.

Kategori 3. Lille merværdi: Moderat forbedring, f.eks. reduktion i ikkealvorlige sygdomssymptomer eller fravær af bivirkninger.

Kategori 4. Ingen merværdi: Ingen merværdi sammenlignet med standardbehandling/andre behandlinger.

Kategori 5. Negativ merværdi: Negativ merværdi sammenlignet med standardbehandling/andre behandlinger.

Kategori 6. Ikkedokumenterbar merværdi: Ikkedokumenterbar merværdi sammenlignet med standardbehandling/ andre behandlinger. Effektforskellen kan ikke kvantificeres ud fra det videnskabelige datagrundlag.

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.

De fælles regionale behandlingsvejledninger er vurderinger af, hvilke lægemidler der er mest hensigtsmæssige til behandling af patienter inden for et terapiområde og dermed grundlag for ensartet høj kvalitet for patienterne på tværs af sygehuse og regioner.

Medicinrådet, Dampfærgevej 27-29, 3. th., 2100 København Ø
www.medicinraadet.dk
Sprog: dansk
Format: pdf
Udgivet af Medicinrådet, den 13. marts 2019.

Forkortelser

BCLC:	*Barcelona Clinic Liver Cancer*
CHMP:	*Committee for Medicinal Products for Human Use*
CI:	Konfidensinterval
EMA:	*European Medicines Agency*
EPAR:	*European Public Assessment Report*
EORTC QLQ-C30:	*European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30*
EORTC QLQ-HCC18:	*European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Hepatocellular carcinoma 18*
ESMO:	*European Society for Medical Oncology*
GRADE:	System til vurdering af evidens (*Grading of Recommendations Assessment, Development and Evaluation System*)
HCC:	Hepatocellulært carcinom
HR:	*Hazard ratio*
ITT:	*Intention to treat*
MeSH:	*Medical Subject Heading*
OS:	Samlet overlevelse (*Overall Survival)*
PICO:	Fokuserede forskningsspørgsmål baseret på Population, Intervention, Komparator og Outcome (effektmål)
RFA:	Radiofrekvensbehandling
RR:	Relativ risiko
SAE:	*Serious Adverse Event*
SD:	Standard afvigelse *(Standard deviation)*

Indhold

1 Formål

Formålet med Medicinrådets vurdering af klinisk merværdi af lenvatinib til hepatocellulært carcinom er at vurdere den kliniske merværdi i forhold til et eller flere lægemidler til samme patientgruppe (komparatorer).

Med udgangspunkt i den kliniske merværdi og en omkostningsanalyse udarbejdet af Amgros vurderer Medicinrådet, om lenvatinib anbefales som mulig standardbehandling.

2 Baggrund

Hepatocellulært carcinom
Primær leverkræft (hepatocellulært karcinom, HCC) er en mindre hyppigt forekommende kræftform i Danmark, som oftest forekommer i patienter med levercirrose [1]. Leverfunktionen hos patienter med leversygdomme såsom cirrose kan opdeles efter, hvor god leverfunktionen er og benævnes i kategorierne Child-Pugh A, B og C, fra bedst til værst leverfunktion.

Der forekommer ca. 430 nye tilfælde af HCC om året, hvor mændene tegner sig for knap ¾ af tilfældene [2]. Ved udgangen af 2015 havde 652 patienter HCC, hvilket afspejler den lave overlevelse for denne patientgruppe. Etårsoverlevelsen er således 37 % for mænd og 40 % for kvinder, mens femårsoverlevelsen kun er 9 % for mænd og 11 % for kvinder [2].

Nuværende behandling
HCC udgør et sygdomskontinuum, hvor Barcelona Clinic Liver Cancer (BCLC) stadiesystemet ofte bruges til stadieinddeling og ligeledes til at beslutte, hvilken behandling patienten har gavn af. Stadierne inddeles efter tumorstadie, leverfunktionsstatus, fysisk status og kræftrelaterede symptomer. Overordnet opdeles HCC-patienter i de med tidlig HCC, som har mulighed for kurativ terapi, de med intermediær og fremskreden sygdom, som har gavn af livsforlængende og palliative behandlinger og endeligt patienter, der har terminal sygdom, som tilbydes symptomatisk behandling [3].

Patienter med tidlig sygdom (BCLC A) vurderes med henblik på kirurgisk fjernelse af tumor, levertransplantation eller perkutan ablation (dvs. destruktion af kræftceller ved hjælp af kemiske substanser eller hyper-/hypotermi, hvor især radiofrekvensbehandling (RFA) har vundet indpas i Danmark) med mulighed for helbredelse. Femårsoverlevelsen er omkring 50-75 % afhængigt af behandlingen [3].

I intermediærstadiet (BCLC stadie B) har patienterne store eller flere levertumorer og leverfunktion svarende til Child-Pugh A eller B, men de har ikke kræftrelaterede symptomer og har ikke makrovaskulær invasion eller spredning uden for leveren. Patienter med sygdom i dette stadie vurderes med henblik på lokal kemoterapi i leveren (transarteriel kemoembolisering) [3].

I det fremskredne stadie (BCLC stadie C) har patienter stadig leverfunktion svarende til Child-Pugh A eller B, men kandiderer ikke længere til lokal behandling idet de har kræftsymptomer og/eller vaskulær invasion eller spredning uden for leveren [3]. De vurderes således med henblik på førstelinje systemisk behandling med multikinaseinhibitoren sorafenib. Det anslås, at ca. 40 patienter behandles med sorafenib om året [4].

Den 30. januar 2018 anbefalede Medicinrådet regorafenib som mulig standardbehandling til andenlinje systemisk behandling til patienter med HCC, med performancestadie 0-1 og leverfunktion svarende til Child-Pugh A, som tidligere er behandlet med og har tolereret sorafenib [5].

Patienter med ekstensiv tumorinvolvering førende til dårligt alment helbred og/eller som har leverfunktion svarende til Child-Pugh C behandles symptomatisk [3].

Anvendelse af det nye lægemiddel
Lenvatinib er indiceret til behandling af patienter med HCC i fremskredent stadie eller patienter med inoperabel HCC, som ikke tidligere er behandlet systemisk. Lenvatinib kan således anvendes som førstelinjebehandling ligesom sorafenib.

Lenvatinib er en multireceptortyrosinkinaseinhibitor, der hæmmer vækstfaktorreceptorerne VEGF receptor 1-3, FGF receptor 1-4 og PDGF receptor α samt proto-onkogenerne RET og KIT, som alle er centrale for kræftudvikling.

Lenvatinib administreres peroralt som tabletter. Dosis er 8 mg (ved kropsvægt < 60 kg) eller 12 mg (ved kropsvægt ≥ 60 kg) én gang dagligt. Fagudvalget vurderer, at hovedparten at de danske HCC-patienter vejer mere end 60 kg. Lenvatinib administreres, så længe klinisk fordel observeres, eller indtil der opstår uacceptable bivirkninger.

Lenvatinib er i forvejen indiceret som monoterapi til behandling af voksne patienter med differentieret thyreoideakarcinom, som er refraktært over for radioaktivt jod og til behandling af voksne patienter med fremskreden nyrecellekarcinom [6,7].

3 Metode

De præspecificerede metoder i protokollen er udarbejdet af Medicinrådet. Ansøgningen er valideret af Medicinrådet.

Ansøger har anvendt og fulgt den præspecificerede metode, jf. protokol som blev godkendt i Medicinrådet den 10. september 2018.

4 Litteratursøgning

Ansøger har i overensstemmelse med protokollen foretaget en systematisk litteratursøgning efter kliniske studier, som omhandler lenvatinib til behandling af leverkræft. Ansøgers PRISMA-diagram og litteraturgennemgang fremgår af ansøgningen.

I søgningen fandt ansøger en publikation af ét studie, som opfyldte kriterierne opstillet i protokollen. Studiet danner basis for Medicinrådets vurderingen af klinisk merværdi for lenvatinib. Studiet er et fase III-studie, som sammenligner effekten af lenvatinib og sorafenib til behandling i første linje af patienter med leverkræft. Studiet er:

- **REFLECT:** Kudo M., Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial, Lancet 2018;391(10126):1163–73. [8]

Ansøger har desuden leveret en alternativ analyse af progressionsfri overlevelse baseret på data fra REFLECT-studiet. Denne analyse er ikke tidligere publiceret. Fagudvalget benytter den alternative analyse som supplement til vurderingen af effektmålet progressionsfri overlevelse, idet analysemetoden anvendt i studiepublikationen kan føre til overestimering af lenvatinibs effekt grundet forskel i *drop-out* mellem studiearmene. Ligeledes har ansøger indsendt en supplerende overlevelsesanalyse for subgruppen af patienter, som modtager potentiel livsforlængende behandling efter deltagelse i REFLECT-studiet. Disse data er tidligere publiceret i form af konference abstracts på *Gastrointestinal Cancers Symposium of the*

American Society of Clinical Oncology (ASCO GI) 2019 [9]. Fagudvalget har orienteret sig i subgruppeanalyserne, men har ikke inddraget dem i vurderingen, idet subgrupperne ikke er specificeret i vurderingens protokol.

Til en kvalitativ gennemgang af bivirkninger har fagudvalget inddraget *EMAs public assessment reports* (EPAR) for lenvatinib [10].

Fra evidens til kategori. Medicinrådet vurderer den kliniske merværdi af et lægemiddel ud fra den indsendte endelige ansøgning, evt. suppleret med andet materiale. I protokollen blev effektmålene angivet som "kritiske", "vigtige" og "mindre vigtige". I vurderingen af klinisk merværdi vægter de kritiske højest, de vigtige næsthøjest og de mindre vigtige indgår ikke.

Den kliniske merværdi kategoriseres først enkeltvis pr. effektmål, hvorefter der foretages en vurdering af den samlede kategori for lægemidlet på tværs af effektmålene. Kategoriseringen pr. effektmål foretages på baggrund af absolutte og relative værdier for det enkelte effektmål. Den relative effekt beskrives med et estimat og et konfidensinterval, der sammenholdes med generiske væsentlighedskriterier. Den absolutte effekt sammenholdes med den i protokollen beskrevne "mindste klinisk relevante forskel". Den endelige kategorisering af lægemidlets kliniske merværdi er en delvis kvalitativ proces, hvor der foretages en vurdering af det samlede datagrundlag på tværs af effektmålene.

Vurdering af evidensens kvalitet foretages med udgangspunkt i GRADE og udtrykker tiltroen til evidensgrundlaget for de enkelte effektstørrelser og den endelige kategori for klinisk merværdi. Evidensens kvalitet inddeles i fire niveauer: høj, moderat, lav og meget lav. GRADE-metoden er et internationalt anerkendt redskab til systematisk vurdering af evidens og udarbejdelse af anbefalinger. I denne vurdering er metoden anvendt til at vurdere evidensens kvalitet.

5 Databehandling

Medicinrådet har ikke fundet anledning til at foretage ændringer af beregninger foretaget af ansøger eller supplere med yderligere beregninger.

Konfidensintervaller for forskellen i medianen for overlevelse og progressionsfri overlevelse og forskellen for overlevelsesraterne for 12 og 24 måneder er udeladt, da der ikke findes en hensigtsmæssig måde at beregne disse.

Alle anførte konfidensintervaller er angivet som 95 % konfidensintervaller.

6 Klinisk merværdi

6.1 Konklusion klinisk spørgsmål

Hvad er den kliniske merværdi af lenvatinib til voksne patienter med fremskredent eller inoperabelt hepatocellulært karcinom, som er kandidater til systemisk behandling, sammenlignet med sorafenib?

Fagudvalget vurderer, at lenvatinib til patienter med hepatocellulært carcinom giver en **ingen klinisk merværdi** (meget lav evidenskvalitet).

6.1.1 Gennemgang af studier

Ansøger identificerede ét klinisk studie omhandlende lenvatinib til besvarelse af det kliniske spørgsmål. Nedenfor følger en beskrivelse af studiet.

Karakteristika

REFLECT: Resultaterne fra REFLECT-studiet er publiceret i 2018 [8]. Studiet er et randomiseret, ublindet, non-inferioritets fase 3-studie. Studiets formål var at evaluere den samlede overlevelse i patienter behandlet med lenvatinib sammenlignet med sorafenib. ClinicalTrials.gov: NCT01761266.

I studiet blev 954 patienter randomiseret i forholdet 1:1 til enten lenvatinib eller sorafenib. Doseringen af lenvatinib var 12 mg/dag (ved kropsvægt ≥ 60 kg) eller 8 mg/dag (ved kropsvægt < 60 kg). Doseringen af sorafenib var 400 mg to gange dagligt. Behandlingspausering og dosisreduktion var tilladt ved lægemiddelrelateret toksicitet. Effektanalysen blev baseret på alle randomiserede patienter (intention to treat), mens sikkerhedsanalysen kun inkluderede patienter, som modtog behandling. Den mediane opfølgningstid var 27,7 måneder i lenvatinibarmen og 27,2 måneder i sorafenibarmen (data cutoff i november 2016). Den mediane behandlingstid var henholdsvis 5,7 måneder (lenvatinib) og 3,7 måneder (sorafenib). Effektmålene i studiet er angivet i skemaet nedenfor.

Tabel 1. Effektmål i REFLECT-studiet

Primært effektmål	**Sekundære effektmål**
Samlet overlevelse	Progressionsfri overlevelse Tid til progression Objektiv responsrate Livskvalitet Sikkerhed (bivirkninger) F*armakokinetik*

Population

Populationen i studiet er præsenteret i tabellen nedenfor.

Tabel 2. Patientkarakteristika i REFLECT-studiet

Patientkarakteristika		
	Lenvatinib (n = 478)	**Sorafenib (n = 476)**
Alder (median, interval)	63 (20-88)	62 (22-88)
% kvinder	15 %	16%
Eastern Cooperative Oncology Group performance status	0: 64 % 1: 36 %	0: 63 % 1: 37 %
Child-Pugh klasse	A: 99 % B: 1 %	A: 99 % B: 1%
Makroskopisk portåre-invasion	Ja: 23 % Nej: 77 %	Ja: 19 % Nej: 81 %
Ekstrahepatisk spredning	Ja: 61 % Nej: 39%	Ja: 62 % Nej: 38 %
Underliggende cirrhosis	Ja: 74 % Nej: 26 %	Ja: 76 % Nej: 24 %
Ætiologi- kronisk leversygdom	Hepatitis B: 53 % Hepatitis C: 19 % Alkohol: 8 % Andet: 8 % Ukendt: 13 %	Hepatitis B: 48 % Hepatitis C: 26 % Alkohol: 4 % Andet: 7 % Ukendt: 14 %
Barcelona Clinic Liver Cancer stadie	B (intermediær): 22 % C (fremskreden): 78 %	B (intermediær): 19 % C (fremskreden): 81 %

Fagudvalget finder, at der ikke er nogen betydende forskelle i baselinekarakteristika mellem lenvatinib- og sorafenibarmen i REFLECT-studiet, men bemærker dog at hepatitis C-ætiologi er ulige fordelt. Fagudvalget forventer ikke, at ubalancen mellem studiearmene vil have betydende indflydelse for effektestimaterne.

Fagudvalget vurderer, at patientkarakteristika i studiet ikke afviger væsentligt fra den danske patientpopulation, men fremhæver dog at populationen i studiet afviger fra den danske population, på den måde, at HCC i Danmark i højere grad opstår hos patienter med alkoholrelateret cirrose, hvorimod HCC i studiepopulationen primært er relateret til viral hepatitis. Dog vurderer fagudvalget, at populationerne i Danmark og studiet er sammenlignelige, da andelen af HCC-patienter med cirrose er af samme størrelse (leverfunktionen har betydning for prognose).

6.1.2 Resultater og vurdering

Resultater og vurdering af de effektmål, som fagudvalget har præspecificeret som hhv. kritiske og vigtige, følger nedenfor.

Samlet overlevelse, OS (kritisk)
Overlevelse er et kritisk effektmål, da HCC er en dødelig sygdom. Fagudvalget ønsker effektmålet opgjort som median overlevelse samt overlevelsesrater ved 12 og 24 måneder.

Tabel 3. Vurdering af klinisk merværdi: Samlet overlevelse

	Forhåndsdefineret grundlag for vurdering		Resultater
Absolutte forskelle	Median overlevelse: 3 måneder 12 måneders overlevelse: 8 %-point 24 måneders overlevelse: 4 %-point		Median overlevelse: 1,3 måneder 12 måneders overlevelse: 5 %-point 24 måneders overlevelse: 3,7 %-point
Relative forskelle	Stor merværdi	Øvre konfidensgrænse < 0,85	
	Vigtig merværdi	Øvre konfidensgrænse < 0,95	
	Lille merværdi	Øvre konfidensgrænse < 1,00	
	Ingen merværdi	Øvre konfidensgrænse > 1,00	HR: 0,92 [0,79;1,06]
	Negativ merværdi	Nedre konfidensgrænse > 1.00	
Evidensens kvalitet	Lav		

Første kolonne indeholder de i protokollen og metodehåndbogen præspecificerede grundlag for vurderingen. Anden kolonne indeholder data på de absolutte og relative værdier fra resultatafsnittet, som indgår i Medicinrådets vurdering.
HR: Hazard ratio

Median overlevelse

I lenvatinibarmen er den mediane samlede overlevelse 13,6 måneder, mens den i sorafenibarmen er 12,3 måneder. Det svarer til en forskel på 1,3 måneder til fordel for lenvatinib. Fagudvalget har vurderet, at en forskel på 3 måneder eller derover er klinisk relevant. Lenvatinib lever ikke op til dette krav.

Den relative effektforskel for den mediane overlevelse hazard ratio (HR) er 0,92 [0,79;1,06] og viser, at der ikke er statistisk signifikant forskel på behandlingerne. Lenvatinib indplaceres i kategorien **ingen klinisk merværdi**, da konfidensintervallet indeholder 1.

Overlevelsesrater

Efter 12 måneders behandling er 55 % af patienterne i live i lenvatinibarmen, mens det tilsvarende tal for sorafenibarmen er 50 %. Der er altså en forskel på 5 %-point til fordel for lenvatinib. Denne forskel er mindre end den forskel på 8 %-point, som er defineret i protokollen, som den mindste klinisk relevante forskel.

Ved 24 måneders behandling ses en forskel i overlevelse på 3,7 %-point, idet 29,9 % af patienterne er i live i lenvatinibarmen, og 26,2 % er i live i sorafenibarmen. Denne forskel er mindre end de 4 %, som fagudvalget har vurderet klinisk relevant.

Den relative effektforskel HR: 0,92 [0,79;1,06] for overlevelsesraterne viser også, at der ikke er statistisk signifikant forskel på behandlingerne. Lenvatinib indplaceres i kategorien **ingen klinisk merværdi**, da konfidensintervallet indeholder 1.

Samlet vurdering for overlevelse

Fagudvalget bemærker, at der ikke er stor forskel i andelen af patienter, som efter studiet modtog anden medicinsk behandling mod deres kræftsygdom mellem lenvatinib- og sorafenibarmen (33 % og 39 % henholdsvis). Da de absolutte og relative effektestimater ikke påviser statistisk signifikant eller klinisk betydende forskel i overlevelse for lenvatinib sammenlignet med sorafenib, vurderer fagudvalget, at lenvatinib tilbyder **ingen klinisk merværdi** for effektmålet overlevelse.

Evidensens kvalitet er lav.

Bivirkninger (kritisk)
Bivirkninger har betydning for patientens livskvalitet og er et kritisk effektmål i vurderingen af lenvatinib. Fagudvalget ønsker bivirkninger ved lenvatinib belyst ved andelen af patienter, der ophører behandling pga. bivirkninger, andelen af patienter som dosisreduceres og antallet af bivirkninger grad 3-5. Dernæst ønsker fagudvalget også at foretage en kvalitativ vurdering af bivirkningsprofilerne.

Andel af patienter der ophører behandling grundet bivirkninger

Tabel 4. Vurdering af klinisk merværdi: Andel af patienter der ophører behandling grundet bivirkninger

	Forhåndsdefineret grundlag for vurdering		Resultater
Absolutte forskelle	5 %-point		2 %-point [-2;5]
Relative forskelle	Stor merværdi	Øvre konfidensgrænse < 0,75	
	Vigtig merværdi	Øvre konfidensgrænse < 0,90	
	Lille merværdi	Øvre konfidensgrænse < 1,00	
	Ingen merværdi	Øvre konfidensgrænse > 1,00	RR: 1,23 [0,79;1,90]
	Negativ merværdi	Nedre konfidensgrænse > 1.00	
Evidensens kvalitet	Meget lav		

RR: relativ risiko

Behandlingsophør på grund af bivirkninger ønskes belyst, idet dette er et mål for, hvor stor en del af patienterne, som oplever så alvorlige eller generende bivirkninger, at de må stoppe behandlingen og dermed muligvis ikke har fået gavn af at modtage lægemidlet.

Ved behandling med lenvatinib ophører ca. 9 % af patienterne med behandlingen på grund af bivirkninger. Det tilsvarende tal for sorafenib er ca. 7 %. Lenvatinib medfører således, at 2 %-point flere patienter ophører behandling sammenlignet med sorafenib. Forskellen er dog ikke så stor, at fagudvalget vurderer den som klinisk relevant. Den forhåndsdefinerede grænse for om forskellen er klinisk relevant er 5 %-point.

Det relative effektestimat for behandlingsophør grundet bivirkninger (relative risiko (RR) = 1,23 [0,79; 1,90] viser at der ikke er statistisk signifikant forskel på grupperne. Da konfidensintervallet indeholder 1, indplaceres lenvatinib i kategorien **ingen klinisk merværdi**, hvad angår behandlingsophør grundet bivirkninger.

Andel af patienter der dosisreduceres

Tabel 5. Vurdering af klinisk merværdi: Andel af patienter der dosisreduceres

	Forhåndsdefineret grundlag for vurdering		Resultater
Absolutte forskelle	10 %-point		-1 %-point [-7; 5]
Relative forskelle	Stor merværdi	Øvre konfidensgrænse < 0,75	
	Vigtig merværdi	Øvre konfidensgrænse < 0,90	
	Lille merværdi	Øvre konfidensgrænse < 1,00	
	Ingen merværdi	Øvre konfidensgrænse > 1,00	RR: 0,97 [0,82; 1,14]
	Negativ merværdi	Nedre konfidensgrænse > 1.00	
Evidensens kvalitet	Meget lav		

RR: Relativ risiko

Dosisreduktion ses for henholdsvis ca. 37 % og 38 % af patienterne i lenvatinib- og sorafenibarmen. Der er en forskel på ca. 1 %-point mellem behandlingerne, som fagudvalget ikke finder klinisk relevant. Den forhåndsdefinerede forskel for, hvornår forskellen er klinisk relevant, er 10 %-point.

Det relative effektestimat for dosisreduktion viser også, at der ikke er signifikant forskel mellem behandlingerne. Konfidensintervallet for den relative risiko på RR: 0,97 [0,82;1,14] indeholder 1, hvilket indplacerer lenvatinib i kategorien **ingen klinisk merværdi**, hvad angår dosisreduktion.

Antal grad 3-5 bivirkninger

Tabel 6. Vurdering af klinisk merværdi: Antal grad 3-5 bivirkninger

	Forhåndsdefineret grundlag for vurdering		Resultater
Absolutte forskelle	10 % relativ forøgelse eller reduktion svarende til 0,18 events/patient-år		-0,20 [-0,42; 0,01] events/patient-år
Relative forskelle	Stor merværdi	Øvre konfidensgrænse < 0,75	
	Vigtig merværdi	Øvre konfidensgrænse < 0,90	
	Lille merværdi	Øvre konfidensgrænse < 1,00	
	Ingen merværdi	Øvre konfidensgrænse > 1,00	Rate ratio: 0,89 [0,78;1,01]
	Negativ merværdi	Nedre konfidensgrænse > 1,00	
Evidensens kvalitet	Meget lav		

Antallet af bivirkninger grad 3-5 er opgjort til 517 events i lenvatinibarmen og 430 events i sorafenibarmen. Imidlertid er behandlingsvarigheden forskellig i de to arme, da den mediane behandlingstid var henholdsvis 5,7 måneder (lenvatinib) og 3,7 måneder (sorafenib).

Når der justeres for behandlingsvarighed, ses 1,59 events/patient-år i lenvatinibarmen og 1,80 events/patient-år i sorafenibarmen. Forskellen mellem de to behandlinger er 0,20 events/patient-år til fordel for lenvatinib, hvilket er en større forskel end den forhåndsdefinerede grænse på 0,18 events/patient-år, svarende til en 10 % relativ forøgelse eller reduktion.

Det relative effektestimat (rate ratio) 0,89 [0,78;1,01] indikerer, at risikoen for en bivirkning pr. patient-år er mindre ved lenvatinib end sorafenib. Men forskellen er ikke statistisk signifikant, hvilket indplacerer lenvatinib i kategorien **ingen klinisk merværdi.**

Kvalitativ gennemgang af bivirkninger

Som supplement til de ovenstående kvantitative vurderinger af bivirkninger har fagudvalget ønsket at beskrive forskelle i bivirkningsprofilerne for lenvatinib og sorafenib. Da REFLECT-studiet direkte sammenligner lenvatinib og sorafenib, er der taget udgangspunkt i publikationen for studiet [8] samt i EMA European public assessment report for lenvatinib [10]. Nedenfor er en kort gennemgang af de væsentligste forskelle.

Uønskede hændelser observeret hyppigst for lenvatinib
I lenvatinibarmen sås oftere forhøjet blodtryk end i sorafenibarmen (42 % versus 30 %). Forhøjet blodtryk håndteres ofte medicinsk i klinikken.

Øget udskillelse af protein fra nyrerne (proteinuri) blev observeret i 25 % af patienter i behandling med lenvatinib, mens det tilsvarende tal for sorafenib var 11 %. Proteinuri kan være et symptom på nefrotisk syndrom og bør derfor overvåges løbende. Såfremt der opstår fulminant nefrotisk syndrom kan håndteringen af dette være svær og kan føre til seponering, og det kan udelukke efterfølgende behandling. Fagudvalget bemærker dog, at grad ≥ 3 proteinuri kun ses i 6 % af patienterne i lenvatinibarmen og 2 % i sorafenibarmen.

Ligeledes er hypothyroidisme også hyppigere i patienter i lenvatinibbehandling (16 %) end i patienter i sorafenibbehandling (2 %).

Uønskede hændelser observeret hyppigst for sorafenib
Patienter, som blev behandlet med sorafenib, oplevede flere hånd-fod-hudreaktioner end patienterne i lenvatinibarmen (52 % versus 27 % henholdsvis). Fagudvalget vurderer, at hånd-fod-hudreaktion oftest kan håndteres ved dosisjustering samt forskellige former for symptomlindring såsom fedtcreme og trykaflastning (skoindlæg).

Diarré blev også observeret mere hyppigt i sorafenibbehandlede patienter end i lenvatinibbehandlede patienter (46 % versus 39 %). Diarré kan ofte afhjælpes medicinsk eller ved dosisjustering.

Hårtab sås i 25 % af sorafenibbehandlede patienter, men kun i 3 % af lenvatinibbehandlede patienter.

Konklusion
Overordnet set er både lenvatinib og sorafenib associeret med mange bivirkninger, idet næsten alle patienter (94 % for lenvatinib og 95 % for sorafenib) oplever en eller flere bivirkninger (enhver grad).

Fagudvalget forventer, at en del af de observerede bivirkninger kan håndteres medicinsk eller ved dosisjustering. I REFLECT-studiet dosisreduceres en stor andel af patienterne (37 % af patienterne i lenvatinibarmen og 38 % i sorafenibarmen). Ligeledes ses pausering af behandling i 40 % af lenvatinibbehandlede patienter og 32 % af sorafenibbehandlede patienter.

Fagudvalget fremhæver, at for patienter med hudlidelser er der dårlige erfaringer med at anvende sorafenib, og at lenvatinib her kan finde anvendelse. Konkret ses færre tilfælde af ≥ 3 hånd-fod-hudreaktioner i lenvatinibarmen (3 % versus 11 %).

Fagudvalget bemærker også, at EMA i sin gennemgang af lenvatinib fremhæver levertoksicitet som en problematik, idet der sås flere alvorlige og dødelige leverrelaterede bivirkninger i lenvatinibarmen end i sorafenibarmen, og at ansøger derfor er blevet pålagt at udføre et fase 4-forsøg for at karakterisere levertoksiciteten bedre.

Overordnet set vurderer fagudvalget, at der ikke er væsentlige betydende forskelle i bivirkningsprofilerne, som gør, at et produkt foretrækkes frem for det andet.

Samlet vurdering for bivirkninger

Gennemgangen af data for behandlingsophør grundet bivirkninger, dosisreduktion som følge af bivirkninger samt antallet af grad 3-5 bivirkninger viser ingen klinisk betydende eller statistiske signifikante forskelle mellem lenvatinib og sorafenib. Ved gennemgang af bivirkningsprofilerne (type og frekvens) ses der ikke betydende forskelle, som betyder, at fagudvalget foretrækker et produkt fremfor et andet. Fagudvalget vurderer derfor, at lenvatinib tilbyder **ingen klinisk merværdi** sammenlignet med sorafenib for effektmålet bivirkninger.

Evidensens kvalitet er meget lav.

Progressionsfri overlevelse (vigtig)
Effektmålet "progressionsfri overlevelse" er medtaget som et mål for effekten af førstelinjebehandling og virker som et supplement til data for effektmålet "samlet overlevelse". Patienter, der progredierer under behandling med lenvatinib og sorafenib, kan modtage behandling i anden linje. Effektmålet "samlet overlevelse" afspejler derfor effekten af både første- og evt. andenlinjebehandling.

Tabel 7. Vurdering af klinisk merværdi: Progressionsfri overlevelse

	Forhåndsdefineret grundlag for vurdering		Resultater
Absolutte forskelle	Median progressionsfri overlevelse: 3 måneder		3,7 måneder
Relative forskelle	Stor merværdi	Øvre konfidensgrænse < 0,75	
	Vigtig merværdi	Øvre konfidensgrænse < 0,90	HR: 0,66 [0,57;0,77]
	Lille merværdi	Øvre konfidensgrænse < 0,10	
	Ingen merværdi	Øvre konfidensgrænse > 1,00	
	Negativ merværdi	Nedre konfidensgrænse > 1.00	
Evidensens kvalitet	Meget lav		

HR: Hazard ratio

For patienter behandlet med lenvatinib eller sorafenib var den mediane tid til progression henholdsvis 7,4 og 3,7 måneder. Det giver en forskel i median tid til progression på 3,7 måneder. Det overskrider den forskel på 3 måneder, som fagudvalget har forhåndsdefineret som klinisk relevant.

Den relative effektforskel viser, at der er en signifikant forskel på progressionsfri overlevelse mellem de to grupper. Hazard ratio var 0,66 [0,57;0,77]. Da den øvre grænse for konfidensintervallet < 0,90, kvalificerer det til at indplacere lenvatinib i kategorien "vigtig merværdi", hvad angår progressionsfri overlevelse. Ifølge lenvatinibs EPAR [10] anvender ansøger en censureringsmetode i dataanalysen af progressionsfri overlevelse, som kan medføre overestimering af lenvatinibs effekt. Det skyldes, at flere patienter forlader studiet *(drop out)* i lenvatinibarmen end i sorafenibarmen. Herved er der flere censureringer i lenvatinibarmen, hvilket betyder, at eventuelle progressionshændelser ikke inkluderes i analysen. Hvis analysen justeres, så censureringen tager højde for uligheden i antallet af patienter, som forlader studiet, er forskellen i progressionsfri overlevelse på 3,6 måneder, HR 0,72 [0,63; 0,83].

Fagudvalget konkluderer, at de to analyser giver overensstemmende resultater. Da den mindste klinisk relevante forskel er opnået, tildeles effektmålet en **vigtig klinisk merværdi**.

Evidensens kvalitet er meget lav.

Livskvalitet (vigtig)
Fagudvalget ønskede livskvalitet opgjort efter 1, 2 og 3 måneders behandling ved hjælp af livskvalitetsværktøjet EORTC QLQ-C30 summary score. Ansøger har ikke leveret de ønskede data, men oplyser, at livskvaliteten falder i begge arme efter opstart af behandling. Ansøger har målt livskvalitet ved EORTC QLQ-C30 og EORT QLQ-HCC18 og har lavet analyser af tid til meningsfuld forværring. Summaryscoren er ikke signifikant forskellig mellem de to arme baseret på hazard ratio (HR 0,87 [0,75;1,01]).

Da de efterspurgte opgørelser efter 1, 2 og 3 måneders behandling ikke er til rådighed, vurderer fagudvalget, at den kliniske merværdi ikke kan bestemmes. Lenvatinib har derfor en **ikkedokumenterbar merværdi** for effektmålet livskvalitet.

6.1.3 Evidensens kvalitet

Evidensens kvalitet for den kliniske merværdi, som lenvatinib tilbyder, er samlet set vurderet som værende **meget lav**.

Der er udarbejdet en GRADE-profil for det kliniske spørgsmål. Evidensens kvalitet er nedgraderet for inkonsistens (der foreligger kun ét studie), risiko for bias (ublindet studie) og imprecision (der foreligger kun ét studie, konfidensintervallet for den relative effekt overlapper 1). Yderligere overvejelser vedrørende evidensens kvalitet kan ses i bilag 2.

6.1.4 Konklusion

Fagudvalget vurderer, at lenvatinib til voksne patienter med fremskredent eller inoperabelt hepatocellulært carcinom med performancestatus 0-1 og bevaret leverfunktion svarende til Child-Pugh A og B (7) giver **ingen klinisk merværdi** sammenlignet med sorafenib (meget lav evidenskvalitet).

Evidensens kvalitet vurderes at være meget lav.

Fagudvalget har primært lagt vægt på, at der ikke ses klinisk betydende eller signifikant forskellig overlevelsesgevinst ved lenvatinib sammenlignet med standardbehandlingen. Fagudvalget bemærker, at der ses en gevinst på 3,6-3,7 måneder i progressionsfri overlevelse ved lenvatinibbehandling, men da denne ikke reflekteres i en øget overlevelse sammenlignet med standardbehandlingen, er den kliniske betydning uvis. Fagudvalget vurderer, at en længere progressionsfri overlevelse ikke nødvendigvis resulterer i øget livskvalitet for HCC-patienter, da en del patienter vil være symptomfri trods progression. Fagudvalget bemærker, at ansøger ikke har leveret data, som viser en betydende forskel i livskvalitet mellem lenvatinib og standardbehandlingen.

Fagudvalget vurderer også, at der overordnet set ikke er væsentlige betydende forskelle i bivirkningsprofilerne, som gør, at lenvatinib foretrækkes fremfor standardbehandlingen eller omvendt. Fagudvalget fremhæver, at for patienter med hudlidelser er der dårlige erfaringer med at anvende sorafenib, og at lenvatinib her er et godt behandlingsalternativ, idet der ses færre hudrelaterede bivirkninger ved lenvatinib sammenlignet med sorafenib.

Tabel 8. Oversigt over effektmål og merværdier i vurderingen

Effektmål	**Vigtighed**	**Merværdi**
Samlet overlevelse	Kritisk	Ingen
Bivirkninger	Kritisk	Ingen
Progressionsfri overlevelse	Vigtig	Vigtig
Livskvalitet	Vigtig	Ikkedokumenterbar
Samlet vurdering		**Ingen klinisk merværdi**

7 Andre overvejelser

Fagudvalget har ikke ønsket at ligestille lenvatinib og sorafenib til førstelinjebehandling af HCC af hensyn til efterfølgende behandlingsmuligheder.

8 Rådets vurdering af samlet klinisk merværdi og samlet evidensniveau

Medicinrådet vurderer, at lenvatinib til voksne patienter med fremskredent eller inoperabelt hepatocellulært carcinom med performancestatus 0-1 og bevaret leverfunktion svarende til Child-Pugh A og B (7) giver:

- **Ingen klinisk merværdi** (meget lav evidenskvalitet)

Medicinrådet finder, at lenvatinib og sorafenib kan ligestilles som førstelinjebehandling til patienter med HCC.

9 Relation til eksisterende behandlingsvejledning

Der er ingen behandlingsvejledninger indenfor leverkræftområdet.

10 Referencer

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11 Sammensætning af fagudvalg og kontaktinformation til Medicinrådet

Medicinrådets fagudvalg vedrørende leverkræft

Formand	***Indstillet af***
Britta Weber Afdelingslæge	Lægevidenskabelige Selskaber
Medlemmer	***Udpeget af***
Gerda Elisabeth Villadsen Overlæge	Region Midtjylland og inviteret af formanden
Merete Krogh Overlæge	Region Syddanmark
Kirsten Kjeldgaard Vistisen Overlæge	Region Hovedstaden
Lone Galmstrup Madsen Specialeansvarlig overlæge, ph.d.	Region Sjælland
Har ikke udpeget	Region Nordjylland
Mette Skalshøi Kjær Overlæge, klinisk lektor	Dansk Selskab for Gastroenterologi og Hepatologi
Mette Kudsk Brink Farmaceut	Dansk Selskab for Sygehusapoteksledelse
Amy Daugaard Asmussen Kvalitetskoordinator, sygeplejerske, MHH	Inviteret af formanden
Niels Jessen Professor, overlæge	Dansk Selskab for Klinisk Farmakologi
Tóra Haraldsen Dahl Patient/patientrepræsentant	Danske Patienter

Tidligere medlemmer, som har taget del i processen: Aleksander Krag, *Professor*.

Medicinrådets sekretariat

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Sekretariatets arbejdsgruppe Gedske Thomsen (projekt- og metodeansvarlig) Thea Christensen (sundhedsvidenskabelig konsulent) Anette Pultera Nielsen (fagudvalgskoordinator) Annemette Anker Nielsen (teamleder)

12 Bilag 1: GRADE-evidensprofiler

12.1 Cochrane Risk of Bias

Risiko for bias i REFLECT-studiet.

Risk of bias	Vurdering	Begrundelse
Random sequence generation (selection bias)	• Lav risiko for bias	Patienter blev randomiseret 1:1 vha. et interaktivt voice-web responssystem i en blokstørrelse på 2. Patienter blev stratificeret efter region (Asia-Pacific/Western), makroskopisk portalvene invasion (ja/nej), ekstrahepatisk spredning (ja/nej), samtidig makroskopisk portalvene invasion og ekstrahepatisk spredning (Ja/nej), performance statur (0/1) og vægt (</≥ 60 kg).
Allocation concealment (selection bias)	• Lav risiko for bias	Randomiseringen blev genereret af en uafhængig statistiker, og investigatorerne blev bekendt med gruppeallokeringen direkte gennem det interaktive voice-web responssystem.
Blinding of participants and personnel (performance bias)		
Overlevelse	• Lav risiko for bias	Studiet var ikke blindet. Det forventes ikke, at manglende blinding påvirker effektmålet.
Bivirkninger	• Høj risiko for bias	Studiet var ikke blindet. Det kan påvirke patients og investigators opmærksomhed på, om der opstår bivirkninger.
Livskvalitet	• Høj risiko for bias	Studiet var ikke blindet. Data for livskvalitet kommer fra spørgeskemaer, patienterne har udfyldt. Udfaldet kan derfor være påvirket af, at patienten ved, hvad vedkommende behandles med.
Progressionsfri overlevelse	• Lav risiko for bias	Studiet var ikke blindet. Det forventes ikke, at manglende blinding påvirker effektmålet.
Blinding of outcome assessment (detection bias)		
Overlevelse	• Lav risiko for bias	Studiet var ikke blindet. Det forventes ikke af manglende blinding påvirker effektmålet.
Bivirkninger	• Høj risiko for bias	Studiet var ikke blindet. Det kan påvirke investigators vurdering af, om en uønsket hændelse er relateret til lægemidlet.
Livskvalitet	• Høj risiko for bias	Studiet var ikke blindet. Data for livskvalitet kommer fra spørgeskemaer, patienterne har udfyldt. Udfaldet kan derfor være påvirket af, at patienten ved, hvad vedkommende behandles med.
Progressionsfri overlevelse	• Lav risiko for bias	Studiet var ikke blindet. Effektmålet blev vurderet af investigator. Resultaterne blev bekræftet af blindet uafhængig review. Derfor forventes det ikke, at manglende blinding påvirker effektmålet.
Incomplete outcome data (attrition bias)	• Lav risiko for bias	Ansøger rapporterer på ITT-populationen.
Selective reporting (reporting bias)	• Uklar risiko for bias	Ansøger rapporterer ikke på effektmålet EQ-5D i hverken publikationen eller den endelige ansøgning. Det fremgår på clinicaltrials.gov, at ansøger også vil benytte denne skala til at måle livskvalitet.
Other bias	• Lav risiko for bias	

12.2 GRADE-evaluering af evidenskvaliteten til vurdering af den kliniske merværdi af Lenvatinib

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Lenvatinib**	**Sorafenib**	**Relative (95 % CI)**	**Absolute (95 % CI)**		
Overall survival (median og overlevelsesrate)												
1	randomised trials	not serious	serious [a]	not serious	serious [b]	none	-/478	-/476	**HR 0,92** (0,79 to 1,06)	Median: 1,3 mdr Rate 12 mdr: 5 %-point Rate 24 mdr: 3,6 %-point	⊕⊕◯◯ LOW	CRITICAL
Bivirkninger: Andel af patienter der ophører behandling grundet bivirkninger												
1	randomised trials	serious [c]	serious [a]	not serious	serious [b]	none	42/476 (8,8%)	34/475 (7,2 %)	**RR 1,23** (0,80 to 1,90)	**2 more per 100** (from 1 fewer to 6 more)	⊕◯◯◯ VERY LOW	CRITICAL
Bivirkninger: Andel af patienter der dosisreduceres												
1	randomised trials	serious [d]	serious [a]	not serious	serious [b]	none	176/476 (37,0%)	181/475 (38,1 %)	**RR 0,97** (0,82 to 1,14)	**1 fewer per 100** (from 5 more to 7 fewer)	⊕◯◯◯ VERY LOW	CRITICAL
Bivirkninger: Antal grad 3-5 bivirkninger												
1	randomised trials	serious [e]	serious [a]	not serious	serious [a]	none	1,59/-	1,8/-	**Rate ratio 0,89** (0,78 to 1,01)	0,21 events/patient-år	⊕◯◯◯ VERY LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Lenvatinib	Sorafenib	Relative (95 % CI)	Absolute (95 % CI)		
Progressionsfri overlevelse												
1	randomised trials	not serious	serious [a]	not serious	serious [a]	none	-/478	-/476	**HR 0,66** (0,57 to 0,77)	Median: 3,7 mdr	⊕⊕◯◯ LOW	IMPORTANT
Livskvalitet												
1	randomised trials	serious [f]	serious [a]	serious [g]	serious [a]	none	Summaryscoren for livskvalitetsværktøjet EORTC QLQ-C30 er ikke signifikant forskellig mellem de to arme i REFLECT-studiet, HR, 0,87 [0,754; 1,013]				⊕◯◯◯ VERY LOW	IMPORTANT

CI: Confidence interval; **HR:** Hazard ratio; **RR:** Risk ratio

Forklaringer

a. Vurderingen er baseret på et studie.

b. Konfidensintervallet for den relative effekt overlapper 1. Og der er kun et studie, som ligger til grund for estimatet.

c. Studiet var ikke blindet. Det kan påvirke patientens og investigators opmærksomhed på, om der opstår bivirkninger, samt om det skal føre til behandlingsophør.

d. Studiet var ikke blindet. Det kan påvirke patientens og investigators opmærksomhed på, om der opstår bivirkninger, samt om det skal føre til dosisreduktion.

e. Studiet var ikke blindet. Det kan påvirke patientens og investigators opmærksomhed på, om der opstår bivirkninger.

f. Studiet var ikke blindet. Patientens vurdering af livskvalitet kan være influeret af kendskab til behandling. Herudover er EQ-5D-data ikke inkluderet i publikationen for REFLECT-studiet (Kudo et al. 2018), men fremgår som effektmål på clinicaltrials.gov.

g. Livskvalitetsdata er ikke opgjort som specificeret i protokollen.

Application for the assessment of clinically added value of LENVIMA for Hepatocellular Carcinoma

31.10.2018

Contents

1 Basic information

TABLE 1.1: CONTACT INFORMATION

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TABLE 1.2: OVERVIEW OF THE PHARMACEUTICAL

Proprietary name	LENVIMA
Generic name	Lenvatinib
Marketing authorization holder in Denmark	Eisai Europe Ltd.
ATC code	L01XE29
Pharmacotherapeutic group	**Antineoplastic agents, protein kinase inhibitors**
Active substance(s)	Lenvatinib
Pharmaceutical form(s)	Hard capsule
Mechanism of action	Lenvatinib is a receptor tyrosine kinase (RTK) inhibitor that selectively inhibits the kinase activities of vascular endothelial growth factor (VEGF) receptors VEGFR1 (FLT1), VEGFR2 (KDR), and VEGFR3 (FLT4), in addition to other proangiogenic and oncogenic pathway-related RTKs including fibroblast growth factor (FGF) receptors FGFR1, 2, 3, and 4, the platelet derived growth factor (PDGF) receptor PDGFRα, KIT, and RET.
Dosage regimen	*Hepatocellular Carcinoma* The recommended daily dose of lenvatinib is 8 mg (two 4 mg capsules) once daily for patients with a body weight of < 60 kg and 12 mg (three 4 mg capsules) once daily for patients with a body weight of ≥ 60 kg. Dose adjustments are based only on toxicities observed and not on body weight changes during treatment. The daily dose is to be modified, as needed, according to the dose/toxicity management plan.
Therapeutic indication relevant for assessment (as defined by the European Medicines Agency, EMA)	LENVIMA is indicated as monotherapy for the treatment of adult patients with advanced or unresectable hepatocellular carcinoma (HCC) who have received no prior systemic therapy.
Other approved therapeutic indications	LENVIMA is indicated as monotherapy for the treatment of adult patients with progressive, locally advanced or metastatic, differentiated (papillary/follicular/Hürthle cell) thyroid carcinoma (DTC), refractory to radioactive iodine (RAI).
Will dispensing be restricted to hospitals?	Yes. LENVIMA treatment should be initiated and supervised by a health care professional experienced in the use of anticancer therapies.
Combination therapy and/or co-medication	Not applicable
Packaging – types, sizes/number of units, and concentrations	LENVIMA 4 mg hard capsules. Polyamide/Aluminium/PVC/Aluminium blisters containing 10 capsules. Each carton contains 30 capsules
Orphan drug designation	No

2 Abbreviations

Abbreviation/term	Definition
AE	Adverse Event
AFP	Alfa-fetoprotein
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
BCLC	Barcelona Clinic Liver Cancer
BID	Twice daily
BP	Blood pressure
BW	Body weight
CBR	Clinical benefit rate
CI	Confidence interval
CT	Computed tomography
DCR	Disease control rate
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EMA	European Medicines Agency
EORTC	European Organization for Research and Treatment of Cancer
EPAR	European public assessment reports
EU	European Union
FAS	Full analysis set
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HR	Hazard ratio
HRQoL	Health Related Quality of Life
IQR	Interquartile range
LCL	Lower Control limit
MRI	Magnetic resonance imaging
ND	Lymph node
NYHA	New York Heart Association
OS	Overall survival
PD	Pharmacodynamic
PFS	Progression-free survival
PK	Pharmacokinetic
PPS	Per protocol analysisset
PPS	Per protocol analysisset
QD	Once daily
SAP	Statistical analysis plan
SY	Subject years
TACE	Transarterial chemoembolization
TEAE	Treatment-emergent adverse events
UCL	Upper control limit
ULN	Upper limit of normal

3 Summary

Currently, there are limited systemic treatment options available for 1st line unresectable HCC patients: sorafenib is the only systemic agent that has been approved for first line treatment of advanced HCC. There is a significant need for new treatments in advanced unresectable HCC that delay progression without negatively impacting patients' HRQoL.

Lenvatinib is a receptor tyrosine kinase (RTK) inhibitor with a novel binding mode that inhibits VEGF receptors (VEGFR1, VEGFR2 and VEGFR3), FGF receptors (FGFR1, FGFR2, FGFR3 and FGFR4) and other RTKs involved in tumor proliferation (including platelet derived growth factor receptor PDGFRα, KIT, and RET).

Lenvatinib has been approved as a monotherapy for the treatment of adult patients with advanced or unresectable hepatocellular carcinoma (HCC) who have received no prior systematic therapy.

Lenvatinib is the first treatment in 10 years to demonstrate a proven overall survival benefit by statistical confirmation of non-inferiority versus sorafenib. In addition:

- Lenvatinib demonstrated a statistically significant and clinically meaningful benefit in terms of progression-free survival (PFS) compared with sorafenib.
- Importantly, results from the EORTC-QLQ (C30 and HCC18) suggest that lenvatinib treatment leads to a clinically meaningful delay in several HRQoL domains, including Role Functioning, Pain, Diarrhoea, Body Image, and Nutrition.
- The adverse event profile of lenvatinib is manageable and predictable.

In addition, in the context of the assessment of OS it is important to note the following:

- Imbalances in baseline characteristics which were potentially important prognostic factors may affect the treatment benefit seen with lenvatinib. Baseline imbalances of note in REFLECT included the proportion of patients with AFP levels ≥200 ng/mL (46.4% in the lenvatinib arm and 39.3% in the sorafenib arm) and the proportion of patients with an aetiology of HCV (19% in the lenvatinib arm (and 26.5% in the sorafenib arm).
    - Notably, after adjustment for imbalances in baseline AFP, lenvatinib was found to be nominally superior to sorafenib in terms of OS. In the presence of imbalances for strong predictors of outcomes, adjustment for such covariates generally improves the precision of the analysis
- More patients had post-progression treatment in the sorafenib arm than in the lenvatinib arm (51% of patients in the sorafenib group had post-progression treatment compared with only 43% in the lenvatinib group). As a result the overall survival results may favour sorafenib.
    - When adjusted for post-treatment anticancer therapy, the HR for OS favoured lenvatinib
- Finally, the exploratory analysis presented in section 5.1.3 demonstrate that, based on the REFLECT data adjusted for imbalances in baseline characteristics an incremental mean OS benefit of at least three months may be reasonable

Lenvatinib represents advancement in the management of HCC. Several other investigational therapies have failed to meet non-inferiority or superiority endpoints for OS versus sorafenib. Patients should be given the opportunity to get the best possible treatment options. Lenvatinib introduction will lead to a predictable and manageable budget impact due to a small target population and no additional resource requirement for the treatment of adverse events.

4 Literature search

The literature search strategy was carried out as defined in the protocol. Only one relevant published article [1] found via literature search. The more detailed information is described in the Appendice Literature search covering inclusion and exclusion criteria, reasons for exclusion of each reference and flow charts showing the number of references identified and the number of included and excluded references.

In addition to the literature search, EMA's relevant scientific discussions for both lenvatinib and comparator sorafenib are included in this application [2,3]. As the newest publicly available EPAR of lenvatinib does not include HCC indication the preliminary EPAR is used for this application. For the same reasons, for the comparator sorafenib the original scientific discussion for the HCC indication is used instead of the newer assessment report as it is focusing on the extension of indication.

Databases and search strategy

The literature search was conducted on 14th September 2018 in the databases MEDLINE (via PubMed) and CENTRAL (via Cochrane Library). Both indexed (eg Medical Subject Headings, MeSH) and Free Text Search has been used.

The searches include the generic name and trade name, combined with terms for the indication:
lenvatinib AND hepatocellular carcinoma
Lenvima AND hepatocellular carcinoma

Database: MEDLINE via PubMed
Time period covered: from 1946 to date of search.
Search string: ("lenvatinib"[Supplementary Concept] OR "lenvatinib"[All Fields]) AND ("carcinoma, hepatocellular"[MeSH Terms] OR ("carcinoma"[All Fields] AND "hepatocellular"[All Fields]) OR "hepatocellular carcinoma"[All Fields] OR ("hepatocellular"[All Fields] AND "carcinoma"[All Fields]))
Search results: 43

As can be expected based on the PubMed search strategy shown above, the search with keywords "Lenvima" and "hepatocellular carcinoma" yielded the same results as the search with "lenvatinib" and "hepatocellular carcinoma".

Database: CENTRAL via Cochrane Library
Time period covered: from 1996 to date of search
Search results for "lenvatinib AND hepatocellular carcinoma": 18
Search results for "Lenvima AND hepatocellular carcinoma": 0

4.1 Relevant studies

Only one study was found relevant and included in this assessment (Table 4.1). It was found via both searched databases. Reasons for exclusion of other preliminary results are described in the Appendix Literature search.

TABLE 4.1: RELEVANT STUDIES INCLUDED IN THE ASSESSMENT

Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)
Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial Kudo, M., Finn, R.S., Qin, S., et al. Lancet 2018 [1]	REFLECT study (E7080-G000-304)	01761266	Study Start March 14, 2013. Expected completion date March 2019

4.2 Main characteristics of included studies

Two studies have been conducted with lenvatinib in HCC, a phase 1/2 proof-of-concept, dose-finding study (202, NCT00946153) and phase 3 non-inferiority study (304, NCT01761266, REFLECT study) of lenvatinib versus sorafenib [2]. As per the protocol only the phase 3 study REFLECT is used in this the assessment [4].

REFLECT was a multicenter, randomised, open-label, non-inferiority phase 3 study to compare the efficacy and safety of lenvatinib versus sorafenib as a first-line systemic treatment in subjects with unresectable HCC.

A total of 954 subjects who met all inclusion criteria and no exclusion criteria were randomised in a 1:1 ratio to one of the following treatment groups:

- Lenvatinib: 12 mg (if baseline BW ≥60 kg) or 8 mg (if baseline BW <60 kg) QD oral dosing
- Sorafenib: 400 mg twice daily (BID) oral dosing

Allocation of randomisation numbers was performed using an interactive voice/web response system (IxRS®) based on the following stratification factors:

- Region: Region 1 (Asia-Pacific); Region 2 (Western regions, such as EU, North America, other)
- Macroscopic portal vein invasion (MPVI) or extrahepatic spread or both: Yes; No
- Eastern Cooperative Oncology Group performance status (ECOG PS): PS = 0; PS = 1
- BW: <60 kg; ≥60 kg.

Enrolment in Study 304 occurred between 01 Mar 2013 (first subject gave informed consent) and 30 Jul 2015 (last subject enrolled) at 183 study sites (number of sites initiated) in Asia, North America, European Union, Russia, and Israel [2]. A resulting total of 154 sites in 20 countries were involved in this study [1].

The data cut-off for the primary analysis occurred on 13 Nov 2016 after the occurrence of 700 deaths.

A total of 1,492 subjects were screened for entry into the study. Of these, 538 subjects were screening failures, and 954 subjects (63.9%) were randomly assigned in a 1:1 ratio to receive either lenvatinib (478 subjects) or sorafenib (476 subjects). Of the 954 randomised subjects, two in the lenvatinib and one in the sorafenib arm were not treated. The two subjects in the lenvatinib arm were not treated because they met

exclusion criteria and were randomised in error. The subject in the sorafenib arm chose not to take study treatment. Therefore, 476 subjects in the lenvatinib and 475 subjects in the sorafenib arm received at least one dose of study treatment (Figure 4.1).

Inclusion and exclusion criteria are presented in appendices, Table 7.2.

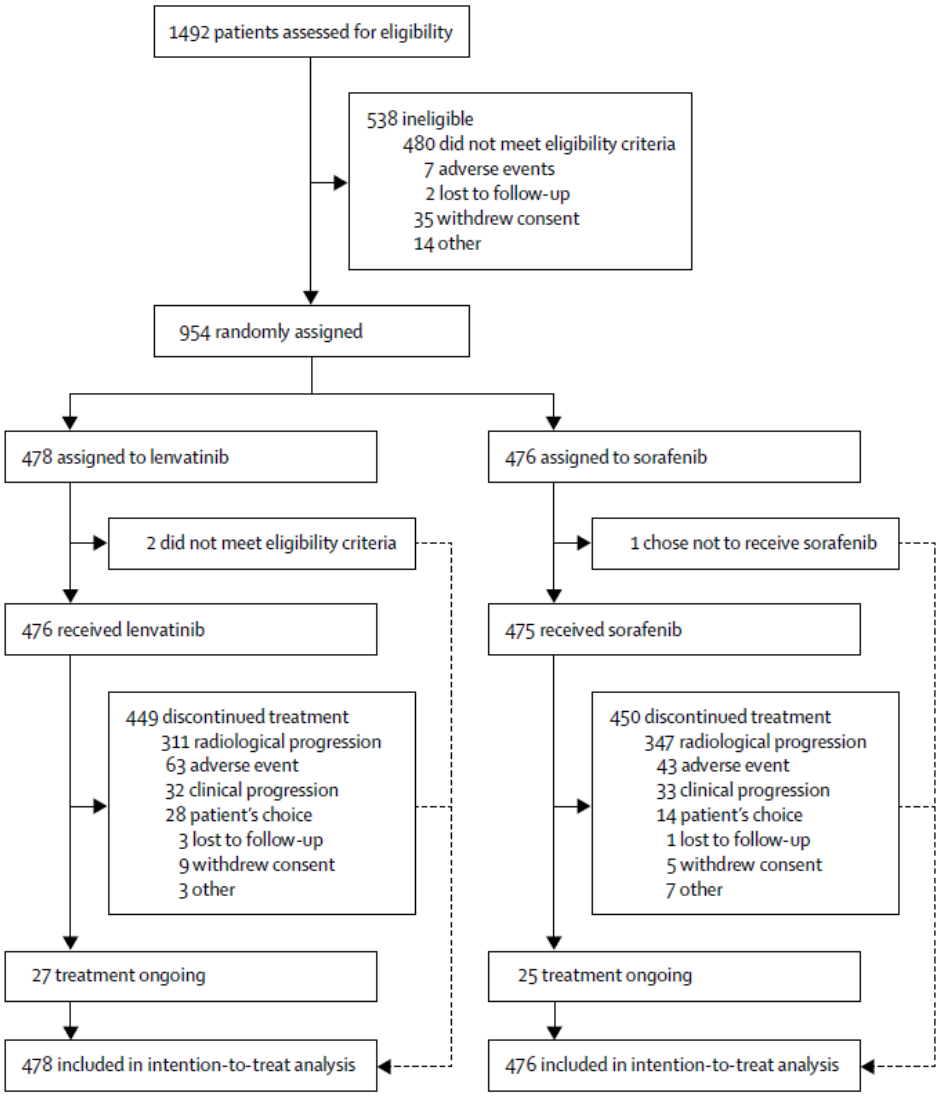


FIGURE 4.1: TRIAL PROFILE [1]

A non-inferiority test of overall survival (OS) between lenvatinib and sorafenib was done using a 2-sided 95% confidence interval (CI) of hazard ratio (HR) (lenvatinib:sorafenib). The HR and the corresponding 2-sided 95% CI were estimated using a Cox proportional hazard model with treatment group as a factor, and stratified by the randomisation (IxRS) stratification factors.

Superiority hypotheses were tested for OS using a stratified log-rank test with the randomisation (IxRS) stratification factors. No multiplicity adjustments were needed for testing of the non-inferiority and superiority of OS due to the closed testing principle. Two interim analyses were performed. Since the study

was not stopped at the first or second interim analysis, non-inferiority for OS was tested first at the final analysis with a non-inferiority margin of 1.08, which indicated that lenvatinib preserved at least 60% (corresponding to $\delta = 0.60$) of the sorafenib treatment effect versus placebo as observed in the sorafenib SHARP and Asia-Pacific trials [5,6]. Non-inferiority was declared if the upper limit of the 2-sided 95% CI for HR was <1.08 at the final analysis. If non-inferiority was declared for OS, then superiority (corresponding to $\delta = 1$) was to be tested for OS. Superiority would be declared if the 2-sided P value was <0.05 using the stratified log-rank test at the final analysis.

As of the data cut-off date of 13 Nov 2016, the median duration of survival follow-up was 27.7 months in the lenvatinib arm and 27.2 months in the sorafenib arm.

The lenvatinib and sorafenib arms were generally well balanced with regard to baseline HCC disease characteristics and disease history with some exceptions.

- The proportion of subjects with baseline alpha-fetoprotein (AFP) levels ≥200 ng/mL (an adverse prognostic factor in HCC), was greater in the lenvatinib arm than in the sorafenib arm: 46% vs 39%, respectively.
- In addition, the proportion of subjects with an HCC aetiology of hepatitis C virus (HCV) was higher in the sorafenib arm than in the lenvatinib arm (26% vs 19%, respectively), an imbalance that may favor sorafenib, since HCV aetiology has been recently shown to be a predictive indicator for sorafenib treatment effect and subjects with HCV appear to derive more clinical benefit from sorafenib therapy than subjects with other aetiologies, particularly hepatitis B virus (HBV) [7].

An overview of the REFLECT study can be found in appendices, Table 7.2.

5 Clinical questions

5.1 Clinical question 1

What is the clinical added value of lenvatinib for adult patients with advanced or inoperable hepatocellular carcinoma who are candidates for systematic treatment, compared with sorafenib?

5.1.1 Presentation of relevant studies

The REFLECT study was a phase 3 trial of lenvatinib versus sorafenib in first-line treatment of patients with unresectable HCC. The primary objective of the REFLECT study was to compare OS in patients treated with lenvatinib versus sorafenib as a first-line treatment for unresectable stage B or C (according to BCLC staging system) HCC and Child Pugh Class A liver disease.

The secondary objectives of the study were:

- To compare Progression-free survival (PFS), Time-to progression and Objective response rate of subjects treated with lenvatinib versus sorafenib using (mRECIST)
- To compare the impact of treatment on generic Health Related Quality of Life (HRQoL) of subjects treated with lenvatinib versus sorafenib using the EORTC QLQ-C30 and QLQ-HCC18 questionnaires
- To compare safety and tolerability of subjects treated with lenvatinib versus sorafenib
- To characterize the PK of lenvatinib using the population approach
- To assess the PK/PD relationship between exposure and efficacy/safety.

The exploratory objectives of the study were:

- To compare DCR of subjects treated with lenvatinib versus sorafenib using mRECIST
- To compare the clinical benefit rate (CBR) of subjects treated with lenvatinib versus sorafenib
- To compare the impact of treatment on generic HRQoL factors for subjects treated with lenvatinib versus sorafenib using the European Quality of Life questionnaire
- To explore blood and tumour biomarkers which may correlate with clinical outcomes-related endpoints.

An overview of the REFLECT study can be found in appendices, Table 7.2.

5.1.2 Results per study

Kudo et al. 2018 [1]

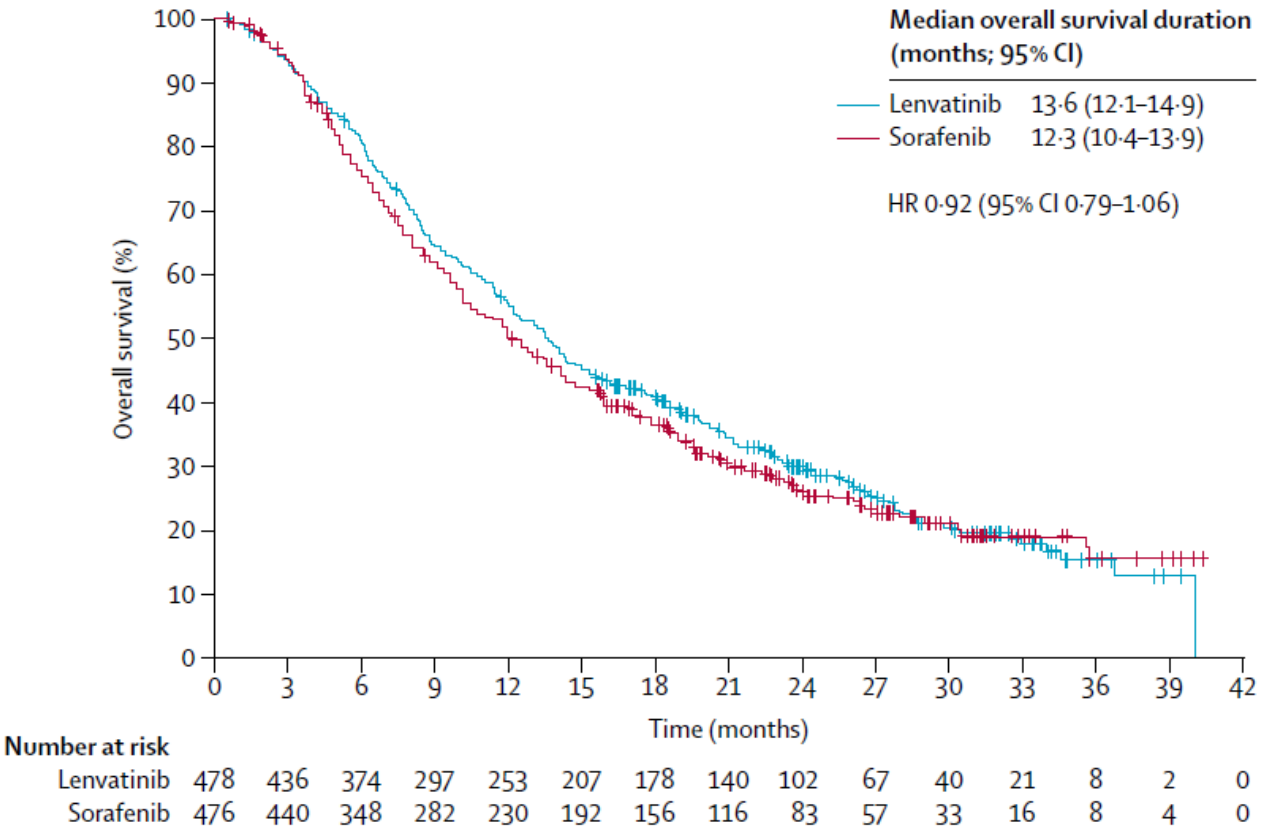
The results of REFLECT study have been published in one article, which was also the only article identified through the literature research [1]. An overview of the results presented in this article is provided in the appendices, Table 7.3.

Overall survival (OS)

Median survival

As of the data cut-off date of 13 Nov 2016, 73.4% of subjects in the lenvatinib and 73.5% of subjects in the sorafenib arms had died. As shown in Table 7.3, Table 5.1 and Figure 5.1, median OS was 13.6 months for lenvatinib and 12.3 months for sorafenib, with an HR of 0.92 and a 95% CI of 0.79 – 1.06. As pre-specified in the protocol, the study met its primary endpoint by demonstrating non-inferiority in OS for lenvatinib compared with sorafenib. Although numerical improvement in median OS and HR was seen, the primary result did not meet the statistical criteria for superiority. Published data and the EMA's scientific discussion are in line regarding OS [1,2].

The results of the primary efficacy analysis of OS based on the full analysis set (FAS) were supported by the results of the analysis based on the PPS, for which median OS was 13.7 months for lenvatinib and 12.3 months for sorafenib (HR: 0.91; 95% CI: 0.78, 1.06) [1,2].



HR=hazard ratio.

FIGURE 5.1: KAPLAN-MEIER ESTIMATES OF OVERALL SURVIVAL BY TREATMENT GROUP - FAS [1]

12-months and 24-months survival

12-months and 24-months survival rates are presented in Table 5.1. 12-months survival was 55.0% for lenvatinib and 50.0% for sorafenib. 24-months survival was 29.9% for lenvatinib and 26.2% for sorafenib.

Although 12-months and 24-months overall survival has not been presented in the published article, those are presented in the EMA's scientific discussion [1,2].

TABLE 5.1: OVERALL SURVIVAL BASED ON RANDOMIZATION STRATIFICATION FACTORS RECORDED IN THE IXRS - FAS [2]

	Lenvatinib (N=478) n (%)	**Sorafenib (N=476) n (%)**
Deaths, n (%)	351 (73.4)	350 (73.5)
Censored Subjects, n (%)	127 (26.6)	126 (26.5)
Lost to follow-up	5 (1.0)	11 (2.3)
Withdrawal of consent	13 (2.7)	8 (1.7)
Alive	109 (22.8)	107 (22.5)
Median Overall Survival (months)[a] (95% CI)	13.6 (12.1, 14.9)	12.3 (10.4, 13.9)
Overall Survival Rate (%) (95% CI) [b] at		
6 Months	80.8 (76.9, 84.1)	75.2 (71.0, 78.8)
12 Months	55.0 (50.4, 59.4)	50.0 (45.4, 54.5)
24 Months	29.9 (25.6, 34.2)	26.2 (22.1, 30.5)
Stratified Cox Model Hazard Ratio (95% CI) [c,d]	0.92 (0.79, 1.06)	

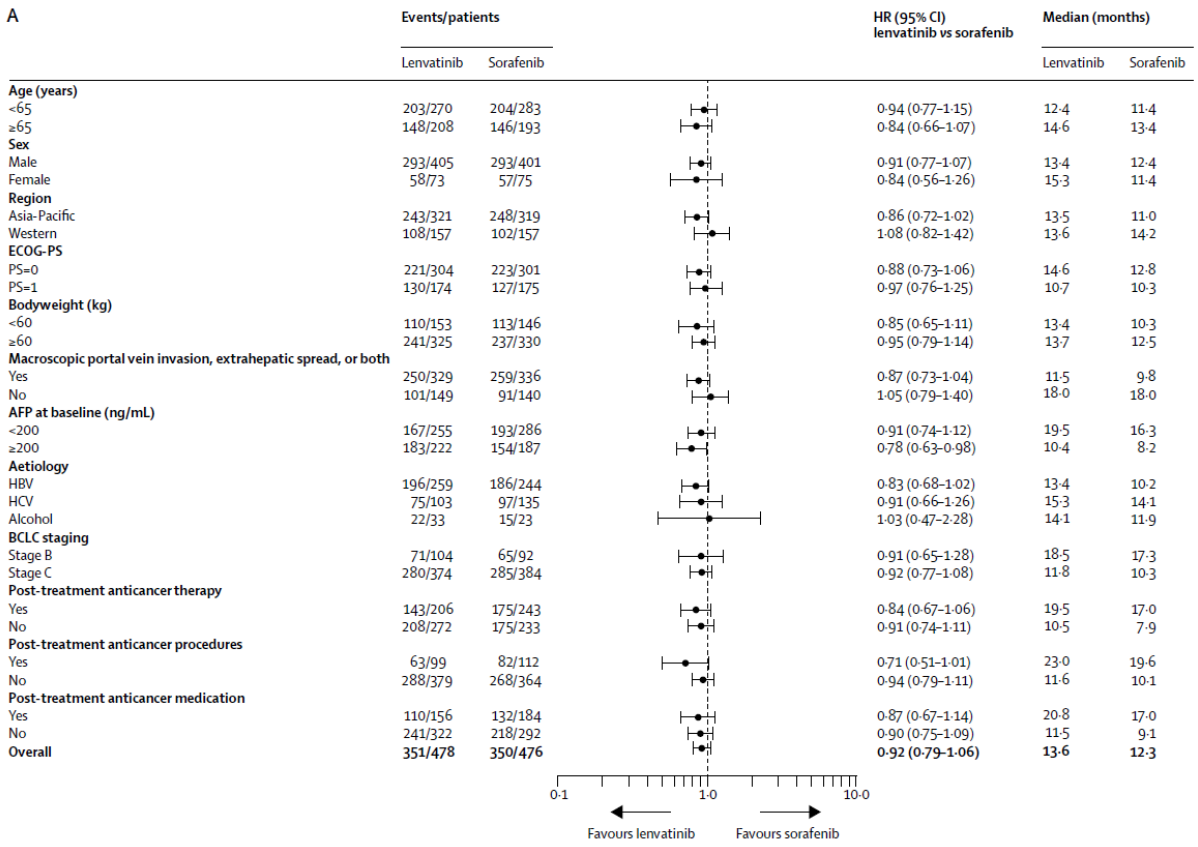
Data cut-off date: 13 Nov 2016.
Noninferiority margin for the HR of lenvatinib versus sorafenib is 1.08.
a: 95% CIs are estimated with a generalized Brookmeyer and Crowley method.
b: OS rate & 95% CI calculated using Kaplan-Meier product-limit method and Greenwood Formula.
c: Hazard ratio is for lenvatinib vs. sorafenib, based on a Cox model including treatment group as a factor. Efron method was used for ties.
d: Stratified by region (Region 1: Asia-Pacific; Region 2: Western), macroscopic portal vein invasion or extrahepatic spread or both (yes, no), ECOG PS (0, 1) and body weight (<60 kg, ≥60 kg).

Overall survival by subgroup

The effect of lenvatinib and sorafenib on OS generally was consistent across subgroups, including age, sex, and BW; HR (lenvatinib:sorafenib) was <1 for most subgroups. A forest plot of HR for lenvatinib vs sorafenib in OS in patient subgroups appears in Figure 5.2 [1].

- The effect of lenvatinib on OS was consistent across the Western and Asia-Pacific regions, while OS for sorafenib was longer in the Western region than in the Asia-Pacific region.
    - In the lenvatinib arm, median OS in the Western region (13.6 months) was consistent with that observed in the Asia-Pacific region (13.5 months).
    - In contrast, median OS with sorafenib in the Western region (14.2 months) was longer than the median OS with sorafenib in the Asia-Pacific region (11.0 months).
- Lenvatinib also demonstrated a consistent effect in both HBV and HCV subgroups, with a median OS of 13.4 and 15.3 months, in contrast to 10.2 and 14.1 months with sorafenib, respectively (HR: 0.83 for HBV and HR 0.91 for HCV subgroups, respectively).

- The effect of lenvatinib was consistent regardless of BW group (median OS 13.4 and 13.7 months for BW<60 kg and ≥60 kg, respectively (HR 0.85 and 0.95, respectively).



A	Events/patients		HR (95% CI) lenvatinib vs sorafenib	Median (months)	
	Lenvatinib	Sorafenib		Lenvatinib	Sorafenib
Age (years)					
<65	203/270	204/283	0·94 (0·77–1·15)	12·4	11·4
≥65	148/208	146/193	0·84 (0·66–1·07)	14·6	13·4
Sex					
Male	293/405	293/401	0·91 (0·77–1·07)	13·4	12·4
Female	58/73	57/75	0·84 (0·56–1·26)	15·3	11·4
Region					
Asia-Pacific	243/321	248/319	0·86 (0·72–1·02)	13·5	11·0
Western	108/157	102/157	1·08 (0·82–1·42)	13·6	14·2
ECOG-PS					
PS=0	221/304	223/301	0·88 (0·73–1·06)	14·6	12·8
PS=1	130/174	127/175	0·97 (0·76–1·25)	10·7	10·3
Bodyweight (kg)					
<60	110/153	113/146	0·85 (0·65–1·11)	13·4	10·3
≥60	241/325	237/330	0·95 (0·79–1·14)	13·7	12·5
Macroscopic portal vein invasion, extrahepatic spread, or both					
Yes	250/329	259/336	0·87 (0·73–1·04)	11·5	9·8
No	101/149	91/140	1·05 (0·79–1·40)	18·0	18·0
AFP at baseline (ng/mL)					
<200	167/255	193/286	0·91 (0·74–1·12)	19·5	16·3
≥200	183/222	154/187	0·78 (0·63–0·98)	10·4	8·2
Aetiology					
HBV	196/259	186/244	0·83 (0·68–1·02)	13·4	10·2
HCV	75/103	97/135	0·91 (0·66–1·26)	15·3	14·1
Alcohol	22/33	15/23	1·03 (0·47–2·28)	14·1	11·9
BCLC staging					
Stage B	71/104	65/92	0·91 (0·65–1·28)	18·5	17·3
Stage C	280/374	285/384	0·92 (0·77–1·08)	11·8	10·3
Post-treatment anticancer therapy					
Yes	143/206	175/243	0·84 (0·67–1·06)	19·5	17·0
No	208/272	175/233	0·91 (0·74–1·11)	10·5	7·9
Post-treatment anticancer procedures					
Yes	63/99	82/112	0·71 (0·51–1·01)	23·0	19·6
No	288/379	268/364	0·94 (0·79–1·11)	11·6	10·1
Post-treatment anticancer medication					
Yes	110/156	132/184	0·87 (0·67–1·14)	20·8	17·0
No	241/322	218/292	0·90 (0·75–1·09)	11·5	9·1
Overall	**351/478**	**350/476**	**0·92 (0·79–1·06)**	**13·6**	**12·3**

FIGURE 5.2: FOREST PLOT OF OS IN PATIENT SUBGROUPS - FAS [1]

Overall survival adjusted by baseline characteristics (pre-planned supportive analyses)

As described in Section 4.2 **Main characteristics of included studies**, there were baseline imbalances between the lenvatinib and sorafenib treatment arms regarding the proportion of patients with AFP levels ≥200 ng/mL, and in the aetiology of HCC (HBV, HCV, alcohol). Covariate analyses were performed to evaluate baseline factors that may have impacted OS in the overall study population, including AFP and HCC aetiology. A plan to perform covariate analyses for supporting the efficacy results was included in the statistical analysis plan (SAP).

- For the FAS, the results adjusted by the individual baseline characteristics generally were consistent with those of the primary OS analysis (HR <1) (
- Table 5.2)
- For baseline AFP, the HR for lenvatinib:sorafenib was nominally superior (HR=0.856), and the upper limit of the 95% CI was <1 (95% CI: 0.736, 0.995).
- The covariate analysis adjusted for aetiology of HCC (hepatitis B, hepatitis C, alcohol) resulted in an HR for lenvatinib:sorafenib of 0.855, with 95% CI of (0.721, 1.013).

TABLE 5.2: OS WITH STRATIFICATION FACTORS IN IXRS, ADJUSTED BY BASELINE CHARACTERISTICS - FAS [1]

Baseline Characteristics	Hazard Ratio for (Lenvatinib: Sorafenib) (95% CI)
Age (<65, ≥65 to <75, ≥75 yrs.)	0.919 (0.791, 1.067)
Sex (Male, Female)	0.916 (0.789, 1.064)
Region (Asia-Pacific, Western Region)	0.915 (0.789, 1.062)
Macroscopic Portal Vein Invasion (Yes, No)	0.910 (0.784, 1.057)
Extrahepatic Spread (Yes, No)	0.915 (0.788, 1.062)
Macroscopic Portal Vein Invasion, Extrahepatic Spread or Both (Yes, No)	0.908 (0.783, 1.054)
ECOG PS (0, ≥1)	0.923 (0.795, 1.071)
Body Weight (<60 kg, ≥60 kg)	0.923 (0.796, 1.071)
Alpha-fetoprotein level at Baseline (<200 ng/mL, ≥200 ng/mL)	0.856 (0.736, 0.995)
Antiviral Therapy for Hepatitis B or Hepatitis C (Yes, No)	0.912 (0.785, 1.059)
No. of Disease Sites at Baseline (1, 2, ≥3)	0.878 (0.755, 1.020)
Aetiology (HBV, HCV, Alcohol)	0.855 (0.721, 1.013)
Underlying Cirrhosis (Yes, No)	0.916 (0.789, 1.063)
BCLC Staging (Stage B, Stage C)	0.918 (0.791, 1.067)
Prior Procedure (Yes, No)	0.902 (0.777, 1.048)

AFP, alpha-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; CI, confidence interval; ECOG-PS, Eastern Cooperative Oncology Group performance status; HBV, hepatitis B virus; HCV, hepatitis C virus.

Effect of post-treatment anticancer therapy on Overall Survival

There was an imbalance between the treatment arms regarding the proportion of patients who received post-treatment anti-cancer therapy (including procedures and medications) during survival follow-up (

Table 5.3). Fewer patients in the lenvatinib arm (43.1%) had post-treatment anti-cancer therapy than patients in the sorafenib arm (51.1%).

TABLE 5.3: ANTICANCER MEDICATIONS (NOT GIVEN FOR ANY PROCEDURE) DURING SURVIVAL FOLLOW-UP - FAS [2]

	Lenvatinib			Sorafenib		
	Western (N=157)	Asia-Pacific (N=321)	Total (N=478)	Western (N-157)	Asia-Pacific (N=319)	Total (N=476)
Received any anti-cancer therapy* during survival follow-up, n (%)	44 (28.0)	162 (50.5)	206 (43.1)	71 (45.2)	172 (53.9)	243 (51.1)
Received any anti-cancer medication (not given for a procedure) during survival follow-up, n (%)	41 (26.1)	115 (35.8)	156 (32.6)	61 (38.9)	123 (38.6)	184 (38.7)
Underwent any anti-cancer procedure during survival follow-up, n (%)	11 (7.0)	111 (34.6)	122 (25.5)	18 (11.5)	112 (35.1)	130 (27.3)

*Posttreatment anti-cancer therapy includes both posttreatment anti-cancer procedures and posttreatment anti-cancer medications received during survival follow-up.

As described in Section Overall survival by subgroup, in the lenvatinib arm, median OS in the Western region (13.6 months) was consistent with that observed in the Asia-Pacific region (13.5 months). In contrast, median OS with sorafenib in the Western region (14.2 months) was longer than the median OS with sorafenib in the Asia-Pacific region (11.0 months).

Table 5.4 presents a post hoc analysis adjusted by use of post-treatment anti-cancer therapy. When adjusted for post-treatment anticancer therapy, the HR for OS was 0.87 (0.75, 1.01) compared to 0.92 (0.79, 1.06) uadjusted. When stratified by geographic region, the HR favoured lenvatinib in both Western and Asia-Pacific regions when adjusted for post-treatment anti-cancer treatment. In the Western region, the adjusted HR (95% CI) was 0.93 (0.70, 1.23) compared with 1.08 (0.82, 1.42) in the unadjusted analysis.

TABLE 5.4: OVERALL SURVIVAL ADJUSTED BY USE OF POST-TREATMENT ANTICANCER TREATMENT, OVERALL AND BY REGION - FAS [2]

	Stratified Cox Model Hazard Ratio (95% CI)*	
	Without adjustment	With adjustment†
Overall	0.92 (0.79, 1.06)	0.87 (0.75, 1.01)
Region		
Asia-Pacific	0.86 (0.72, 1.02)	0.83 (0.70, 1.00)
Western	1.08 (0.82, 1.42)	0.93 (0.70, 1.23)

Supplementary exploratory overall survival analysis

As presented in section 4.2 Main characteristics of included studies the proportion of subjects with baseline alpha-fetoprotein (AFP) levels ≥200 ng/mL (an adverse prognostic factor in HCC), was greater in the lenvatinib arm than in the sorafenib arm: 46% vs 39%, respectively. In addition, the proportion of subjects

with an HCC aetiology of hepatitis C virus (HCV) was higher in the sorafenib arm than in the lenvatinib arm (26% vs 19%, respectively), an imbalance that may favor sorafenib, since HCV aetiology has been recently shown to be a predictive indicator for sorafenib treatment effect and subjects with HCV appear to derive more clinical benefit from sorafenib therapy than subjects with other aetiologies, particularly hepatitis B virus (HBV) [7]. Of principal concern was the imbalance in baseline AFP levels between treatment arms; AFP has been demonstrated to be a strong independent predictor of outcomes regardless of treatment type [8], and the proportion of patients with AFP levels ≥200 ng/mL was higher in the lenvatinib arm (46.4%) than the sorafenib arm (39.3%).

As presented in section 5.1.2 Effect of post-treatment anticancer therapy on Overall Survival there was an imbalance between the treatment arms regarding the proportion of patients who received post-treatment anti-cancer therapy.

Survival analysis
At the data cut-off of 13th November 2016, 73.4% of patients in the lenvatinib arm and 73.5% of patients in the sorafenib arm had died. The Kaplan-Meier estimator for sorafenib PFS was 6% at the last observed data point. Therefore, there is justification for using statistical survival analysis to extrapolate beyond the end of REFLECT. Survival analysis is commonly used in cost-effectiveness analysis to model health benefits for the lifetime of the average patient. The imbalances in baseline characteristics and post-treatment therapy can be explored within estimation of parametric survival models.

The National Institute for Health and Care Excellence (NICE) is currently evaluating Lenvatinib (ID1089) [9]. The Company Submission used a multivariable adjustment to account for the imbalance in baseline characteristics.

- Current EMA guidance on adjustment for baseline characteristics in clinical trials suggests that in the presence of imbalances for strong predictors of outcomes, adjustment for such covariates generally improves the precision and efficiency of the analysis and avoids conditional bias from chance covariate imbalance [10].

The Evidence Review Group (ERG) conducted an independent assessment of the REFLECT clinical data and the company submission concluding it was appropriate to adjust for baseline imbalances resulting in "an undiscounted incremental mean OS benefit of 3.1 months". Furthermore the ERG preferred to include the effect of imbalances in post-treatment therapy which resulted in an "undiscounted incremental mean OS benefit of 4.1 months" [9].

These results demonstrate that, based on the REFLECT data adjusted for imbalances in baseline characteristics an incremental modelled mean OS benefit of at least three months may be reasonable.

Adverse Events (AE)

The information presented in this section comes from the published article and the EMA's scientific discussion [1,2] which include information about the treatment-emergent adverse events (TEAE). TEAEs are defined as AEs that occurred on or after the first dose of study drug up to 30 days following last dose of study drug.

Grades 3-5 adverse events

The vast majority (>98%) of subjects in both the lenvatinib and sorafenib arms had at least one TEAE. Grade 3 or higher TEAEs occurred in 357 subjects (75%) in the lenvatinib arm and 316 subjects (66.5%) in the sorafenib arm (

Table 5.5).

TABLE 5.5: SUMMARY OF TEAES - SAFETY ANALYSIS SET [1,2]

Adverse events	Lenvatinib (N=476) n (%)	Sorafenib (N=475) n (%)
Patient with any TEAE	470 (98.7)	472 (99.4)
Patients with any related TEAE	447 (93.9)	452 (95.2)
Patients with any TEAE ≥grade 3	357 (75.0)	316 (66.5)
Patient with any related TEAE ≥grade 3	270 (56.7)	231 (48.6)

Abbreviation: TEAE, treatment-emergent adverse event

Qualitative review of adverse events

As of the 13 Nov 2016 data cut-off, median duration of exposure was 5.7 months in the lenvatinib arm and 3.7 months in the sorafenib arm; exposure to lenvatinib therapy was approximately 1.5-times longer than exposure to sorafenib therapy. The total number of subject years (SY) of exposure, including dose interruptions, was 324.2 in the lenvatinib arm and 239.1 in the sorafenib arm. In the lenvatinib arm, 12.2% of subjects received study drug for 12 to 18 months; an additional 10.7% received lenvatinib for 18 months or longer. In the sorafenib arm, 5.9% of subjects took study drug for 12 to 18 months and 6.9% received sorafenib for 18 months or longer. Because of the longer treatment duration in the lenvatinib arm, safety data have been analysed by subject incidence and by number of episodes adjusted for SY of exposure to study drug [2].

As stated above, the exposure was 1.5-times longer with lenvatinib than with sorafenib. Therefore, TEAEs have also been adjusted by treatment duration (

table 5.6).

- The rate of TEAE episodes adjusted for treatment duration was 18.89 episodes/SY and 19.73 episodes/SY for the lenvatinib and sorafenib arms, respectively.
- The rate of Grade ≥3 TEAEs adjusted by treatment duration in the lenvatinib and sorafenib arms was 3.16 and 3.33 episodes/SY, respectively.
- When adjusted by treatment duration, the overall rate of SAEs was 1.26 episodes/SY for the lenvatinib arm and 0.97 episodes/SY for the sorafenib arm.
- When adjusted by treatment duration, the rate of fatal AEs was 0.19 episodes/SY in the lenvatinib and 0.15 episodes/SY in the sorafenib arm [2].

The most frequently reported TEAEs (in >30% of subjects in either treatment arm) were hypertension, diarrhoea, decreased appetite, and weight decreased for lenvatinib and palmar-plantar erythrodysaesthesia syndrome, diarrhoea, and hypertension for sorafenib. These AEs are consistent with the known safety profile of the two agents [2].

TABLE 5.6: SUMMARY OF TEAES BY TREATMENT EXPOSURE (EPISODES/SY) - SAFETY ANALYSIS SET [2]

Adverse events	Lenvatinib (N=476) Total duration= 324.2 years n (AE rate)	Sorafenib (N=475) Total duration= 239.1 years n (AE rate)
Any TEAE episodes	6,124 (18.89)	4,718 (19.73)
Related TEAE episodes	3,546 (10.94)	2,865 (11.98)
Any TEAE ≥grade 3 episodes	1,023 (3.16)	795 (3.33)
Related TEAE ≥grade 3 episodes	517 (1.59)	430 (1.80)
Serious AE episodes	409 (1.26)	232 (0.97)
Fatal serious TEAE episodes †	61 (0.19)	36 (0.15)
Non-fatal serious TEAE episodes	379 (1.17)	207 (0.87)

*8 mg and 12 mg were the lenvatinib starting doses based on the subjects' body weight (<60 kg, ≥60 kg) at baseline; †Fatal AE episodes were counted only once per patient, if more than one fatal AE was reported for the same patient.
Abbreviations: AE, adverse event; HCC, hepatocellular carcinoma; TEAE, treatment-emergent adverse event.

Treatment discontinuation and dose reduction due to adverse events

As per the published article, treatment-related TEAEs led to lenvatinib drug interruption in 190 (40%) patients, dose reduction in 176 (37%) patients, and drug withdrawal in 42 (9%) patients. In the sorafenib arm, treatment-related TEAEs led to drug interruption in 153 (32%) patients, dose reduction in 181 (38%), and drug withdrawal in 34 (7%) patients [1].

Note published data related to AEs are different vs. the EMA's scientific discussion. The published article presents treatment-related TEAEs leading to dose reduction while the EMA's scientific discussion presents any TEAEs leading to treatment modification. This is also applicable to treatment discontinuation where the published article presents treatment-related TEAEs leading to treatment discontinuation whereas EMA's scientific discussion presents either any AEs as a primary reason(s) or any TEAEs leading to treatment discontinuation [1,2].

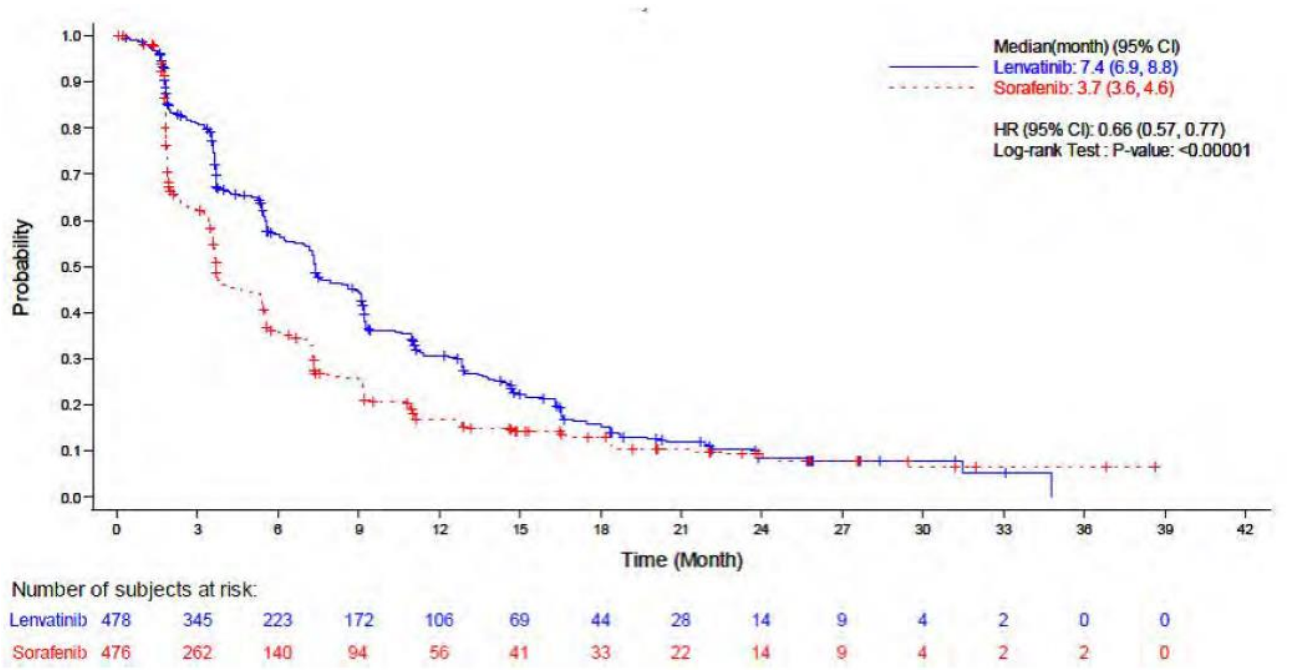
Progression-free survival (PFS)

For PFS, censoring rules followed Food and Drug Administration (FDA) guidance [11], where patients were censored when they discontinued treatment for any reason other than disease progression.

Median progression-free survival

Lenvatinib treatment resulted in a statistically significant and clinically meaningful improvement in PFS compared with sorafenib. As shown in Figure 5.3, median PFS doubled with lenvatinib compared with sorafenib, 7.4 months vs 3.7 months, respectively (HR = 0.66; 95% CI of 0.57, 0.77; P<0.00001). Published data and the EMA's scientific discussion are in line regarding PFS [1,2].

The results of the analysis of PFS based on the FAS are supported by the results of the analysis based on the per protocol analysis set (PPS). For the PPS, the median PFS was 7.4 months for lenvatinib versus 3.7 months for sorafenib (HR = 0.66; 95% CI of 0.57, 0.77; P<0.00001). This analysis was presented only in EMA's scientific discussion [2].



HR=hazard ratio.

FIGURE 5.3: KAPLAN-MEIER CURVES AND ANALYSIS OF PROGRESSION-FREE SURVIVAL WITH STRATIFICATION FACTORS RECORDED IN THE IXRS - FAS [2]

Progression-free survival by subgroup

Median PFS was longer with lenvatinib than sorafenib in each of the subgroups tested. As seen in the overall population, lenvatinib treatment resulted in clinically meaningful improvement in PFS compared with sorafenib; the HR (lenvatinib:sorafenib) was <1 in each subgroup tested. A forest plot of HR for lenvatinib vs sorafenib in PFS with stratification factors in the IxRS appears in Figure 5.4 [1,2].

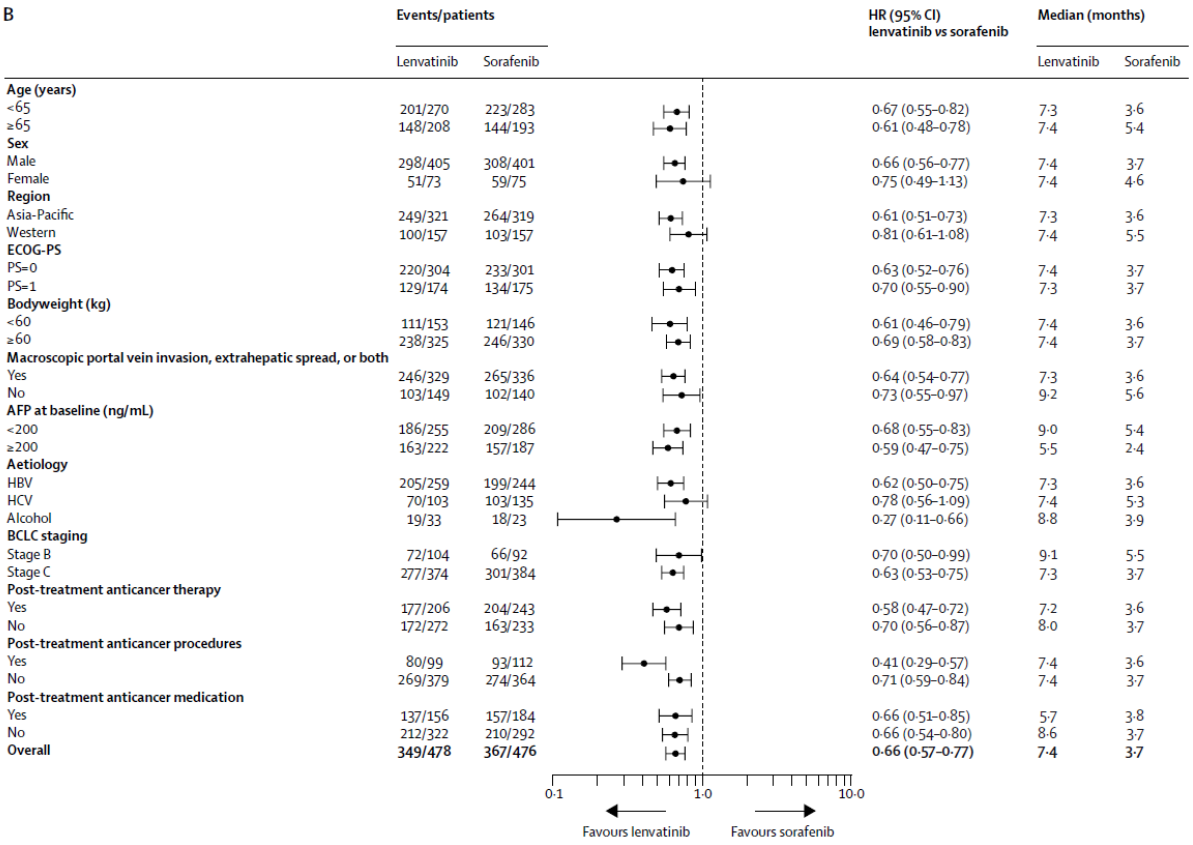


FIGURE 5.4: FOREST PLOT OF PFS IN PATIENT SUBGROUPS - FAS [1]

Quality of life

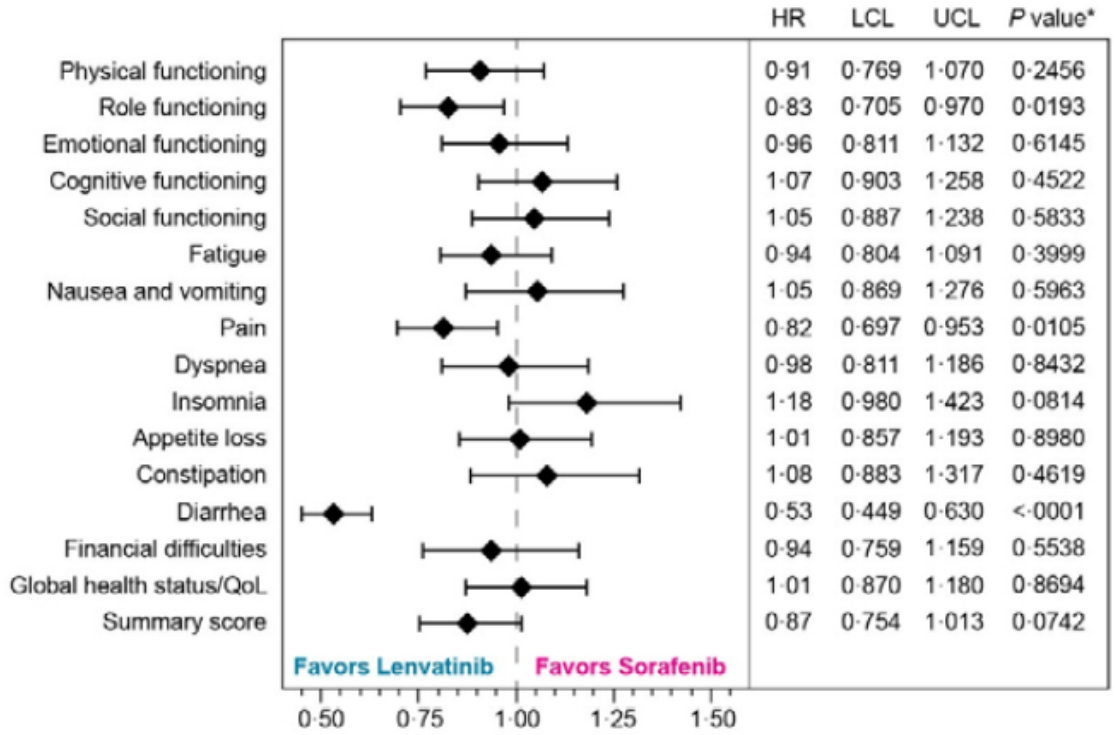
As HRQoL summary score measured at 1, 2 and 3 months have not been presented in the published article either in the EMA's scientific discussion, that information requested on the provided protocol could not be presented [1,2].

Assessments of health related quality of life (HRQoL) scores were performed using the generic cancer HRQoL instrument (EORTC QLQ-C30), the HCC-specific module (EORTC QLQ-HCC18), and the generic HRQoL instrument, EQ-5D [2].

During the Randomization Phase, the EORTC QLQ-C30, EORTC QLQ-HCC18, and EQ-5D were administered at Baseline, Day 1 of each cycle after Cycle 1, and at the off-treatment visit. During the Extension Phase, the EORTC QLQ-C30, EORTC QLQ-HCC18, and EQ-5D were administered on Day 1 of each treatment and during the off-treatment visit [2].

Baseline scores on the EORTC QLQ-C30 and EORTC QLQ-HCC18 health questionnaires were similar in the lenvatinib and sorafenib treatment groups. Following treatment, scores declined in both groups. Analysis of time to clinically meaningful deterioration showed that role functioning (nominal p=0.0193), pain (nominal p=0.0105), and diarrhoea (nominal p<0.0001) from EORTC QLQ-C30, and nutrition (nominal p=0.0113) and body image (nominal p=0.0051) from EORTC QLQ-HCC18 were observed earlier in patients treated with

sorafenib than in those treated with lenvatinib. For between-group comparison, the summary score was not significantly different between the treatment arms (HR 0.87, 95% CI 0.754–1.013) [1,2].



HR, hazard ratio; LCL, lower control limit; QLQ-C30, quality-of-life questionnaire C30; UCL, upper control limit.

FIGURE 5.5: HAZARD RATIO OF TIME TO CLINICALLY MEANINGFUL WORSENING OF EQ-5D, EORTC QLQ-C30 DOMAINS [1]

5.1.3 Comparative analyses

As only one relevant study was identified through the literature research no additional comparative analysis has been conducted.

As per the previous section, lenvatinib has demonstrated the following:

- A proven overall survival benefit by statistical confirmation of non-inferiority versus sorafenib.
- A statistically significant and clinically meaningful benefit in terms of progression-free survival (PFS) compared with sorafenib.
- Results from the EORTC-QLQ (C30 and HCC18) show that lenvatinib treatment leads to a clinically meaningful and statistically significant delay in several Health Related Quality of Life (HRQoL) domains, for role functioning, pain and diarrhoea, body image, and nutrition.
- In addition, the adverse event profile of lenvatinib is manageable and predictable.

Currently, there are limited systemic treatment options available for first line unresectable HCC patients. Sorafenib is the only systemic agent that has been approved for first line treatment of advanced HCC. Therefore, there is a significant need for new treatments in advanced unresectable HCC that delay progression without negatively impacting patients' HRQoL.

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7 Appendices

Literature search

Based on the protocol, literature was searched in MEDLINE (via PubMed) and CENTRAL (via Cochrane Library) databases. Both indexed (eg Medical Subject Headings, MeSH) and Free Text Search has been used.

The searches include generic and trade name, combined with terms for the indication.
lenvatinib AND hepatocellular carcinoma
Lenvima AND hepatocellular carcinoma

The searches were conducted on 14th September 2018.
Search in MEDLINE covered time period from 1946 to date of search.
Search in CENTRAL covered time period from 1996 to date of search.

Inclusion and exclusion criteria

The criteria for selection of literature has been made based on the provided protocol and are presented in Table 7.1.

TABLE 7.1: INCLUSION AND EXCLUSION CRITERIA

Inclusion criteria	Population: Hepatocellular carcinoma Intervention OR Comparator: Lenvatinib Outcomes: Overallsurvival (OS) OR Adverse Events (AE) OR Progression-free survival (PFS) OR Quality of life Study design: Randomized clinical trial, other than phase 1 trial
Exclusion criteria	Population: Other than Hepatocellular carcinoma Intervention OR Comparator: No Lenvatinib Outcomes: Does not report effect goals Study design: Not randomized clinical trial OR phase 1 trial

Searches and results

MEDLINE/PubMed:

lenvatinib AND hepatocellular carcinoma

("lenvatinib"[Supplementary Concept] OR "lenvatinib"[All Fields]) AND ("carcinoma, hepatocellular"[MeSH Terms] OR ("carcinoma"[All Fields] AND "hepatocellular"[All Fields]) OR "hepatocellular carcinoma"[All Fields] OR ("hepatocellular"[All Fields] AND "carcinoma"[All Fields]))

Search Details

Query Translation:

```
("lenvatinib"[Supplementary Concept] OR "lenvatinib"[All
Fields]) AND ("carcinoma, hepatocellular"[MeSH Terms] OR
("carcinoma"[All Fields] AND "hepatocellular"[All Fields]) OR
"hepatocellular carcinoma"[All Fields] OR
("hepatocellular"[All Fields] AND "carcinoma"[All Fields]))
```

Search URL

Result:

43

Translations:

lenvatinib	"lenvatinib"[Supplementary Concept] OR "lenvatinib"[All Fields]
hepatocellular carcinoma	"carcinoma, hepatocellular"[MeSH Terms] OR ("carcinoma"[All Fields] AND "hepatocellular"[All Fields]) OR "hepatocellular carcinoma"[All Fields] OR ("hepatocellular"[All Fields] AND "carcinoma"[All Fields])

Database:

PubMed

User query:

(lenvatinib) AND hepatocellular carcinoma

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Lenvima AND hepatocellular carcinoma

("lenvatinib"[Supplementary Concept] OR "lenvatinib"[All Fields] OR "lenvima"[All Fields]) AND ("carcinoma, hepatocellular"[MeSH Terms] OR ("carcinoma"[All Fields] AND "hepatocellular"[All Fields]) OR "hepatocellular carcinoma"[All Fields] OR ("hepatocellular"[All Fields] AND "carcinoma"[All Fields]))

Search Details

Query Translation:

```
("lenvatinib"[Supplementary Concept] OR "lenvatinib"[All
Fields] OR "lenvima"[All Fields]) AND ("carcinoma,
hepatocellular"[MeSH Terms] OR ("carcinoma"[All Fields] AND
"hepatocellular"[All Fields]) OR "hepatocellular
carcinoma"[All Fields] OR ("hepatocellular"[All Fields] AND
"carcinoma"[All Fields]))
```

Search URL

Result:

43

Translations:

Lenvima	"lenvatinib"[Supplementary Concept] OR "lenvatinib"[All Fields] OR "lenvima"[All Fields]
hepatocellular carcinoma	"carcinoma, hepatocellular"[MeSH Terms] OR ("carcinoma"[All Fields] AND "hepatocellular"[All Fields]) OR "hepatocellular carcinoma"[All Fields] OR ("hepatocellular"[All Fields] AND "carcinoma"[All Fields])

Database:

PubMed

User query:

(Lenvima) AND hepatocellular carcinoma

As can be expected based on the PubMed search strategy shown above, the search with keywords "Lenvima" and "hepatocellular carcinoma" yielded the same results as the search with "lenvatinib" and "hepatocellular carcinoma":

1: Hiraoka A, Kumada T, Kariyama K, Takaguchi K, Itobayashi E, Shimada N, Tajiri K, Tsuji K, Ishikawa T, Ochi H, Hirooka M, Tsutsui A, Shibata H, Tada T, Toyoda H, Nouso K, Joko K, Hiasa Y, Michitaka K; Real-life Practice Experts for HCC (RELPEC) Study Group and HCC 48 Group (hepatocellular carcinoma experts from 48 clinics in Japan). Therapeutic potential of lenvatinib for unresectable hepatocellular carcinoma in clinical practice: Multicenter analysis. Hepatol Res. 2018 Aug 24. doi: 10.1111/hepr.13243. [Epub ahead of print] PubMed PMID: 30144256.

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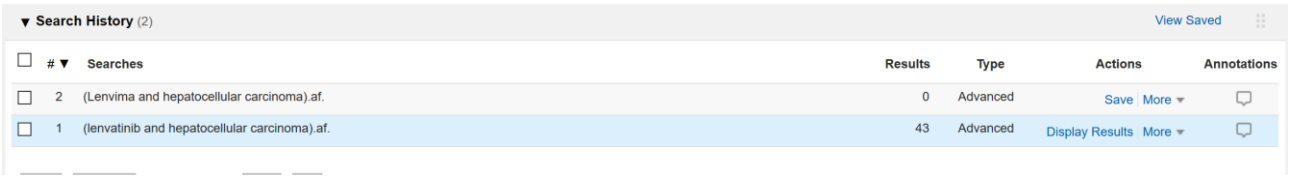
Control searches with similar keywords in Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) 1946 to September 14, 2018



The search with keywords “lenvatinib” and “hepatocellular carcinoma” yielded the same results as the corresponding search in PubMed.

Cochrane Library, CENTRAL

lenvatinib AND hepatocellular carcinoma

Cochrane Reviews 0 | Cochrane Protocols 0 | **Trials 18** | Editorials 0 | Special collections 0 | Clinical Answers 0 | Other Reviews

18 Trials matching on 'lenvatinib in Title Abstract Keyword AND "hepatocellular carcinoma" in Title Abstract Keyword - (Word variations have been searched)**'**

Cochrane Central Register of Controlled Trials
Issue 9 of 12, September 2018

1. A Multicenter, Open-Label, Phase 3 Trial to Compare the Efficacy and Safety of Lenvatinib (E7080) Versus Sorafenib in First-Line Treatment of Subjects With Unresectable Hepatocellular Carcinoma, NCT01761266, Https://clinicaltrials.gov/show/nct01761266, 2013 | added to CENTRAL: 31 May 2018 | 2018 Issue 5

CLINICAL TRIAL SUMMARY AT CLINICALTRIALS.GOV

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3. J-C Nault, PR Galle, JU Marquardt. The role of molecular enrichment on future therapies in hepatocellular carcinoma. Journal of hepatology, 2018, (no pagination) | added to CENTRAL: 30 June 2018 | 2018 Issue 6, Embase

4. S Hudgens, D Misurski, G Meier. Time to clinically meaningful worsening in hepatocellular carcinoma patients treated with lenvatinib or sorafenib. Value in health. Conference: ISPOR 20th annual european congress. United kingdom, 2017, 20(9), A416 | added to CENTRAL: 31 January 2018 | 2018 Issue 1, Embase

CONFERENCE ABSTRACT

5. M Muller-Schilling. Hepatocellular carcinoma: epidemiology, risk factors and current treatment strategies. Journal of gastrointestinal and liver diseases. Conference: 5th romanian-german symposium of gastroenterology. Romania, 2018, 27(Supplement 1), 24-25 | added to CENTRAL: 31 August 2018 | 2018 Issue 8, Embase

CONFERENCE ABSTRACT

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CONFERENCE ABSTRACT

7. M Kudo, RS Finn, S Qin, K-H Han, K Ikeda, F Piscaglia, A Baron, J-W Park, G Han, J Jassem, JF Blanc, A Vogel, D Komov, TRJ Evans, C Lopez, C Dutcus, M Guo, K Saito, S Kraljevic, T Tamai, M Ren, A-L Cheng. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial. Lancet, 2018, 391(10126), 1163-1173 | added to CENTRAL: 30 June 2018 | 2018 Issue 6, Embase

8. W Sun, R Cabrera. Systemic Treatment of Patients with Advanced, Unresectable Hepatocellular Carcinoma: emergence of Therapies. Journal of gastrointestinal cancer, 2018, 1-9 | added to CENTRAL: 30 April 2018 | 2018 Issue 4, Embase

9. M Ikeda. Chemotherapy for hepatocellular carcinoma: molecular targeted agents, hepatic arterial infusion chemotherapy or both? Annals of oncology. Conference: 15th annual meeting of japanese society of medical oncology, JSMO 2017. Japan, 2017, 28(Supplement 9), ix43 | added to CENTRAL: 31 January 2018 | 2018 Issue 1, Embase

CONFERENCE ABSTRACT

10. S Hudgens, D Misurski, G Meier. Detrimental impact of toxicity on quality of life in hepatocellular carcinoma patients treated with lenvatinibor sorafenib. Value in health. Conference: ISPOR 20th annual european congress. United kingdom, 2017, 20(9), A411-A412 | added to CENTRAL: 31 January 2018 | 2018 Issue 1, Embase

CONFERENCE ABSTRACT

11. A Vogel, S Qin, M Kudo, S Hudgens, T Yamashita, J-H Yoon, L Fartoux, K Simon, CL Lopez, M Sung, CE Dutcus, S Kraljevic, T Tamai, N Grunow, G Meier, V Breder. Health-related quality of life (HRQOL) and disease symptoms in patients with unresectable hepatocellular carcinoma (HCC) treated with lenvatinib (LEN) or sorafenib (SOR). Hepatology. Conference: 68th annual meeting of the american association for the study of liver diseases, AASLD 2017. United states, 2017, 66(Supplement 1), 734A | added to CENTRAL: 30 November 2017 | 2017 Issue 11, Embase

CONFERENCE ABSTRACT

12. A Vogel, S Qin, M Kudo, S Hudgens, T Yamashita, J-H Yoon, L Fartoux, K Simon, C Lopez Lopez, M Sung, C Dutcus, S Kraljevic, T Tamai, N Grunow, G Meier, V Breder. Health-related quality of Life (HRQOL) and disease symptoms in patients with unresectable hepatocellular carcinoma (HCC) treated with lenvatinib (LEN) or sorafenib (SOR). Annals of oncology. Conference: 42nd ESMO congress, ESMO 2017. Spain, 2017, 28(Supplement 5), v210 | added to CENTRAL: 31 January 2018 | 2018 Issue 1, Embase

CONFERENCE ABSTRACT

13.A Vogel, S Qin, M Kudo, S Hudgens, T Yamashita, J Yoon, L Fartoux, K Simon, C Lopez, M Sung, C Dutcus, S Kraljevic, T Tamai, N Grunow, G Meier, V Breder. Health-related quality of life (HRQOL) and disease symptoms in patients with unresectable hepatocellular carcinoma (HCC) treated with lenvatinib (LEN) or sorafenib (SOR). Value in health. Conference: ISPOR 20th annual european congress. United kingdom, 2017, 20(9), A454-A455 | added to CENTRAL: 31 January 2018 | 2018 Issue 1, Embase

CONFERENCE ABSTRACT

14.A-L Cheng, RS Finn, S Qin, K-H Han, K Ikeda, F Piscaglia, A Baron, J-W Park, G Han, J Jassem, JF Blanc, A Vogel, D Komov, TJ Evans, C Lopez, C Dutcus, M Ren, S Kraljevic, T Tamai, M Kudo. Phase 3 trial of lenvatinib (LEN) vs sorafenib (SOR) in first-line treatment of patients (pts) with unresectable hepatocellular carcinoma (uHCC). Oncology research and treatment. Conference: jahrestagung der deutschen, osterreichischen und schweizerischen gesellschaften fur hamatologie und medizinische onkologie 2017. Germany, 2017, 40(Supplement 3), 211 | added to CENTRAL: 30 November 2017 | 2017 Issue 11, Embase

CONFERENCE ABSTRACT

15.A-L Cheng, RS Finn, S Qin, K-H Han, K Ikeda, F Piscaglia, A Baron, J-W Park, G Han, J Jassem, JF Blanc, A Vogel, D Komov, TRJ Evans, C Lopez, C Dutcus, M Ren, S Kraljevic, T Tamai, J Bower, M Kudo. Phase III trial of lenvatinib (LEN) vs sorafenib (SOR) in first-line treatment of patients (PTS)with unresectable hepatocellular carcinoma (uHCC). Asia-pacific journal of clinical oncology. Conference: 44th annual scientific meeting of the clinical oncology society of australia, COSA 2017. Australia, 2017, 13(Supplement 4), 116 | added to CENTRAL: 31 January 2018 | 2018 Issue 1, Embase

CONFERENCE ABSTRACT

16.RS Finn, M Kudo, A-L Cheng, L Wyrwicz, R Ngan, J-F Blanc, AD Baron, A Vogel, M Ikeda, F Piscaglia, K-H Han, S Qin, Y Minoshima, Y Funahashi, M Ren, R Dairiki, P Sachdev, T Tamai, C Dutcus, TRJ Evans. Analysis of serum biomarkers (BM) in patients (pts) from a phase 3 study of lenvatinib (LEN) vs sorafenib (SOR) as first-line treatment for unresectable hepatocellular carcinoma (uHCC). Annals of oncology. Conference: 42nd ESMO congress, ESMO 2017. Spain, 2017, 28(Supplement 5), v617 | added to CENTRAL: 31 January 2018 | 2018 Issue 1, Embase

CONFERENCE ABSTRACT

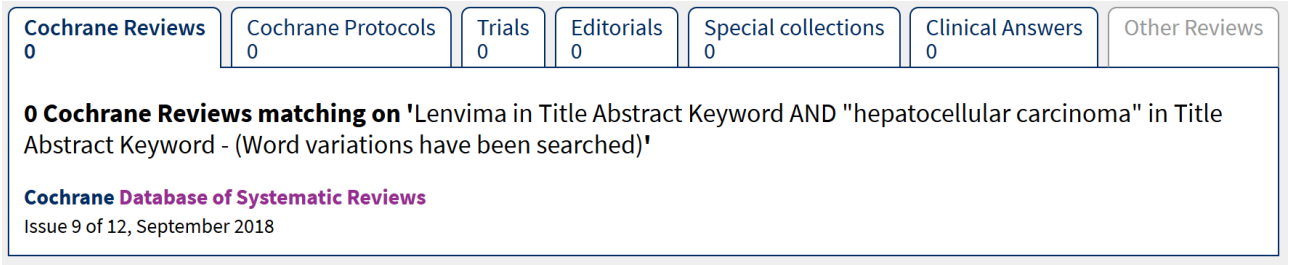
17.A Ribeiro de Souza, M Reig, J Bruix. Systemic treatment for advanced hepatocellular carcinoma: the search of new agents to join sorafenib in the effective therapeutic armamentarium. Expert opinion on pharmacotherapy, 2016, 17(14), 1923-1936 | added to CENTRAL: 30 November 2016 | 2016 Issue 11, Embase

18.J Furuse. Current status and clinical trials in progress of chemotherapy for unresectable hepatobiliary and pancreatic cancers in Japan. Journal of hepato-biliary-pancreatic sciences. Conference: joint congress of the 6th biennial congress of the asian-pacific hepato-pancreato-biliary association and the 29th meeting of japanese society of hepato-biliary-pancreatic surgery. Japan, 2017, 24, A16 | added to CENTRAL: 30 September 2017 | 2017 Issue 9, Embase

CONFERENCE ABSTRACT

Lenvima AND hepatocellular carcinoma

Search yielded 0 results



Exclusion

The articles listed below were excluded because they met at least one of the following exclusion criteria:

- not a randomized clinical trial
- phase 1 trial
- population other than selected
- did not report at least one of the critical or important effect goals.

PubMed

1: Hiraoka A, Kumada T, Kariyama K, Takaguchi K, Itobayashi E, Shimada N, Tajiri K, Tsuji K, Ishikawa T, Ochi H, Hirooka M, Tsutsui A, Shibata H, Tada T, Toyoda H, Nouso K, Joko K, Hiasa Y, Michitaka K; Real-life Practice Experts for HCC (RELPEC) Study Group and HCC 48 Group (hepatocellular carcinoma experts from 48 clinics in Japan). Therapeutic potential of lenvatinib for unresectable hepatocellular carcinoma in clinical practice: Multicenter analysis. Hepatol Res.2018 Aug 24. doi: 10.1111/hepr.13243.

Reason for exclusion: Open label retrospective multicenter analysis. Not a randomized controlled trial

2: Medavaram S, Zhang Y. Emerging therapies in advanced hepatocellular carcinoma. Exp Hematol Oncol. 2018 Aug 3;7:17. doi: 10.1186/s40164-018-0109-6.

Reason for exclusion: Review article. Not a randomized controlled trial.

3: Zschäbitz S, Grüllich C. Lenvatinib: A Tyrosine Kinase Inhibitor of VEGFR 1-3, FGFR 1-4, PDGFRα, KIT and RET. Recent Results Cancer Res. 2018;211:187-198. doi: 10.1007/978-3-319-91442-8_13.

Reason for exclusion: Review article. Not a randomized controlled trial.

4: Llovet JM, Montal R, Sia D, Finn RS. Molecular therapies and precision medicine for hepatocellular carcinoma. Nat Rev Clin Oncol. 2018 Jul 30. doi: 10.1038/s41571-018-0073-4.

Reason for exclusion: Review article. Not a randomized controlled trial.

5: Xie F, Feng S, Sun L, Mao Y. The first-line treatment for unresectable hepatocellular carcinoma patients: lenvatinib versus sorafenib, or beyond? Hepatobiliary Surg Nutr. 2018 Jun;7(3):221-224. doi: 10.21037/hbsn.2018.06.06.

Reason for exclusion: Review article/Journal comment. Not a randomized controlled trial.

6: Liu PH, Huo TI, Miksad RA. Hepatocellular Carcinoma with Portal Vein Tumor Involvement: Best Management Strategies. Semin Liver Dis. 2018 Aug;38(3):242-251. doi: 10.1055/s-0038-1666805.

Reason for exclusion: Review article. Not a randomized controlled trial.

7: Pinter M, Peck-Radosavljevic M. Review article: systemic treatment of hepatocellular carcinoma. Aliment Pharmacol Ther. 2018 Sep;48(6):598-609. doi: 10.1111/apt.14913.

Reason for exclusion: Review article. Not a randomized controlled trial.

8: Suyama K, Iwase H. Lenvatinib: A Promising Molecular Targeted Agent for Multiple Cancers. Cancer Control. 2018 Jan-Dec;25(1):1073274818789361. doi: 10.1177/1073274818789361.

Reason for exclusion: Review article. Not a randomized controlled trial.

9: Personeni N, Pressiani T, Santoro A, Rimassa L. Regorafenib in hepatocellular carcinoma: latest evidence and clinical implications. Drugs Context. 2018 Jun 27;7:212533. doi: 10.7573/dic.212533.

Reason for exclusion: Review article. Not a randomized controlled trial.

10: Qiu MJ, He XX, Bi NR, Wang MM, Xiong ZF, Yang SL. Effects of liver-targeted drugs on expression of immune-related proteins in hepatocellular carcinoma cells. Clin Chim Acta. 2018 Oct;485:103-105. doi: 10.1016/j.cca.2018.06.032.

Reason for exclusion: Editorial. Not a randomized controlled trial.

11: Yamamoto S, Kondo S. Oral chemotherapy for the treatment of hepatocellular carcinoma. Expert Opin Pharmacother. 2018 Jun;19(9):993-1001. doi: 10.1080/14656566.2018.1479398.

Reason for exclusion: Review article. Not a randomized controlled trial.

12: Schultheiß M, Bettinger D, Fichtner-Feigl S, Thimme R. [Hepatocellular Carcinoma: New multimodal therapy concepts]. Dtsch Med Wochenschr. 2018 Jun;143(11):815-819. doi: 10.1055/s-0043-124158.

Reason for exclusion: Review article. Not a randomized controlled trial.

13: Baxter MA, Glen H, Evans TR. Lenvatinib and its use in the treatment of unresectable hepatocellular carcinoma. Future Oncol. 2018 Aug;14(20):2021-2029. doi: 10.2217/fon-2017-0689.

Reason for exclusion: Review article. Not a randomized controlled trial.

14: Raoul JL, Kudo M, Finn RS, Edeline J, Reig M, Galle PR. Systemic therapy for intermediate and advanced hepatocellular carcinoma: Sorafenib and beyond. Cancer Treat Rev. 2018 Jul;68:16-24. doi: 10.1016/j.ctrv.2018.05.006.

Reason for exclusion: Review article. Not a randomized controlled trial.

15: Contratto M, Wu J. Targeted therapy or immunotherapy? Optimal treatment in hepatocellular carcinoma. World J Gastrointest Oncol. 2018 May 15;10(5):108-114. doi: 10.4251/wjgo.v10.i5.108.

Reason for exclusion: Review article. Not a randomized controlled trial.

16: Matsuki M, Hoshi T, Yamamoto Y, Ikemori-Kawada M, Minoshima Y, Funahashi Y, Matsui J. Lenvatinib inhibits angiogenesis and tumor fibroblast growth factor signaling pathways in human hepatocellular carcinoma models. Cancer Med. 2018 Jun;7(6):2641-2653. doi: 10.1002/cam4.1517.

Reason for exclusion: Journal article investigating the antitumor activity of lenvatinib in preclinical HCC models and exploring the mechanisms underlying its antitumor activity. Not a randomized controlled trial.

17: Eso Y, Marusawa H. Novel approaches for molecular targeted therapy against hepatocellular carcinoma. Hepatol Res. 2018 Jul;48(8):597-607. doi:10.1111/hepr.13181.

Reason for exclusion: Review article. Not a randomized controlled trial.

18: Kudo M. Lenvatinib May Drastically Change the Treatment Landscape of Hepatocellular Carcinoma. Liver Cancer. 2018 Mar;7(1):1-19. doi: 10.1159/000487148.

Reason for exclusion: Editorial. Not a randomized controlled trial.

19: Ettrich TJ, Ebert M, Lorenzen S, Moehler M, Vogel A, Witkowski L, Seufferlein T, Reinacher-Schick A. [ASCO- and ESMO-update 2017 - highlights of the 53. meeting of the American Society of Clinical Oncology/ASCO 2017 and European Society for Medical Oncology/ESMO congress 2017]. Z Gastroenterol. 2018 Apr;56(4):384-397. doi: 10.1055/s-0044-101757.

Reason for exclusion: Conference proceedings. Not a randomized controlled trial.

20: Yee NS. Update in Systemic and Targeted Therapies in Gastrointestinal Oncology. Biomedicines. 2018 Mar 16;6(1). pii: E34. doi: 10.3390/biomedicines6010034.

Reason for exclusion: Conference proceedings. Not a randomized controlled trial.

21: Nault JC, Galle PR, Marquardt JU. The role of molecular enrichment on future therapies in hepatocellular carcinoma. J Hepatol. 2018 Jul;69(1):237-247. doi: 10.1016/j.jhep.2018.02.016.

Reason for exclusion: Review article. Not a randomized controlled trial.

22: Thomas H. Liver cancer: Lenvatinib non-inferior to sorafenib for hepatocellular carcinoma. Nat Rev Gastroenterol Hepatol. 2018 Apr;15(4):190. doi: 10.1038/nrgastro.2018.20.

Reason for exclusion: In brief news article. Not a randomized controlled trial.

23: Sun W, Cabrera R. Systemic Treatment of Patients with Advanced, Unresectable Hepatocellular Carcinoma: Emergence of Therapies. J Gastrointest Cancer. 2018 Jun;49(2):107-115. doi: 10.1007/s12029-018-0065-8.

Reason for exclusion: Review article. Not a randomized controlled trial.

24: Forner A, Reig M, Bruix J. Hepatocellular carcinoma. Lancet. 2018 Mar 31;391(10127):1301-1314. doi: 10.1016/S0140-6736(18)30010-2.

Reason for exclusion: Review article. Not a randomized controlled trial.

25: Kudo M. Immuno-Oncology in Hepatocellular Carcinoma: 2017 Update. Oncology. 2017;93 Suppl 1:147-159. doi: 10.1159/000481245.

Reason for exclusion: Review article. Not a randomized controlled trial.

26: Kudo M. Systemic Therapy for Hepatocellular Carcinoma: 2017 Update. Oncology. 2017;93 Suppl 1:135-146. doi: 10.1159/000481244.

Reason for exclusion: Review article. Not a randomized controlled trial.

27: Ikeda M, Morizane C, Ueno M, Okusaka T, Ishii H, Furuse J. Chemotherapy for hepatocellular carcinoma: current status and future perspectives. Jpn J Clin Oncol. 2018 Feb 1;48(2):103-114. doi: 10.1093/jjco/hyx180.

Reason for exclusion: Review article. Not a randomized controlled trial.

28: Kudo M. Lenvatinib in Advanced Hepatocellular Carcinoma. Liver Cancer. 2017 Nov;6(4):253-263. doi: 10.1159/000479573.

Reason for exclusion: Editorial. Not a randomized controlled trial.

29: Raoul JL, Gilabert M, Adhoute X, Edeline J. An in-depth review of chemical angiogenesis inhibitors for treating hepatocellular carcinoma. Expert Opin Pharmacother. 2017 Oct;18(14):1467-1476. doi: 10.1080/14656566.2017.1378346.

Reason for exclusion: Review article. Not a randomized controlled trial.

30: Kudo M. A New Era of Systemic Therapy for Hepatocellular Carcinoma with Regorafenib and Lenvatinib. Liver Cancer. 2017 Jun;6(3):177-184. doi: 10.1159/000462153.

Reason for exclusion: Editorial. Not a randomized controlled trial.

31: de Rosamel L, Blanc JF. Emerging tyrosine kinase inhibitors for the treatment of hepatocellular carcinoma. Expert Opin Emerg Drugs. 2017 Jun;22(2):175-190. doi: 10.1080/14728214.2017.1336538.

Reason for exclusion: Review article. Not a randomized controlled trial.

32: Tamai T, Hayato S, Hojo S, Suzuki T, Okusaka T, Ikeda K, Kumada H. Dose Finding of Lenvatinib in Subjects With Advanced Hepatocellular Carcinoma Based on Population Pharmacokinetic and Exposure-Response Analyses. J Clin Pharmacol. 2017 Sep;57(9):1138-1147. doi: 10.1002/jcph.917.

Reason for exclusion: Dose finding PK study. Combines data from several Phase 1 studies and one Phase 2 study. Does not report effect goals.

33: Hussein Z, Mizuo H, Hayato S, Namiki M, Shumaker R. Clinical Pharmacokinetic and Pharmacodynamic Profile of Lenvatinib, an Orally Active, Small-Molecule, Multitargeted Tyrosine Kinase Inhibitor. Eur J Drug Metab Pharmacokinet. 2017 Dec;42(6):903-914. doi: 10.1007/s13318-017-0403-4.

Reason for exclusion: Review article. Not a randomized controlled trial.

34: Ikeda K, Kudo M, Kawazoe S, Osaki Y, Ikeda M, Okusaka T, Tamai T, Suzuki T, Hisai T, Hayato S, Okita K, Kumada H. Phase 2 study of lenvatinib in patients with advanced hepatocellular carcinoma. J Gastroenterol. 2017 Apr;52(4):512-519. doi: 10.1007/s00535-016-1263-4.

Reason for exclusion: Single-arm, open-label multicenter study of lenvatinib monotherapy. Not a randomized controlled trial.

35: Trojan J, Waidmann O. Role of regorafenib as second-line therapy and landscape of investigational treatment options in advanced hepatocellular carcinoma. J Hepatocell Carcinoma. 2016 Sep 21;3:31-36.

Reason for exclusion: Review article. Not a randomized controlled trial.

36: Oikonomopoulos G, Aravind P, Sarker D. Lenvatinib: a potential breakthrough in advanced hepatocellular carcinoma? Future Oncol. 2016 Feb;12(4):465-76. doi: 10.2217/fon.15.341.

Reason for exclusion: Review article. Not a randomized controlled trial.

37: Ikeda M, Okusaka T, Mitsunaga S, Ueno H, Tamai T, Suzuki T, Hayato S, Kadowaki T, Okita K, Kumada H. Safety and Pharmacokinetics of Lenvatinib in Patients with Advanced Hepatocellular Carcinoma. Clin Cancer Res. 2016 Mar 15;22(6):1385-94. doi: 10.1158/1078-0432.CCR-15-1354.

Reason for exclusion: Phase 1 study.

38: Waidmann O, Trojan J. Novel drugs in clinical development for hepatocellular carcinoma. Expert Opin Investig Drugs. 2015;24(8):1075-82. doi: 10.1517/13543784.2015.1058776.

Reason for exclusion: Review article. Not a randomized controlled trial.

39: Gu Q, Zhang B, Sun H, Xu Q, Tan Y, Wang G, Luo Q, Xu W, Yang S, Li J, Fu J, Chen L, Yuan S, Liang G, Ji Q, Chen SH, Chan CC, Zhou W, Xu X, Wang H, Fang DD. Genomic characterization of a large panel of patient-derived hepatocellular carcinoma xenograft tumor models for preclinical development. Oncotarget. 2015 Aug 21;6(24):20160-76.

Reason for exclusion: Methodological article. Not a randomized controlled trial.

40: Scott LJ. Lenvatinib: first global approval. Drugs. 2015 Apr;75(5):553-60. doi: 10.1007/s40265-015-0383-0.

Reason for exclusion: Review article. Not a randomized controlled trial.

41: Chuma M, Terashita K, Sakamoto N. New molecularly targeted therapies against advanced hepatocellular carcinoma: From molecular pathogenesis to clinical trials and future directions. Hepatol Res. 2015 Oct;45(10):E1-E11. doi: 10.1111/hepr.12459.

Reason for exclusion: Review article. Not a randomized controlled trial.

42: Ikeda M, Mitsunaga S, Shimizu S, Ohno I, Takahashi H, Okuyama H, Kuwahara A, Okusaka T. Current status of hepatocellular carcinoma in Japan. Chin Clin Oncol. 2013 Dec;2(4):40. doi: 10.3978/j.issn.2304-3865.2013.09.01.

Reason for exclusion: Review article. Not a randomized controlled trial.

CENTRAL

1: P Gholam. The role of Sorafenib in hepatocellular carcinoma. Clinical advances in hematology & oncology, 2015, 13(4), 232-234. | added to CENTRAL: 30 June 2015 | 2015 Issue 6, Embase.

Reason for exclusion: Review article / expert interview. Not a randomized controlled trial.

2: J-C Nault, PR Galle, JU Marquardt. The role of molecular enrichment on future therapies in hepatocellular carcinoma Journal of hepatology, 2018, (no pagination) | added to CENTRAL: 30 June 2018 | 2018 Issue 6, Embase

Reason for exclusion: Review article. Not a randomized controlled trial.

3: W Sun, R Cabrera. Systemic Treatment of Patients with Advanced, Unresectable Hepatocellular Carcinoma: emergence of Therapies. Journal of gastrointestinal cancer, 2018, 1-9 | added to CENTRAL: 30 April 2018 | 2018 Issue 4, Embase

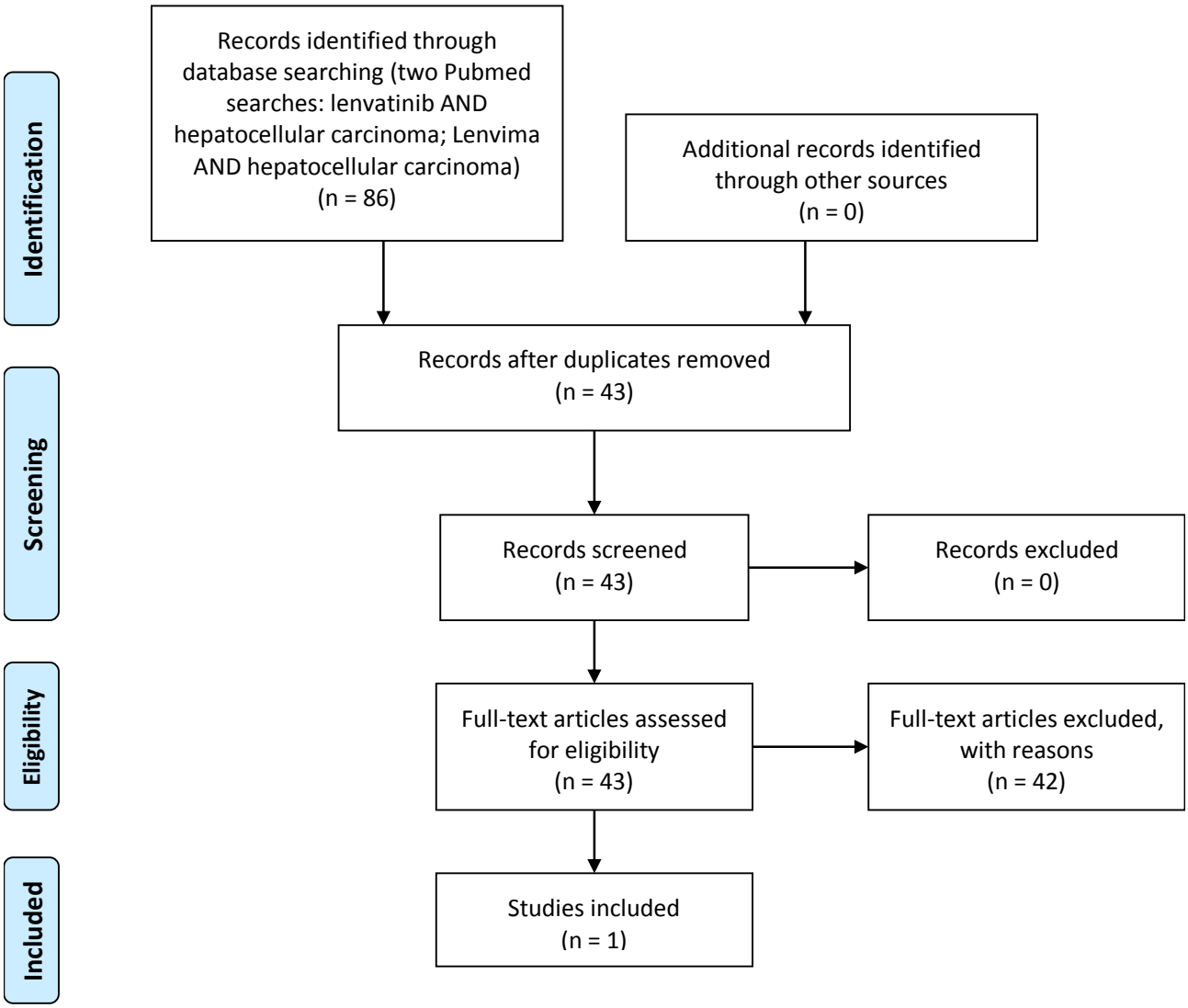
Reason for exclusion: Review article. Not a randomized controlled trial.

4: A Ribeiro de Souza, M Reig, J Bruix. Systemic treatment for advanced hepatocellular carcinoma: the search of new agents to join sorafenib in the effective therapeutic armamentarium. Expert opinion on pharmacotherapy, 2016, 17(14), 1923-1936 | added to CENTRAL: 30 November 2016 | 2016 Issue 11, Embase

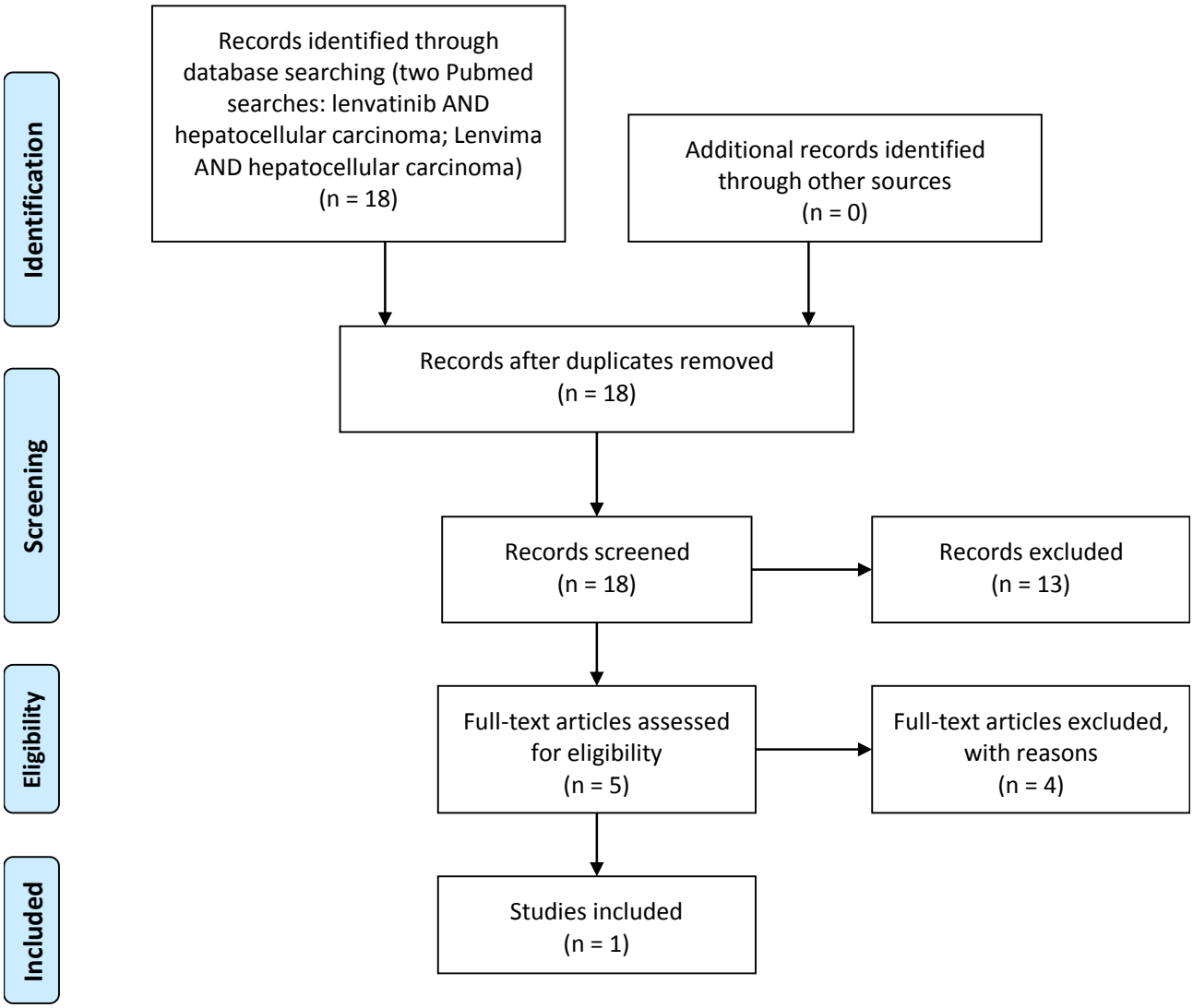
Reason for exclusion: Review article. Not a randomized controlled trial.

PRISMA flow charts

PRISMA 2009 Flow Diagram for PubMed (Medline) search



PRISMA 2009 Flow Diagram for Cochrane Library CENTRAL search



Main characteristics of included studies

Study characteristics

TABLE 7.2: MAIN STUDY CHARACTERISTICS

Trial name	REFLECT study (304, NCT01761266)
NCT number	01761266
Objective	The aim was to compare overall survival in patients treated with lenvatinib versus sorafenib as a first-line treatment for unresectable hepatocellular carcinoma.
Publications – title, author, journal, year	Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial, Kudo, M., Finn, R.S., Qin, S., et al. Lancet 2018
Study type and design	A multicentre, randomised, open-label, non-inferiority Phase III trial. Comparator-controlled (sorafenib). Patients were randomly assigned (1:1) via an interactive voice–web response system—with region; macroscopic portal vein invasion, extrahepatic spread, or both; Eastern Cooperative Oncology Group performance status; and bodyweight as stratification factors.
Follow-up time	March 01, 2013 - November 13, 2016 (at 701 deaths) The median duration of follow-up was 27.7 months (IQR 23.3–32.8) in the lenvatinib group and 27.2 months (22.6–31.3) in the sorafenib group.
Population (inclusion and exclusion criteria)	Inclusion Criteria 1. Subjects must have confirmed diagnosis of unresectable HCC with any of the following criteria: ○ Histologically or cytologically confirmed diagnosis of HCC ○ Clinically confirmed diagnosis of HCC according to American Association for the Study of Liver Diseases (AASLD) criteria, including cirrhosis of any etiology or with chronic hepatitis B or C infection criteria 2. At least one measurable target lesion according to mRECIST meeting the following criteria: ○ Hepatic lesion 1. The lesion can be accurately measured in at least one dimension as greater than or equal to 1.0 cm (viable tumor for typical; and longest diameter for atypical), and 2. The lesion is suitable for repeat measurement ○ Nonhepatic lesion c. Lymph node (LN) lesion that measures at least one dimension as greater than or equal to 1.5 cm in the short axis, except for porta hepatis LN that measures greater

	than or equal to 2.0 cm in the short axis d. Non-nodal lesion that measures greater than or equal to 1.0 cm in the longest diameter Lesions previously treated with radiotherapy or locoregional therapy must show radiographic evidence of disease progression to be deemed a target lesion. 3. Subjects categorized to stage B (not applicable for transarterial chemoembolization [TACE]) or stage C based on Barcelona Clinic Liver Cancer (BCLC) staging system 4. Adequate bone marrow function, defined as: o Absolute neutrophil count (ANC) greater than or equal to 1.5 X 10^9/L o Hemoglobin (Hb) greater than or equal to 8.5 g/dL o Platelet count greater than or equal to 75 X 10^9/L 5. Adequate liver function, defined as: o Albumin greater than or equal to 2.8 g/dL o Bilirubin less than or equal to 3.0 mg/dL o Aspartate aminotransferase (AST), alkaline phosphatase (ALP), and alanine aminotransferase (ALT) less than or equal to 5 X the upper limit of normal (ULN) 6. Adequate blood coagulation function, defined as international normalized ratio (INR) less than or equal to 2.3 7. Adequate renal function defined as creatinine clearance greater than 40 mL/min calculated per the Cockcroft and Gault formula 8. Adequate pancreatic function, defined as amylase and lipase less than or equal to 1.5 X ULN 9. Adequately controlled blood pressure (BP) with up to 3 antihypertensive agents, defined as BP less than or equal to 150/90 mm Hg at Screening and no change in antihypertensive therapy within 1 week prior to the Cycle1/Day1 10. Child-Pugh score A 11. ECOG-PS 0 or 1 12. Survival expectation of 12 weeks or longer after starting study drug 13. Males or females aged at least 18 years (or any age greater than 18 years as determined by country legislation) at the time of informed consent 14. Females must not be lactating or pregnant at Screening or Baseline (as documented by a negative beta-human chorionic gonadotropin [B-hCG] test with a minimum sensitivity of 25 IU/L or equivalent units of B-hCG). A separate baseline assessment is required if a negative screening pregnancy test was obtained more than 72 hours before the first dose of study drug. 15. All females will be considered to be of childbearing potential unless they are postmenopausal (amenorrheic for at least 12 consecutive months, in the appropriate age group and without other known or

	suspected cause) or have been sterilized surgically (ie, bilateral tubal ligation, total hysterectomy or bilateral oophorectomy, all with surgery at least 1 month before dosing) 16. Females of childbearing potential must not have had unprotected sexual intercourse within 30 days before study entry and must agree to use a highly effective method of contraception (e.g., total abstinence, an intrauterine device, a double-barrier method [such as condom plus diaphragm with spermicide], a contraceptive implant, an oral contraceptive, or have a vasectomized partner with confirmed azoospermia) throughout the entire study period and for 30 days after study drug discontinuation. If currently abstinent, the subject must agree to use a double barrier method as described above if she becomes sexually active during the study period or for 30 days after study drug discontinuation. Females who are using hormonal contraceptives must have been on a stable dose of the same hormonal contraceptive product for at least 4 weeks before dosing and must continue to use the same contraceptive during the study and for 30 days after study drug discontinuation. 17. Male subjects must have had a successful vasectomy (confirmed azoospermia) or they and their female partners must meet the criteria above (i.e., not of childbearing potential or practicing highly effective contraception throughout the study period and for 30 days after study drug discontinuation). No sperm donation is allowed during the study period and for 30 days after study drug discontinuation. 18. Provide written informed consent 19. Willing and able to comply with all aspects of the protocol Exclusion Criteria 1. Imaging findings for HCC corresponding to any of the following: o HCC with greater than or equal to 50 percent liver occupation o Clear invasion into the bile duct o Portal vein invasion at the main portal branch (Vp4) 2. Subjects who have received any systemic chemotherapy, including anti-VEGF therapy, or any systemic investigational anticancer agents, including lenvatinib, for advanced/unresectable HCC. Note: Subjects who have received local hepatic injection chemotherapy are eligible. 3. Subjects who have received any anticancer therapy (including surgery, percutaneous ethanol injection, radio frequency ablation, transarterial [chemo] embolization, hepatic intra-arterial chemotherapy, biological, immunotherapy, hormonal, or radiotherapy) or any blood enhancing treatment (including blood transfusion, blood products, or agents that stimulate blood cell production, eg, granulocyte colony-stimulating factor [G-CSF]) within 28 days prior to randomization 4. Subjects who have not recovered from toxicities as a result of prior anticancer therapy, except alopecia and infertility. Recovery is defined as less than Grade 2 severity per Common Terminology Criteria for

	Adverse Events Version 4.0 (CTCAE v4.0). 5. Significant cardiovascular impairment: history of congestive heart failure greater than New York Heart Association (NYHA) Class II, unstable angina, myocardial infarction or stroke within 6 months of the first dose of study drug, or cardiac arrhythmia requiring medical treatment at Screening 6. Prolongation of QTc interval to greater than 480 ms 7. Gastrointestinal malabsorption or any other condition that might affect the absorption of lenvatinib in the opinion of the investigator 8. Bleeding or thrombotic disorders or use of anticoagulants requiring therapeutic INR monitoring, eg, warfarin or similar agents. Treatment with low molecular weight heparin and factor X inhibitors which do not require INR monitoring is permitted. Antiplatelet agents are prohibited throughout the study. 9. Gastrointestinal bleeding event or active hemoptysis (bright red blood of at least 0.5 teaspoon) within 28 days prior to randomization 10. Gastric or esophageal varices that require interventional treatment within 28 days prior to randomization. Prophylaxis with pharmacologic therapy (eg, nonselective beta-blocker) is permitted. 11. Active malignancy (except for HCC or definitively treated melanoma in-situ, basal or squamous cell carcinoma of the skin, or carcinoma in-situ of the cervix) within the past 36 months 12. Subjects whose only target lesion(s) is in bone will be excluded 13. Meningeal carcinomatosis 14. Any history of or current brain or subdural metastases 15. Subjects having greater than 1+ proteinuria on urine dipstick testing will undergo a 24-hour urine collection for quantitative assessment of proteinuria. Subjects with a urine protein greater than or equal to 1 g/24 hours will be ineligible. 16. Surgical arterial-portal venous shunt or arterial-venous shunt 17. Any medical or other condition that in the opinion of the investigator would preclude the subject's participation in a clinical study 18. Known intolerance to lenvatinib or sorafenib (or any of the excipients) 19. Human immunodeficiency virus (HIV) positive or active infection requiring treatment (except for hepatitis virus) 20. Any history of drug or alcohol dependency or abuse within the prior 6 months 21. Any subject who cannot be evaluated by either triphasic liver CT or triphasic liver MRI because of allergy or other contraindication to both CT and MRI contrast agents 22. Major surgery within 3 weeks prior to randomization or scheduled for surgery during the study

	23. Subject has had a liver transplant
Intervention	Lenvatinib (n=478): 12 mg/day for bodyweight ≥60 kg or 8 mg/day for bodyweight <60 kg oral dosing Sorafenib (n=476): 400 mg twice daily (BID) oral dosing 28-days cycles
Baseline characteristics	Patient baseline characteristics were similar between treatment groups, except for baseline hepatitis C aetiology (lenvatinib 91 (19 %) and sorafenib 126 (26 %)) and α-fetoprotein concentrations median (IQR) (lenvatinib 133.1 and sorafenib 71.2 ng/mL). Age: median 62 years (range 20-88) Sex: male 84 %, female 16 % Bodyweight: < 60 kg 31 %, ≥ 60 kg 69 % Region: Western 33 %, Asia-Pacific 67 % Race: White 29 %, Asian 69 %, Other 2 % Eastern Cooperative Oncology Group performance status: 0 63 %, 1 37 % Child-Pugh class A 99 %, B 1 % Macroscopic portal vein invasion: yes 21 %, no 79 % Extrahepatic spread: yes 61 %, no 39 % Macroscopic portal vein invasion, extrahepatic spread, or both: Yes 61 %, No 39 % Underlying cirrhosis based on masked independent imaging review: Yes 70 %, No 30 % Barcelona Clinic Liver Cancer stage: B (intermediate stage) 21 %, C (advanced stage) 79 % Involved disease sites: Liver 91 % , Lung 32 % Involved disease sites per patient: One patient had no baseline target lesion, 1 43 %, 2 37 %, ≥3 20 % Aetiology of chronic liver disease: Hepatitis B 50 %, Hepatitis C 23 %, Alcohol 6 %, Other 7 %, Unknown 14 % Baseline α-fetoprotein concentration group (ng/mL): <200 57 %, ≥200 43 % Concomitant systemic antiviral therapy for hepatitis B or C: 33 % Previous anticancer procedures: 70 % Previous radiotherapy: 11 %
Primary and secondary endpoints	The primary endpoint was overall survival (OS) measured from the date of randomisation until the date of death from any cause. Secondary endpoints were progression-free survival (PFS), time to progression (TPP), objective response rate (ORR), quality-of-life measurements (HRQoL), and plasma pharmacokinetics lenvatinib exposure parameters.
Method of analysis	The efficacy analysis followed the intention-to-treat principle, and only patients who received treatment were included in the safety analysis. The primary endpoint of *overall survival* was first tested for non-inferiority, then for superiority. Using a non-inferiority test by the 95% CI lower-limit method on log HR for overall survival with assumed true HR of 0·80 and a non-inferiority margin of 1·08.

	HR and 95% CI were estimated from a Cox proportional hazard model with treatment group as a factor, and with the analysis stratified according to the same factors applied for randomisation for primary and subgroup analyses where appropriate. A fixed sequence procedure was used to control the overall type I error rate of analyses for both the primary and secondary efficacy endpoints at α=0·05 (two-sided). Differences in *progression-free survival and time to progression* were evaluated using a stratified log-rank test with randomisation stratification factors, with the associated HR and 95% CI. A difference in the *objective response rate* was evaluated using the Cochran-Mantel-Haenszel χ^2 test with randomisation stratification factors as strata, with associated odds ratio (OR) and 95% CI. To assess futility, two interim analyses (at 30% and 70% of the target number of events) were done using Bayesian predictive probability in a non-inferiority design. Programming and statistical analyses were done with SAS version 9 or higher.
Subgroup analyses	For the subgroup analysis, the analyses mentioned above were done within each subgroup: Age, Sex, Region, ECOG-PS, Bodyweight, Macroscopic portal vein invasion, AFP at baseline, Aetiology, Barcelona Clinic Liver Cancer staging, Post-treatment anticancer therapy, Post-treatment anticancer procedures, Post-treatment anticancer medication.

Results per study

Note the table below has been updated following questions from the authorities received on the 22.10.18 and the 02.11.18 to provide values for difference (Lenva-Sora) and estimated relative difference in effect.

TABLE 7.3: RESULTS OF STUDY [1]

Outcome	Study arm	N	Result (CI)	Difference (Lenva-Sora)	Estimated relative difference in effect	Comments	Source in the submission
Median overall survival	Lenvatinib	478	13.6 (12.1-14.9) months	1.3 months CI: (-0.9, 3.4) months	HR: 0.92 CI: 0.79-1.06	Diff (Lenva-Sora)	Figue 5.1 Table 5.1
	Sorefenib	476	12.3 (10.4-13.9) months				
12 months survival rate	Lenvatinib	478	55.0 (50.4, 59.4) %	5%	HR: 0.92 CI: 0.79-1.06	HR and 95% CI were estimated from a Cox proportional hazard model with treatment group as a factor.	Table 5.1
	Sorefenib	476	50.0 (45.4, 54.5) %				
24 months survival rate	Lenvatinib	478	29.9 (25.6, 34.2) %	3.6%	HR: 0.92 CI: 0.79-1.06	Difference adjusted to account for rounding	Table 5.1
	Sorefenib	476	26.2 (22.1, 30.5) %				
Treatment related grade 3-5 TEAEs adjusted by subject year (SY)	Lenvatinib	324.2 years	517 [1.59]	-0.20 (AE rate diff) CI: (-0.42,0.01) (CI for the AE rate diff)	Rate Ratio: 0.89 CI: (0.78, 1.01)	The Rate Ratio and its C.I. are calculated under the assumption of Poisson Distribution.	Section "Qualitative review of adverse events"
	Sorefenib	239.1 years	430 [1.80]				
Percentage of patients with treatment-related TEAEs leading to drug withdrawal	Lenvatinib	476	42 [9%]	2% CI: (-2%, 5%)	Relative Risk: 1.233 CI: (0.799,1.902)	RR: relative risk calculated as (42/476)/(34/475)=1.233.	Section "Treatment discontinuation and dose reduction due to adverse events"
	Sorefenib	475	34 [7%]				
Percentage of patients with	Lenvatinib	476	176 [37.0%]	-1% CI: (-7%, 5%)	Relative Risk: 0.970	RR: calculated as (176/476)/(181/475)=0.970	Section "Treatment
	Sorefenib	475	181 [38.1%]				

treatment-related TEAEs leading to dose reduction					CI: (0.824,1.143)		discontinuation and dose reduction due to adverse events"
Progression-free survival	Lenvatinib Sorefenib	478 476	7.4 (6.9-8.8) months 3.7 (3.6-4.6) months	3,7 months CI: (2.5, 4.8) months	HR: 0.66 CI: 0.57–0.77 P value: <0·0001	Differences were evaluated using a stratified log-rank test with randomisation stratification factors, with the associated HR and 95% CI.	Figure 5.3
Quality of life Summrary score for between-group comparison for time to clinically meaningful worsening of EQ-5D, EORTC QLQ-C30 domains			HR: 0.87 CI: 0.75–1.01 P value: 0.0742				Figure 5.5

Results per PICO (clinical question)

Not applicable

Results referring to clinical question 1 are presented in Table 7.3.

Application for the assessment of clinically added value of LENVIMA for Hepatocellular Carcinoma in Denmark

Response to questions from DMC received 02.11.18

Questions from DMC: we have noted the following:

1. **The CI interval for the relative effect estimate for the outcome "Percentage of patients with treatment-related TEAEs leading to drug withdrawal" is missing. Please provide the confidence interval.**
2. **The CI interval for the absolute effect estimate for the outcome " Treatment related grade 3-5 TEAEs adjusted by subject year (SY)" is missing. Please provide the confidence interval.**
3. **The CI interval for the relative effect estimate for the outcome "Percentage of patients with treatment-related TEAEs leading to dose reduction" is missing. Please provide the confidence interval.**
4. **The method for censoring results for PFS is still not clear. Please provide a description on how PFS was censored.**

If any of the above points is in fact included in your application, please let me know where.

Response for questions 1 to 3

Table 7.3 in the application document has been corrected by our statistics team who ensured all appropriate values are provided in the relevant columns "difference Lenva-Sora" and "Estimated relative difference in effect". If however there is a need for further clarification please do not hesitate contact us.

Response for question 4

For PFS, censoring rules followed Food and Drug Administration (FDA) guidance (35), where patients were censored when they discontinued treatment for any reason other than disease progression.

The PFS censoring rules in the statistical analysis plan (SAP) and definition of progression date follow the Food and Drug Administration (FDA) "Guidance for Industry Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics (2007)" as stated above. To provide further clarity to the authorities, the wording below has been extracted from the statistical plan. We also attach the FDA document for your reference.

Definition of Progression Date: Progression date is assigned to the first time at which radiological progression can be declared (in line with appendix 2 from FDA document).

For progression based on a new lesion, the progression date is the date of the initial detection of the new lesion, if there were multiple new lesions detected, then the earliest date of initial detection will be used.

- **If multiple assessments based on the sum of target lesion diameters are done at different times, the progression date is the date of the first radiological assessment of target lesions that shows a predefined increase of ≥ 20% against the nadir (the smallest sum of target lesion diameters among baseline and post-baseline tumor assessments) in the sum**

of the target lesion diameters which also must demonstrate at least 5mm absolute increase.

- **If progression is based on only non-target lesions, the progression date is the date of the first radiological assessment of non-target lesions for the time point that shows progression.**

The table below shows the primary censoring rules for the derivation of PFS based up on investigator's tumor assessment.

Censoring Rules for Analysis of Progression-Free Survival (in line with appendix 3 from the FDA guidelines)

No.	Situation	Date of Progression or Censoring	Outcome
1	No baseline tumor assessments	Date of randomization	Censored
2	Progression documented between scheduled visits	Date of first radiologic PD assessment	Progressed
3	No progression at the time of data cut-off or discontinuation from study treatment	Date of last adequate radiologic assessment prior to or on date of data cut-off or discontinuation from study treatment	Censored
4	New anticancer treatment started	Date of last adequate radiologic assessment prior to or on date of new anticancer treatment	Censored
5	Death before first PD assessment	Date of death	Progressed
6	Death between adequate assessment visits*	Date of death	Progressed
7	Death or progression after more than one missed visit** or after 28 days from the last dose of study treatment	Date of last adequate radiologic assessment before missed tumor assessments	Censored

CR = complete response, PD = progressive disease, PR = partial response, SD = stable disease,

* Adequate tumor assessment is a radiologic assessment of CR, PR, SD, non-CR/non-PD or PD as determined by investigators.

** More than one missed visit is defined if the duration between the last tumor assessment and death or PD is longer than 16 weeks + 2 weeks (i.e. the date of death or PD – the date of last adequate tumor assessment > 125 days) for subjects on the every 8 week scanning schedule in this study: The priority of the censoring rules is as follows:

1. If the subject had PD or death, the following sequence will be applied:

- If a subject did not have baseline tumor assessment (No. 1), the subject will be censored on date of randomization. However, if the subject died within 56 days (8 weeks) after randomization and did not receive new anticancer treatment, the date of death will be the PFS event date (not censored).
- If a subject had new anticancer treatment before PD or death (No. 4), the subject will be censored on the date of the last tumor assessment prior to or on the date of new anticancer treatment.
- If a subject missed more than one assessment before PD or death (No. 7), the subject will be censored on the date of the last tumor assessment before PD or death. Note that if a subject is censored by both this criterion and the anticancer treatment criteria, the earliest censoring date will be used.
- Otherwise, if a subject had an event (No. 2, No. 5, or No. 6), the earliest event date will be used.

2. If a subject did not have PD or death, the censoring date will be the earliest censoring date if the subject met multiple censoring criteria (No. 1, No. 3, No. 4, No. 7).

Response to draft Clinical Impact Assessment of Medicinal Products for lenvatinib for the treatment of hepatocellular carcinoma (12/12/2018)

Please find enclosed Eisai's response to the draft clinical impact assessment of lenvatinib in hepatocellular carcinoma (HCC). We would like to supplement our application with additional evidence from, and further clarification of, the REFLECT clinical trial results, that show the added clinical value of lenvatinib in the treatment of HCC.

The systematic literature review (SLR) has been updated in accordance with guidelines to include all relevant analyses of efficacy and safety from the REFLECT clinical study. The updated protocol and results are provided as an appendix to this response and all full text references are included in a separate folder (References/SLR References).

A statement of expert opinion from a clinical expert is also enclosed to provide additional evidence.

1. Summary: REFLECT quality of evidence

The Medicines Council used the Cochrane GRADE approach to evaluate evidence quality from the REFLECT study. According to the Medicine Council's assessment report, the open-label nature of REFLECT impacted the level of evidence quality with respect to:

- Blinding of subjects (performance bias) - adverse events and health-related quality of life (HRQoL)
- Blinding of outcome assessment (detection bias) - adverse events and HRQoL

An open-label design was necessary in the interests of patient safety because dose modification guidelines due to toxicity were different for lenvatinib and sorafenib for the same toxicities. In addition, the differences in formulation between lenvatinib (capsule) and sorafenib (tablet) would have required preparation of multiple matching placebo capsules or tablets to permit dose reductions. This would have been confusing for very ill patients and would have resulted in a high risk for dosing errors.

Nevertheless, REFLECT provides reliable direct comparative safety and efficacy data from a robust, large, multinational, randomised Phase 3 study versus the only relevant approved comparator in first line treatment for advanced unresectable HCC. Furthermore, the applicant created a Data Integrity Protection Plan, which ensured that relevant data fields were masked so that the clinical and statistical team members were blinded to treatment for each patient in order to minimise bias. In addition, it is stated in the European Pharmaceutical Assessment Report (EPAR) that the trial was well–conducted. Very few randomised subjects were not treated (3 in total) and the rate of major protocol deviations was low (2.5%) and balanced across the treatment arms.

It is however important to note that there were some baseline characteristic imbalances with respect to prognostic factors: a greater proportion with baseline alpha-fetoprotein (AFP) >200 ng/ml in the lenvatinib arm and more subjects with underlying hepatitis C in the sorafenib arm. The EPAR recognised that both of these imbalances may favour the sorafenib arm. Further details are provided in the overall survival section 2.1.

The Medicines Council noted incomplete data for progression-free survival (PFS) due to FDA-preferred analysis used for reporting this efficacy outcome. This has been addressed in the progression-free survival section 2.3.

The sparsity of published results for HRQoL was also highlighted by the Council. The primary manuscript (1) did not include full reporting of HRQoL data from the REFLECT study. However, multiple additional published studies are available and these studies have now been included in the updated SLR.

Significantly, despite the open-label study design, baseline scores for all domains were similar at baseline, >98% patients completed the questionnaires at each time point, and a separate statistical analysis plan (SAP) was in place to ensure analytic rigor. Further information is provided in the HRQoL section 2.4.

2. REFLECT efficacy results

2.1. Overall survival

Medicines council draft assessment report:

Lenvatinib has demonstrated overall survival benefit by statistical confirmation of non-inferiority when compared with sorafenib in the Phase III REFLECT trial. Whilst overall survival (OS) was numerically higher in the lenvatinib group (13.6 months) than the sorafenib group (12.3 months [hazard ratio (HR) 0.92, 95% confidence interval (CI): 0.79–1.06]), as highlighted in Medicinrådets' assessement report, the difference was not large enough to confirm statistical superiority of lenvatinib.

REFLECT included the following stratification factors:

- Region: Region 1 (Asia-Pacific); Region 2 (Western regions, such as EU, North America, other)
- Macroscopic portal vein invasion or extrahepatic spread or both: Yes; No
- Eastern Cooperative Oncology Group Performance Status (ECOG PS): PS = 0; PS = 1
- Body weight: <60 kg; ≥60 kg

In order not to compromise the robustness of the data, it was not possible to include alpha-fetoprotein (AFP) as an additional stratification factor. However, the statistical analysis plan (SAP) allowed for baseline characteristics to be used as covariates in supportive analyses for the endpoints.

Demographics and baseline characteristics were generally well balanced between the lenvatinib and sorafenib treatment arms of the study, however there were notable exceptions A greater proportion of patients had baseline AFP >200 ng/ml (a marker of poor HCC prognosis (2)) in the lenvatinib arm and more subjects with underlying hepatitis C in the sorafenib arm These baseline imbalances had the potential to impact OS in the overall study population in favour of sorafenib. As provided for in the SAP, covariate adjustment was used to explore the impact on overall survival. After adjustment for baseline AFP, lenvatinib was found to be nominally superior to sorafenib in terms of OS (median OS 13.6 months vs 12.3 months, respectively; HR 0.856 [95% CI:0.736, 0.995], p=0.0342) (1).

Furthermore, there was an imbalance between treatment arms regarding the proportion of patients who received post-treatment anti-cancer therapy during survival follow-up. Fewer patients in the lenvatinib (LEN) arm (43.1%) had post-treatment anti-cancer therapy than patients in the sorafenib (SOR) arm (51.1%) which may have favoured sorafenib. In the subgroup analysis for efficacy, patients who had post-treatment anticancer therapy had a numerically longer overall survival (LEN 19.5 vs SOR 17.0 months) compared to patients that did not (LEN 10.5 vs SOR 7.9 months)

Considering the effect of post-treatment therapy on overall survival and the imbalance between arms, a post-hoc adjustment was conducted and the resulting hazard ratios published in the EPAR. When adjusted for post-treatment anticancer therapy, the HR for OS favoured lenvatinib in both regions and in the ITT

population the HR for lenvatinib versus sorafenib reduced to 0.87 (95% CI: 0.75 - 1.01) in the adjusted analysis compared with 0.92 (95% CI 0.79- 1.06) in the unadjusted analysis.

Supplementary multivariate analysis on overall survival

Current EMA guidance on adjustment for baseline characteristics in clinical trials suggests that in the presence of imbalances for strong predictors of outcomes, adjustment for such covariates generally improves the precision and efficiency of the analysis and avoids conditional bias from chance covariate imbalance (3). Therefore the applicant conducted a post-hoc supplementary multivariable analysis to simultaneously adjust for all relevant prognostic baseline characteristics which may have impacted overall survival. This analysis is planned to be published and therefore is not included in this document so as not to compromise the publication.

Statistical survival analysis extrapolation of overall survival

As stated in section 5.1.2 'Supplementary exploratory overall survival analysis' of the applicant's original submission, at the data cut-off of 13th November 2016, 73.4% of patients in the lenvatinib arm and 73.5% of patients in the sorafenib arm had died. The Kaplan-Meier estimator for sorafenib PFS was 6% at the last observed data point. Therefore, there is justification for using statistical survival analysis to extrapolate beyond the end of REFLECT.

As part of the National Institute for Health and Care Excellence (NICE) review of lenvatinib in HCC, the Evidence Review Group (ERG) conducted an independent assessment of the REFLECT clinical data and the applicant's submission, concluding for the purposes of cost-effectiveness modelling that it was appropriate to adjust for baseline imbalances resulting in "an undiscounted incremental mean OS benefit of 3.1 months" (4).

In conclusion, imbalances in important prognostic baseline characteristics and post-treatment therapy use between arms may have favoured sorafenib. Pre-specified covariate analysis adjusting for AFP yielded a nominally significant OS HR of 0.856 [95% CI: 0.736, 0.995], highlighting the importance of this characteristic on overall survival. Supplementary multivariable adjustment also produced a nominally significant OS HR when adjusting for all relevant baseline characteristics simultaneously (data not included in this document so as not to compromise the publication). Using statistical survival analysis a mean incremental overall survival gain of 3.1 may be reasonable.

2.2. Adverse events (side effects)

Frequency of adverse events, treatment associated dose reduction or discontinuation

As noted by the Medicines Council, there was no significant difference between arms in the proportion of patients who had a dose reduction or treatment discontinuation due to treatment adverse events (AEs) (as indicated by the relative effect estimates).

In addition, the median duration of exposure to therapy was 1.5x longer with lenvatinib than sorafenib. When AEs were adjusted for treatment duration, the rate of grade ≥3 TEAEs and fatal AEs was similar between treatments.

Qualitative review of adverse events

Grade 3 or 4 TEAEs that occurred in ≥5% of the lenvatinib arm were hypertension, weight decreased, proteinuria, platelet count decreased, blood bilirubin increased, aspartate aminotransferase increased and gamma-glutamyl transferase increased. Grade 3 or 4 TEAEs that occurred in ≥5% of the sorafenib arm were hypertension, aspartate aminotransferase increased, blood bilirubin increased and palmar-plantar erythrodysaesthesia syndrome.

Although, as discussed above, the rate of grade ≥3 TEAEs was similar between treatments, the type of adverse events varied between treatment arms. Indeed, lenvatinib and sorafenib have safety profiles that are consistent with other VEGF/VEGFR-targeted therapies; however, the nature and extent of AEs differed between the treatments based on their mechanisms of action.

The most frequently reported TEAEs (>30% of patients) with lenvatinib were hypertension, diarrhoea, decreased appetite, and weight decreased. The most frequently reported TEAEs (>30% of patients) with sorafenib were palmar-plantar erythrodysaesthesia syndrome, diarrhoea, and hypertension.

The medicines council specifically highlights “that in patients with skin disorders, there is poor experience with the use of sorafenib and that lenvatinib may be used here. Specifically, fewer cases of ≥ 3 hand-foot skin reactions in the lenvatinib arm (3% versus 11%) are seen”

It is therefore apparent that lenvatinib offers a different side effect profile to sorafenib and this difference would benefit certain patients. Tolerability of each drug would depend on the patient and physicians may use lenvatinib instead of sorafenib based on individual patient characteristics.

Adverse events of interest

The medicines council highlights the rates of hepatic toxicity observed in the lenvatinib arm. The increased rate of hepatotoxicity (hepatic failure/ hepatic encephalopathy) with lenvatinib can to some extent be attributed to imbalances in baseline risk factors.

As presented in Table 1, hepatotoxicity was observed in 47.7% (227/476) of patients in the lenvatinib arm, and in 41.7% (198/475) of patients in the sorafenib arm. Taking into account treatment exposure, the hepatotoxicity rate was similar in both treatment arms (1.96 episodes/SY in the lenvatinib arm and 2.01 episodes in the sorafenib arm).

Table 1: Overview of Hepatotoxicity – All monotherapy Safety Sets

For Hepatotoxicity per CMQ, Subjects with at least 1:	HCC Randomized Safety Set		All HCC Lenvatinib Safety Set	Non-HCC Lenvatinib Monotherapy Safety Set
	Lenvatinib 8 or 12 mg (N=476) SY=324.2	Sorafenib 800 mg (N=475) SY=239.1	Lenvatinib 8 or 12 mg (N=496) SY=340.0	Lenvatinib (N=1327) SY=1544.7
TEAE, n (%)	227 (47.7)	198 (41.7)	236 (47.6)	309 (23.3)
TEAE, no. of episodes (episodes/SY)	635 (1.96)	481 (2.01)	659 (1.94)	619 (0.50)
TEAEs with maximum CTCAE Grade of,a n (%)				
1	43 (9.0)	39 (8.2)	47 (9.5)	111 (8.4)
2	60 (12.6)	48 (10.1)	62 (12.5)	122 (9.2)
≥3	124 (26.1)	111 (23.4)	127 (25.6)	76 (5.7)
3	89 (18.7)	91 (19.2)	92 (18.5)	67 (5.0)
4	18 (3.8)	16 (3.4)	18 (3.6)	4 (0.3)
5	17 (3.6)	4 (0.8)	17 (3.4)	5 (0.4)
SAE, n (%)	71 (14.9)	34 (7.2)	73 (14.7)	19 (1.4)
SAE, no. of episodes (episodes/SY)	97 (0.30)	40 (0.17)	100 (0.29)	25 (0.02)
TEAE leading to treatment discontinuation, n (%)	26 (5.5)	14 (2.9)	27 (5.4)	11 (0.8)
TEAE leading to study drug modification,b n (%)				
Dose Reduction	35 (7.4)	20 (4.2)	36 (7.3)	25 (1.9)
Dose Interruption	58 (12.2)	45 (9.5)	58 (11.7)	50 (3.8)

Data cutoff date for HCC Randomized and All HCC Lenvatinib Safety Sets: 13 Nov 2016. Data cutoff date for Non-HCC Lenvatinib Monotherapy Safety Set: 01 Sep 2016 (for ongoing studies). In the Non-HCC Lenvatinib Monotherapy Safety Set, 85% of subjects received a starting dose of 24 mg QD. Serious AEs include any events that met the criteria for seriousness, whether fatal or nonfatal. For each row category, a subject with 2 or more AEs in that category was counted only once. AE Rate (episode/SY) = total occurrence of TEAE episodes (n) divided by the total exposure (SY) for the specified treatment group. AE = adverse event; CMQ = customized MedDRA query; CTCAE = Common Terminology Criteria for Adverse
Events; HCC = hepatocellular carcinoma; ISS = Integrated Summary of Safety; MedDRA = Medical Dictionary for Regulatory Activities; QD = once daily; SAE = serious adverse event; SY = subject year; TEAE = treatment emergent adverse event.
a: If a subject had more than 1 TEAE, the subject was only counted once at the maximum grade.
b: Study drug modification includes dose reduction or interruption. A subject could be counted in both categories if the subject had TEAEs leading to both dose interruption and dose reduction.

It is notable that the percentage of subjects with cirrhosis at baseline per the IIR was higher in subjects with hepatic encephalopathy than in the overall population. Lenvatinib-treated subjects who developed hepatic encephalopathy, particularly within 30 days of starting study drug, had worse baseline liver disease than subjects in the lenvatinib arm overall and sorafenib-treated subjects who developed hepatic encephalopathy. Baseline characteristics included higher mean/median ammonia concentration, greater frequency of MPVI, greater proportion of subjects with a CP score ≥6 (including 2 subjects with the score of 7), greater liver tumour burden (measured by sums of the diameters) and cirrhosis. Most subjects had either Grade 0 or Grade 1 baseline AST, ALT and ALP levels and no correlation with the occurrence of hepatic encephalopathy was seen.

In addition, no significant relationship between lenvatinib exposure and hepatic encephalopathy was detected within the exposure range of the REFLECT study.

An observational clinical trial (post-authorisation safety study [PASS] category 3 study in the risk-management plan) will be performed to further characterise safety (mainly hepatic-related events). Accurate reporting of baseline disease-related, other baseline characteristics and AEs in this study would allow further correlative analysis of risk factor for hepatic-related toxicity.

Finally, and as stated in the EPAR assessment report, the overall benefit/risk of Lenvima as monotherapy is positive for the treatment of adult patients with advanced or unresectable hepatocellular carcinoma who have received no prior systemic therapy.

In conclusion, lenvatinib and sorafenib have safety profiles that are consistent with other VEGF/VEGFR-targeted therapies. The nature and extent of AEs differed between treatments based on their mechanisms of action. Significantly, lenvatinib has a different side effect profile than sorafenib (e.g. fewer cases of hand-foot skin reactions) which will provide a clinical benefit to certain patients (e.g. those with skin disorders), who currently have no other treatment options.

2.3. Progression-free survival

The primary analysis of progression-free survival was conducted based on FDA preferred analysis methods (5) where patients were censored when they discontinued treatment for any reason other than disease progression. The primary analysis was accepted by the EMA and was included in the lenvatinib summary of product characteristics.

PFS according to EMA censoring rules

A sensitivity analysis (presented in Table 2) was conducted according to EMA censoring rules (6), where all progressive disease and deaths were considered as events (i.e. patients were not censored at discontinuation if there was one or more missed visits, treatment discontinuation, or new anti-cancer treatment). The results of this sensitivity analysis (median PFS 7.3 months in the lenvatinib arm and 3.7 months in the sorafenib arm [HR: 0.72; 95% CI: 0.63, 0.83; p<0.00001]) were consistent with the primary PFS analysis based on FDA censoring guidance (median PFS 7.4 months in the lenvatinib arm and 3.7 months in the sorafenib arm [HR: 0.66; 95% CI: 0.57, 0.77; p<0.00001]).

These results confirm the statistically significant improvement in progression-free survival of lenvatinib compared to sorafenib.

Table 2: Progression-free survival sensitivity analysis based on randomisation stratification factors and treating all progressive disease and deaths as events – Full Analysis Set

	Lenvatinib N=478	Sorafenib N=476
Patients with events, n (%)	424 (88.7)	431 (90.5)
Progressive disease	329 (68.8)	374 (78.6)
Death	95 (19.9)	57 (12.0)
Censored patients, n (%)	54 (11.3)	45 (9.5)
No baseline tumour assessment	1 (0.2)	0
No post-baseline tumour assessment	6 (1.3)	3 (0.6)
No progression at the time of data cut-off	43 (9.0)	39 (8.2)
No progression at the time of consent withdrawal	4 (0.8)	3 (0.6)
Progression-free survival (months)*		
Median (95% CI)	7.3 (5.8, 7.5)	3.7 (3.6, 4.7)
Q1 (95% CI)	3.6 (3.4, 3.6)	1.9 (1.8, 1.9)
Q3 (95% CI)	13.2 (11.3, 14.7)	9.0 (7.4, 9.2)
Progression-free survival rate (%) (95% CI)[†] at		
6 Months	54.1 (49.5, 58.5)	36.1 (31.8, 40.5)
12 Months	28.6 (24.6, 32.9)	16.9 (13.6, 20.5)
18 Months	13.1 (10.1, 16.5)	11.3 (8.5, 14.4)
24 Months	6.9 (4.7, 9.8)	8.0 (5.7, 10.9)
Stratified cox model hazard ratio (95% CI)[‡,§]	0.72 (0.63, 0.83)	
Stratified log-rank test p-value[§]	p<0.00001	

*Quartiles are estimated by Kaplan-Meier method, and the 95% confidence intervals are estimated with a generalised Brookmeyer and Crowley method; †PFS rate and 95% CI were calculated using the Kaplan-Meier product-limit method and the Greenwood Formula; ‡Hazard ratio is for lenvatinib vs sorafenib, based on a Cox model including treatment group as a factor; §Stratified by region (Region 1: Asia-Pacific; Region 2: Western regions), macroscopic portal vein invasion or extrahepatic spread or both (yes, no), ECOG PS (0, 1) and body weight (<60 kg, ≥60 kg);

Abbreviations: CI, confidence interval; PD, progressive disease; PFS, progression-free survival; Q, quartile.

2.4. Health-related quality of life (HRQoL)

Assessments of HRQoL scores were performed using the generic cancer HRQoL instrument (EORTC QLQC30), the HCC-specific module (EORTC QLQ-HCC18), and the generic HRQoL instrument, EQ-5D. During the Randomization Phase, the EORTC QLQ-C30, EORTC QLQ-HCC18, and EQ-5D were administered at Baseline, Day 1 of each cycle after Cycle 1, and at the off-treatment visit. During the Extension Phase, the EORTC QLQ-C30, EORTC QLQ-HCC18, and EQ-5D were administered on Day 1 of each treatment and during the off-treatment visit.

Compliance was high (>95%) and consistent for all measures throughout the course of the Randomisation phase (7).Time-to-symptom worsening (TSW) hazard ratio results are reported for all EORTC QLQ-C30, EORTC QLQ-HCC18 domains and EQ-5D visual analogue scale (VAS) and health utility index (HUI). The median months to clinically meaningful worsening for the EQ-5D health utility index (HUI) and visual

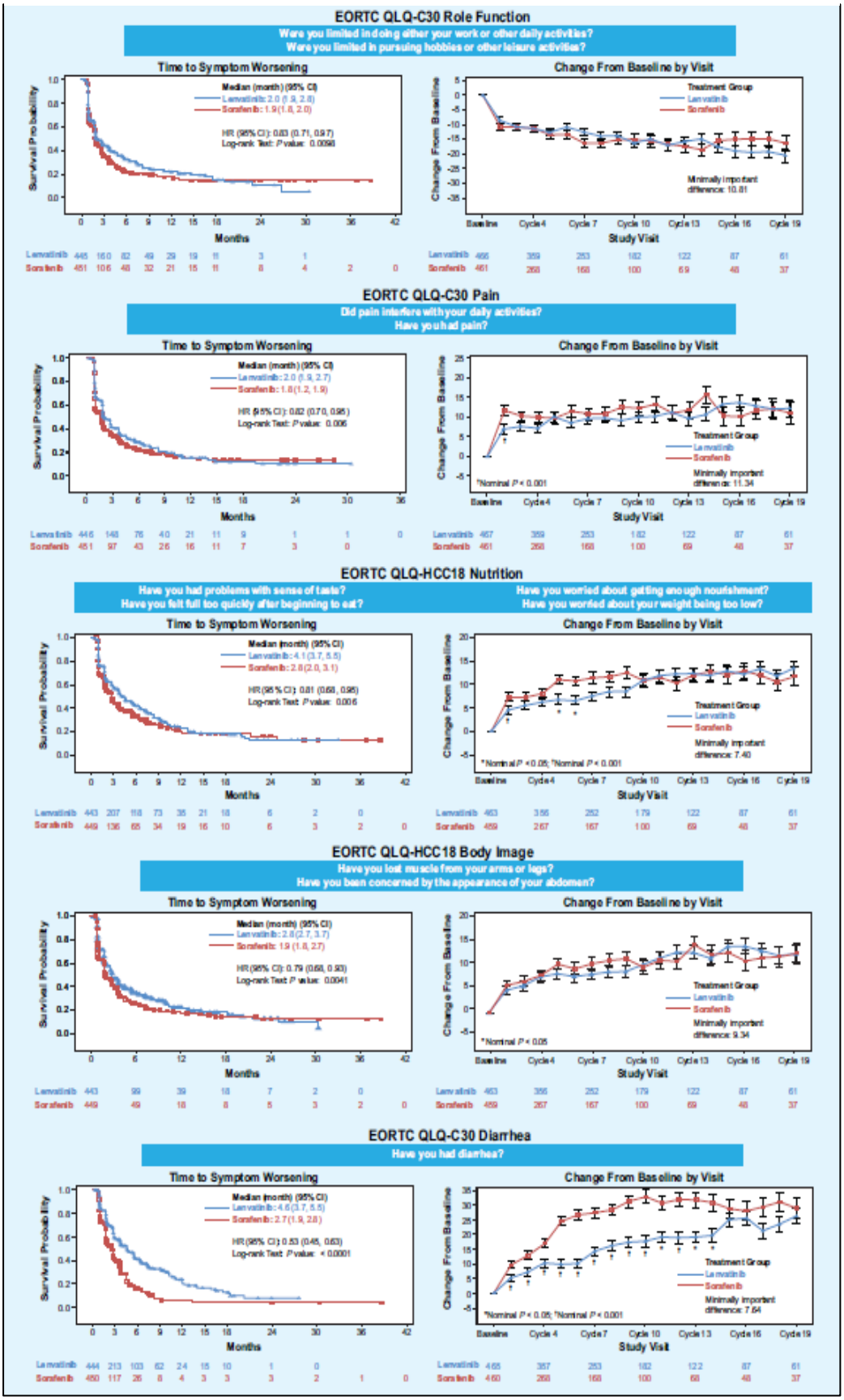
analogue scale (VAS) domains were numerically higher and in favour of the lenvatinib arm, but were nonsignificant (P > 0.05) (8).

For most domains, the impact on HRQoL was generally similar between lenvatinib and sorafenib. There were no nominally significant improvements in any of the HRQoL domains with sorafenib compared to lenvatinib. Domains which did demonstrate a statistically significant delay in TSW in favour of lenvatinib were role functioning, pain, diarrhea, (EORTC QLQ-C30), nutrition and body image (EORTC QLQ-HCC18) (9).

- QLQ-C30 domains (median month, HR, p-value [log-rank test]):
  - Role Functioning: 2.0 versus 1.9 months in the lenvatinib and sorafenib arms, respectively.
    HR (95% CI): 0.83 (0.71, 0.97), p = 0.0098
  - Pain: 2.0 versus 1.8 months, respectively
    HR (95% CI): 0.82 (0.70, 0.95), p = 0.0060
  - Diarrhoea: 4.6 versus 2.7 months, respectively
    HR (95% CI): 0.53 (0.45, 0.63), p < 0.0001
- QLQ HCC18 domains (median month, HR, p-value [log-rank test]):
  - Body Image: 2.8 versus 1.9 months, respectively
    HR (95% CI): 0.79 (0.68, 0.93), p = 0.0041
  - Nutrition: 4.1 versus 2.8 months, respectively;
    HR: 0.81 (0.68, 0.95), p = 0.0060
  - All other domains were similar between treatment groups (p > 0.05).

These results confirm that for most domains, the impact on HRQoL was generally similar between lenvatinib and sorafenib. Patients on lenvatinib experienced statistically significant and clinically meaningful delays in deterioration in role function, general cancer pain, diarrhea, nutrition, and body image versus sorafenib.

Figure 1: Time-to-symptom worsening and change from baseline by visit for selected EORTC QLQ-C30 & EORTC QLQ-HCC18 domains (Vogel, 2017)



3. Treatment guidelines

Lenvatinib is recommended as a first-line, systemic therapy in both the EASL and ESMO guidelines:

- Lenvatinib has been shown to be non-inferior to sorafenib and is also recommended in first-line therapy for HCC given its approval. It is recommended for patients with well-preserved liver function (Child-Pugh A class), good performance status and with advanced tumours – BCLC-C without main portal vein invasion – or those tumours progressing upon or unsuitable for loco-regional therapies. Strength of evidence was considered to be high; recommendation strong (10)

- Lenvatinib showed non-inferiority efficacy compared with sorafenib and can be considered in patients with advanced HCC without main portal vein invasion and with ECOG PS 0–1 as a front-line systemic treatment (11)

4. Other considerations

4.1. Position of lenvatinib in treatment pathway

In the REFLECT trial, around 50% of patients had post-treatment anti-cancer therapy (43.1% in the lenvatinib arm, 51.1% in the sorafenib arm). Therefore, a significant number of patients do not undergo post-treatment anti-cancer therapy, and should be given the opportunity to get the best possible treatment option as a first line treatment.

From the REFLECT trial, lenvatinib showed a statistically significant and clinically meaningful benefit in terms of progression-free survival (PFS), time-to progression (TTP), objective response rate (ORR), and the HRQoL domains of role functioning, pain, diarrhoea, body image, compared with sorafenib. As stated above in section 2.2, there are also significant differences in the side-effect profile of lenvatinib and sorafenib, and the choice of treatment will depend on individual patient characteristics. Therefore, lenvatinib offers clear benefits over sorafenib and represents an important treatment option for patients.

Further data on treatment sequencing from REFLECT will be published at the ASCO GI 2019 conference, with the title: “Subsequent anticancer medication following first-line lenvatinib: A post hoc responder analysis from the phase 3 REFLECT study in unresectable hepatocellular carcinoma”

4.2. Unmet need

Treatment options for advanced HCC are limited and sorafenib is currently the only EMA approved targeted systemic therapy for the first-line treatment of HCC. Lenvatinib is expected to be used as an alternative to sorafenib within its licensed indication. Since the approval of sorafenib in 2006, there have been no new first-line therapies approved for advanced HCC. Several other investigational therapies have failed to meet the endpoints of non-inferiority or superiority for OS compared with sorafenib. Median survival for patients with advanced HCC is less than one year; 4–8 months if untreated and 6–11 months with sorafenib treatment (12). There is therefore a clear unmet need for new treatments which delay progression and improve survival without negatively impacting patients’ quality of life. The most appropriate treatment option should be provided to patients as early as possible; given the median survival for patients with advanced HCC is less than a year.

Lenvatinib has demonstrated a significantly improved PFS and a clear potential to improve OS (nominal superiority vs. sorafenib after adjustment for baseline imbalance in AFP, an established prognostic factor of HCC). Furthermore, the overall rate of response (ORR) in the lenvatinib arm was more than double the ORR in the sorafenib arm: 24.1% and 9.2%, respectively. The difference between the treatment arms was 14.8% (95% CI: 10.2, 19.4), and the odds ratio was 3.13 (95% CI: 2.15, 4.56), which was statistically significant (P<0.00001) in favor of lenvatinib treatment. Six subjects in the lenvatinib arm had a CR (1.3%) compared with 2 subjects (<1%) in the sorafenib arm, and 22.8% of lenvatinib compared with 8.8% of sorafenib subjects had PR. Stable disease occurred in 51.5% of subjects in the lenvatinib and 51.3% in the sorafenib arm.

The increased ORR to lenvatinib is relevant in clinical practice because lenvatinib is highly effective in reducing tumor size, and achievement of tumor downstaging facilitates the use of more curative treatments (e.g., resection, ablation, and superselective cTACE), which in turn improves patient survival even further (13,14).

In addition, lenvatinib and sorafenib have safety profiles that are consistent with other VEGF/VEGFR-targeted therapies; however, the nature and extent of adverse events (AEs) differed between the two agents based on their different mechanisms of action. The most frequently (>30% of patients) reported TEAEs were hypertension, diarrhoea, decreased appetite, and weight decreased with lenvatinib and palmar-plantar erythrodysaesthesia syndrome, diarrhoea, and hypertension with sorafenib. The AE profile of lenvatinib may be more favourable compared with sorafenib from a patient perspective due to lower rates of palmar plantar erythrodysaesthesia syndrome and diarrhoea, which can have a substantial impact for patients.

In conclusion, giving physicians and, most importantly, patients an alternative treatment option, depending on individual patient characteristics, will provide the opportunity for a personalised approach ensuring patients receive the most appropriate treatment as early as possible. Lenvatinib, with its distinctive side-effect profile, and statistically and clinically significant response rates in comparison to current standard of care, can provide a meaningful benefit to patients who currently have no other treatment options.

5. Appendices: Systematic literature review - Methodology

5.1. Information sources

5.1.1. Electronic databases

The electronic databases searched for the literature review are outlined in Table 3.

Table 3: Bibliographic databases included in literature review

Database	Platform	Span of search	Date searched
MEDLINE, MEDLINE In-Process and e-publications ahead-of-print	Ovid	From inception to the day prior to search	11th December 2018
Cochrane library; CENTRAL	Ovid	From database inception to October 2018	11th December 2018

Abbreviations: CENTRAL, Cochrane Central Register of Controlled Trials.

5.1.2. Hand-searching

Additional hand-searching of conference proceedings was conducted as a supplementary measure to identify relevant studies not captured by the electronic databases searched. The following conferences were searched from the last three years (2016-2018):

- Annual meeting of the American Society of Clinical Oncology (ASCO)
- Annual meeting of the European Society for Medical Oncology (ESMO)
- Annual Meeting of the American Association for the Study of Liver Diseases (AASLD)
- International Society for Pharmacoeconomics and Outcomes Research (ISPOR)

5.1.3. Search strings

Table 4: MEDLINE search string

#	Searches	Results
1	Liver Neoplasms/ or Carcinoma, Hepatocellular/	141015
2	(hepatocellular carcinoma* or carcinoma* hepatocellular or hepatoma* or liver carcinoma* or hepatocarcinoma or liver cell carcinoma* or primary carcinoma of liver or hepatic cancer).ti,ab.	106764
3	(((liver or hepato*) and (carcinom* or cancer* or neoplasm* or malign* or tumo*)) or HCC).ti,ab.	222222
4	or/1-3	278145
5	(unresect* or inoperable or advanced or metastatic).ti,ab.	564744
6	4 and 5	44073
7	(lenvatinib or lenvima).ti,ab.	315
8	6 and 7	42

Table 5: Cochrance CENTRAL search string

#	Searches	Results
1	Liver Neoplasms/ or Carcinoma, Hepatocellular/	2535
2	(hepatocellular carcinoma* or carcinoma* hepatocellular or hepatoma* or liver carcinoma* or hepatocarcinoma or liver cell carcinoma* or primary carcinoma of liver or hepatic cancer).ti,ab.	3372
3	(((liver or hepato*) and (carcinom* or cancer* or neoplasm* or malign* or tumo*)) or HCC).ti,ab.	8326
4	or/1-3	8933
5	(unresect* or inoperable or advanced or metastatic).ti,ab.	53184
6	4 and 5	3261
7	(lenvatinib or lenvima).ti,ab.	132
8	6 and 7	23

5.2. Eligibility criteria

The **P**opulation, **I**ntervention, **C**omparator(s), **O**utcomes and **S**tudy design (PICOS) elements used to assess study eligibility are shown in Table 6.

Table 6: Literature review inclusion criteria (PICOS)

Characteristic	Inclusion criteria
Population	Treatment naive adult (aged ≥18 years) patients with advanced, unresectable, or/and metastatic hepatocellular carcinoma
Interventions/comparators	Lenvatinib
Outcomes	• Overall survival (OS) • Progression free survival (PFS) • Tumor response rate: complete response (CR), partial response (PR), overall response rate (ORR) • Time to response, duration of response • Adverse events: Serious, leading to discontinuation, occurring in >=5% of patients • HRQoL
Study design	Randomised controlled trials, phase II or phase III
Language	English language
Date limits	Unlimited
Countries	Unlimited

Abbreviations: CR, Complete response; HRQoL, Health-related quality of life; ORR, Overall response rate, PFS, Progression free survival; PR, Partial response.

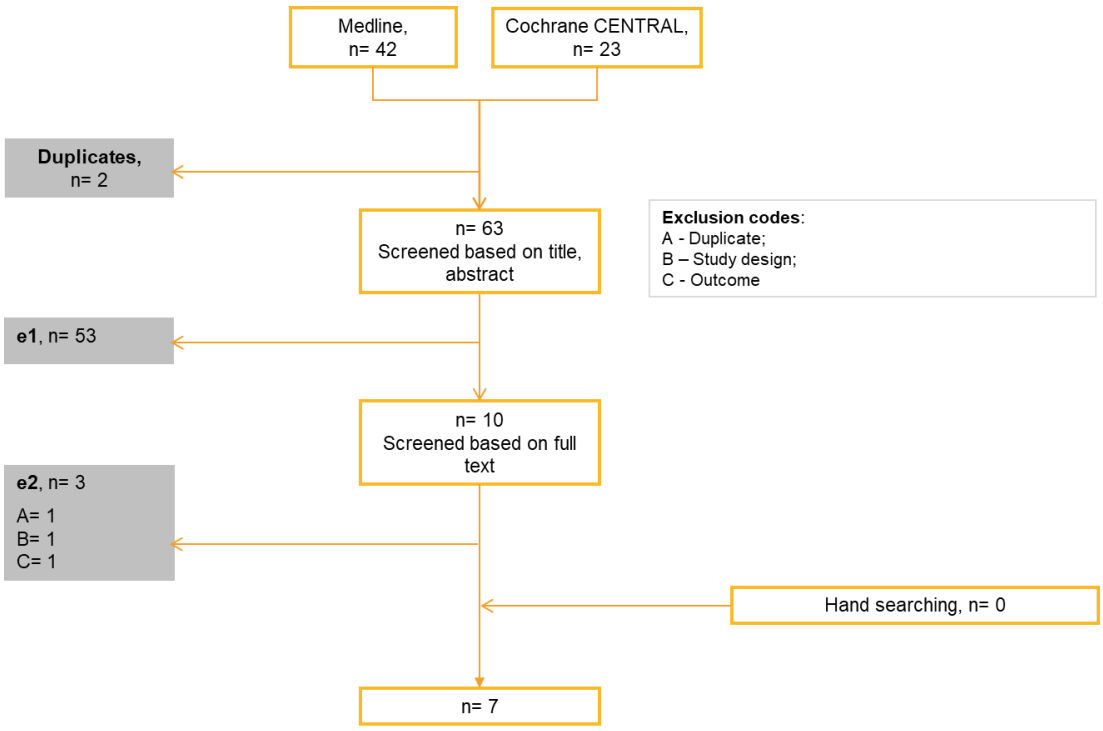
5.3. Results

5.3.1. Identification of included studies

The electronic database search identified 65 citations, of which 2 were identified as duplicates and excluded. The remaining 63 citations were screened on the basis of title and abstract, and 53 were then excluded leaving 10 citations to be screened on the basis of the full publications. During full text screening, three publications were subsequently excluded resulting in seven publications from the electronic database searches to be included in the literature review. Hand searching identified no additional citations that met the eligibility criteria. Therefore, a total of seven studies were identified for final inclusion in the literature review.

The overall flow of the studies through the literature review is illustrated in Figure 2. The full list of studies excluded on the basis of full publication is provided in section 5.5, along with the rationale for exclusion.

Figure 2: PRISMA flow diagram



5.4. List of included studies

A full list of the included studies is provided in Table 7.

Table 7: List of included studies

	Reference
1	Han KH, Qin S, Piscaglia F, Park JW, Komov D, Ryoo BY, et al. Efficacy and safety of lenvatinib for unresectable hepatocellular carcinoma in patients with baseline hepatitis B virus (HBV). Hepatology. 2017;Conference: 68th annual meeting of the american association for the study of liver diseases, AASLD. 2017. United states 66(Supplement 1):740A-1A.
2	Hudgens S, Copher R, Meier G. Longitudinal analysis of adjusted EQ-5D utility score at baseline, progression-free survival, and progression for lenvatinib versus sorafenib. Value in health. 2018;Conference: 23rd annual meeting of the international society for pharmacoeconomics and outcomes research, ISPOR. 2018. United states 21(Supplement 1):S35.
3	Hudgens S, Copher R, Meier G. Evaluation of the disease-specific items on the EORTC in hepatocellular carcinoma patients treated with lenvatinib or sorafenib. Value in health. 2018;Conference: 23rd annual meeting of the international society for pharmacoeconomics and outcomes research, ISPOR. 2018. United states 21(Supplement 1):S37.
4	Hudgens S, Misurski D, Meier G. Time to clinically meaningful worsening in hepatocellular carcinoma patients treated with lenvatinib or sorafenib. Value in health. 2017;Conference: ISPOR 20th annual european congress. United kingdom. 20(9):A416.
5	Hudgens S, Misurski D, Meier G. Detrimental impact of toxicity on quality of life in hepatocellular carcinoma patients treated with lenvatinibor sorafenib. Value in health. 2017;Conference: ISPOR 20th annual european congress. United kingdom. 20(9):A411-A2.
6	Kudo M, Finn RS, Qin S, Han KH, Ikeda K, Piscaglia F, et al. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial. Lancet (london, england). 2018;391(10126):1163-73.
7	Vogel A, Qin S, Kudo M, Hudgens S, Yamashita T, Yoon J, et al. Health-related quality of life (HRQOL) and disease symptoms in patients with unresectable hepatocellular carcinoma (HCC) treated with lenvatinib (LEN) or sorafenib (SOR). Value in health. 2017;Conference: ISPOR 20th annual european congress. United kingdom. 20(9):A454-A5.

5.5. List of publications excluded based on full text review

A list of publications excluded based on full text review is provided in Table 8, along with the rationale for exclusion.

Table 8: List of publications excluded on full text review (n=3)

	Reference	Rationale for exclusion
1	Cheng AL, Finn RS, Qin S, Han KH, Ikeda K, Piscaglia F, et al. Phase 3 trial of lenvatinib (LEN) vs sorafenib (SOR) in first-line treatment of patients (pts) with unresectable hepatocellular carcinoma (uHCC). Oncology research and treatment. 2017;Conference: jahrestagung der deutschen, osterreichischen und schweizerischen gesellschaften fur hamatologie und medizinische onkologie. 2017. Germany 40(Supplement 3):211.	Superseded by Kudo 2018
2	Finn RS, Kudo M, Cheng AL, Wyrwicz L, Ngan R, Blanc JF, et al. Analysis of serum biomarkers (BM) in patients (pts) from a phase 3 study of lenvatinib (LEN) vs sorafenib (SOR) as first-line treatment for unresectable hepatocellular carcinoma (uHCC). Annals of oncology. 2017;Conference: 42nd ESMO congress, ESMO. 2017. Spain 28(Supplement 5):v617.	Outcomes
3	Ikeda K, Kudo M, Kawazoe S, Osaki Y, Ikeda M, Okusaka T, et al. Phase 2 study of lenvatinib in patients with advanced hepatocellular carcinoma. J Gastroenterol. 2017;52(4):512-9.	Study design

6. References

1. Kudo M, Finn RS, Qin S, Han K-H, Ikeda K, Piscaglia F, et al. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial. The Lancet. 2018 Mar 24;391(10126):1163–73.

2. Llovet JM, Peña CEA, Lathia CD, Shan M, Meinhardt G, Bruix J, et al. Plasma biomarkers as predictors of outcome in patients with advanced hepatocellular carcinoma. Clin Cancer Res. 2012 Apr 15;18(8):2290–300.

3. Guideline on adjustment for baseline covariates in clinical trials. :11.

4. Single Technology Appraisal Lenvatinib for advanced, unresectable, untreated hepatocellular carcinoma [ID1089] Committee Papers [Internet]. [cited 2018 Dec 18]. Available from: https://www.nice.org.uk/guidance/gid-ta10150/documents/committee-papers

5. Food and Drug Administration. Guidance for industry clinical trial endpoints for the approval of cancer drugs and biologics. 2007. Biotechnology Law Report. 2007 Aug;26(4):375–86.

6. European Medicines Agency. Appendix 1 to the guideline on the evaluation of anticancer medicinal products in man. EMA/CHMP/27994/2008/Rev1 2011 [Internet]. [cited 2018 Dec 18]. Available from: https://www.ema.europa.eu/documents/scientific-guideline/appendix-1-guideline-evaluation-anticancer-medicinal-products-man_en.pdf

7. Hudgens S, Copher R, Meier G. PCN162 - Evaluation Of The Disease-Specific Items On The Eortc In Hepatocellular Carcinoma Patients Treated With Lenvatinib Or Sorafenib. Value in Health. 2018 May 1;21:S37.

8. Hudgens S, Misurski D, Meier G. Time To Clinically Meaningful Worsening In Hepatocellular Carcinoma Patients Treated With Lenvatinib or Sorafenib. Value in Health. 2017 Oct 1;20(9):A416.

9. Vogel A, Qin S, Kudo M, Hudgens S, Yamashita T, Yoon J, et al. Health-Related Quality of Life (HRQOL) and Disease Symptoms in Patients with Unresectable Hepatocellular Carcinoma (HCC) Treated with Lenvatinib (LEN) or Sorafenib (SOR). Value in Health. 2017 Oct 1;20(9):A454–5.

10. Galle PR, Forner A, Llovet JM, Mazzaferro V, Piscaglia F, Raoul J-L, et al. EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma. Journal of Hepatology. 2018 Jul;69(1):182–236.

11. Jelic S, Sotiropoulos GC, On behalf of the ESMO Guidelines Working Group. Hepatocellular carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology. 2010 May 1;21(Supplement 5):v59–64.

12. Verslype C, Rosmorduc O, Rougier P, ESMO Guidelines Working Group. Hepatocellular carcinoma: ESMO-ESDO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2012 Oct;23 Suppl 7:vii41-48.

13. Kudo M. Extremely High Objective Response Rate of Lenvatinib: Its Clinical Relevance and Changing the Treatment Paradigm in Hepatocellular Carcinoma. Liver Cancer. 2018 Sep;7(3):215–24.

14. Cheng A-L, Finn RS, Qin S, Han K-H, Ikeda K, Piscaglia F, et al. Phase III trial of lenvatinib (LEN) vs sorafenib (SOR) in first-line treatment of patients (pts) with unresectable hepatocellular carcinoma (uHCC). Journal of Clinical Oncology [Internet]. 2017 May 30 [cited 2018 Dec 18]; Available from: http://ascopubs.org/doi/abs/10.1200/JCO.2017.35.15_suppl.4001

Supplementary information – Lenvima HCC

Data has recently been made publicly available at the Gastrointestinal Cancers Symposium of the American Society of Clinical Oncology (ASCO GI) conference relevant to Lenvima treatment in hepatocellular carcinoma, and are summarized below. The relevant abstracts and posters are provided along with this document.

Subsequent anticancer medication following first-line lenvatinib (LEN): A posthoc responder analysis from the phase 3 REFLECT study (1)

A posthoc responder analysis of patients who received first-line LEN in the REFLECT trial and subsequent anti-cancer medication during survival follow up was conducted. In REFLECT, one third of the overall study population (156/478 patients randomized to LEN and 184/476 to sorafenib (SOR)) received subsequent anticancer medication. ECOG performance status and laboratory assessments, including liver function tests, were comparable between arms prior to subsequent treatments.

The results are summarized in Table 1 below. Among these patients, median overall survival (mOS) was 21 vs 17 months and ORR was 27.6% vs 8.7% for LEN vs SOR arms, respectively. In a subset analysis of LEN responders who received any subsequent anticancer medication (n=43), mOS was 26 mo (95% CI 18.5–34.6). For SOR responders who received any subsequent anticancer medication (n=16), mOS was 22 mo (95% CI, 14.6–NE). For LEN responders who subsequently received SOR (n=35), mOS was 26 mo (95% CI 18.2–34.6). These results show that there is data and experience in the use of subsequent anticancer medication following first-line LEN treatment in the REFLECT study.

Table 1: Subsequent anticancer medication following first-line treatment

Patients first line treatment	Median OS in patients who received ANY subsequent anticancer medication	Median OS of RESPONDERS who received ANY subsequent anticancer medication	Median OS of RESPONDERS who subsequently received SORAFENIB
lenvatinib	21 months	26 months (n=43)	26 months (n=35)
sorafenib	17 months	22 months (n=16)	N/A

Analysis of survival and objective response (OR) in patients with hepatocellular carcinoma in a phase III study of lenvatinib (REFLECT) (2)

The relationship between objective response (OR) and overall survival (OS) was analysed in the REFLECT trial. OR assessed by investigators per mRECIST were used to analyze the association between OR and OS of patients treated with lenvatinib (LEN) or sorafenib (SOR). The median OS of responders (CR or PR) was compared to that of nonresponders (SD, PD, or UNK/NE) irrespective of treatment.

Landmark analyses were performed by OR status at several fixed time points as sensitivity analyses, and the effect on OS was evaluated by Cox regression with OR as a time-

dependent covariate, with other prognostic factors. Median OS was 22.4 months for responders and 11.4 months for nonresponders. Hazard ratios (HR) of landmark analyses at 2, 4, and 6 months were 0.75 (95% CI, 0.57–0.98), 0.72 (95% CI, 0.56–0.92), and 0.73 (95% CI, 0.57–0.93). These results showed that in the REFLECT trial, OR was an independent predictor of OS in patients with HCC regardless of treatment.

References:

1. Alsina et al. Subsequent anticancer medication following first-line lenvatinib: A posthoc responder analysis from the phase 3 REFLECT study in unresectable hepatocellular carcinoma. [Internet]. [cited 2019 Jan 18]. Available from: https://meetinglibrary.asco.org/record/168787/abstract

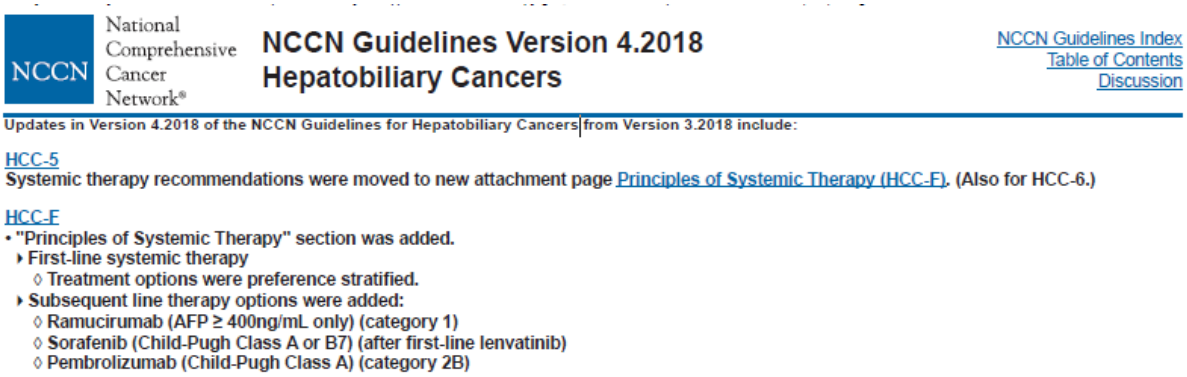
2. Kudo et al. Analysis of survival and objective response (OR) in patients with hepatocellular carcinoma in a phase III study of lenvatinib (REFLECT). [Internet]. [cited 2019 Jan 18]. Available from: https://meetinglibrary.asco.org/record/169298/abstract

Lenvima HCC treatment sequencing

1. Treatment pathway

- Sorafenib, strictly per indication, is not indicated as a first-line treatment only. According to the EPAR: “Nexavar is indicated for the treatment of hepatocellular carcinoma”

- NCCN guidelines have been updated and list sorafenib as an option after first-line lenvatinib treatment of HCC (recent update, see Figure 1 below)


National Comprehensive Cancer Network®

NCCN Guidelines Version 4.2018
Hepatobiliary Cancers

NCCN Guidelines Index
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Discussion

Updates in Version 4.2018 of the NCCN Guidelines for Hepatobiliary Cancers from Version 3.2018 include:

HCC-5
Systemic therapy recommendations were moved to new attachment page Principles of Systemic Therapy (HCC-F). (Also for HCC-6.)

HCC-F
- **"Principles of Systemic Therapy" section was added.**
  - **First-line systemic therapy**
    - **Treatment options were preference stratified.**
  - **Subsequent line therapy options were added:**
    - **Ramucirumab (AFP ≥ 400ng/mL only) (category 1)**
    - **Sorafenib (Child-Pugh Class A or B7) (after first-line lenvatinib)**
    - **Pembrolizumab (Child-Pugh Class A) (category 2B)**

Figure 1: Updated NCCN guidelines

2. Elligibility for second line treatment

- Given the poor survival rates (median overall survival of less than 1 year without treatment), it should be a priority to give the best treatment options as early as possible.
- Based on a real-world German study of over 2000 patients, (1) only 31% of patients go on to a second-line treatment. Therefore, few patients will receive second line treatment

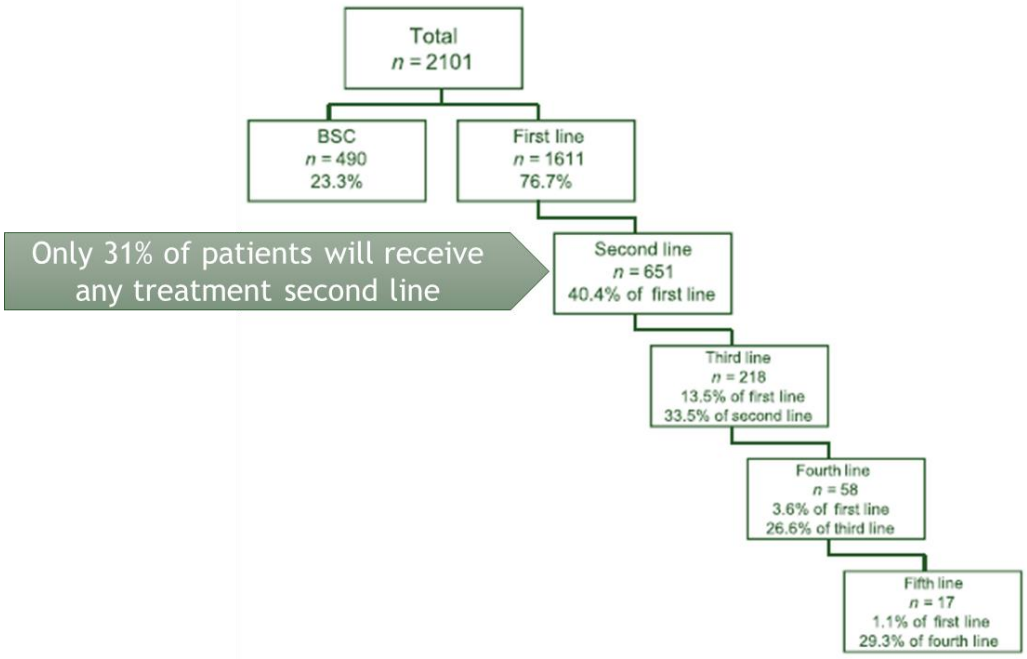

Figure 2: HCC treatment pathway

- The patient population eligible for second-line regorafenib treatment is limited.
    - Regorafenib is recommended *"as possible standard treatment for patients with hepatocellular carcinoma with performance status 0-1 and with liver function similar to Child Pugh A, as before treated with and have tolerated sorafenib"* according to the Medicine Council's report
    - In the real-world GIDEON study looking at the European subpopulation, only 64.8% of the patients had Child Pugh A status, with 45.4% with ECOG 0 status, and 39.2% of the patients with ECOG 1 status. (2)
- Lenvatinib is recommended as a first-line, systemic therapy in both the EASL and ESMO guidelines. (3)(4)

References:

1. Kirstein MM, Schweitzer N, Winter T, Lappas K, Graen N, Kunstmann I, et al. Patterns and challenges of treatment sequencing in patients with hepatocellular carcinoma: Experience from a German referral center. Journal of Gastroenterology and Hepatology. 2017;32(10):1730–8.

2. Daniele B, Croitoru A, Papandreou C, Bronowicki J-P, Mathurin P, Serejo F, et al. Impact of sorafenib dosing on outcome from the European patient subset of the GIDEON study. Future Oncology. 2015 Jul 9;11(18):2553–62.

3. Galle PR, Forner A, Llovet JM, Mazzaferro V, Piscaglia F, Raoul J-L, et al. EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma. Journal of Hepatology. 2018 Jul;69(1):182–236.

4. Vogel A, Cervantes A, Chau I, Daniele B, Llovet JM, Meyer T, et al. Hepatocellular carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2019 Jan 31;

Protokol for vurdering af den kliniske merværdi af lenvatinib til hepatocellulært karcinom

Handelsnavn	Lenvima
Generisk navn	Lenvatinib
Firma	Eisai
ATC-kode	L01XE29
Virkningsmekanisme	Lenvatinib er en multireceptortyrosinekinase inhibitor der hæmmer vækstfaktorreceptorerne VEGF 1–3, FGF 1–4, PDGF α og proto-onkogenerne KIT and RET.
Administration/dosis	Lenvatinib administreres oralt som tabletter. Dosis er 8 mg (ved kropsvægt < 60 kg) eller 12 mg (ved kropsvægt ≥ 60 kg) en gang dagligt. Behandlingen fortsættes så længe klinisk fordel observeres eller indtil der opstår uacceptable bivirkninger.
EMA-indikation	Lenvima is indicated as monotherapy for the treatment of adult patients with advanced or unresectable hepatocellular carcinoma (HCC) who have received no prior systemic therapy.
Godkendelsesdato Offentliggørelsesdato Dokumentnummer Versionsnummer	10. september 2018 11. september 2018 20138 1.0

Indhold

Forkortelser

BCLC:	*Barcelona Clinic Liver Cancer*
CHMP:	*Committee for Medicinal Products for Human Use*
CI:	Konfidensinterval
EMA:	*European Medicines Agency*
EORTC QLQ-C30:	*European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30*
EORTC QLQ-HCC18:	*European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Hepatocellular carcinoma 18*
ESMO:	*European Society for Medical Oncology*
GRADE:	System til vurdering af evidens (*Grading of Recommendations Assessment, Development and Evaluation System*)
HCC:	Hepatocellulært carcinom
HR:	*Hazard Ratio*
ITT:	*Intention to treat*
MeSH:	*Medical Subject Heading*
OR:	*Odds Ratio*
OS:	Samlet overlevelse (*Overall Survival)*
PICO:	Fokuserede forskningsspørgsmål baseret på Population, Intervention, Komparator og Outcome (effektmål)
RFA:	Radiofrekvensbehandling
RR:	Relativ Risiko
SAE:	*Serious Adverse Event*
SD	Standard afvigelse *(Standard deviation)*

1 Formål

Protokollen har til formål at definere de kliniske spørgsmål, der ønskes belyst i vurderingen af lenvatinib som mulig standardbehandling af patienter med hepatocellulært karcinom. I protokollen angives en definition af populationer, komparator og effektmål, der skal præsenteres i den endelige ansøgning, samt de metoder der ønskes anvendt til den komparative analyse. Arbejdet med protokollen er igangsat på baggrund af den foreløbige ansøgning vedrørende lenvatinib som er modtaget 25.05.2018.

Protokollen danner grundlaget for den endelige ansøgning for vurderingen af den kliniske merværdi af lenvatinib sammenlignet med dansk standardbehandling. Alle effektmål, der er opgivet i denne protokol skal besvares med en sammenlignende analyse mellem lenvatinib og sorafenib af både absolutte og relative værdier for den udspecificerede population i de angivne måleenheder (se tabel 1). Litteratursøgning og databehandling udføres som beskrevet i protokollen.

2 Baggrund

Primær leverkræft (hepatocellulært karcinom, HCC) er en mindre hyppigt forekommende kræftform i Danmark. Incidensen er for perioden 2011-2015 429 nye tilfælde pr. år (303 tilfælde hos mænd; 126 tilfælde hos kvinder) [1]. Udvikling af HCC forekommer oftest i patienter der har levercirrose [2]. Leverfunktionen hos patienter med leversygdomme såsom cirrose kan opdeles efter hvor god leverfunktionen er, og benævnes i kategorierne Child-Pugh A, B og C, fra bedst til værst leverfunktion.

Ved udgangen af 2015 havde 652 patienter HCC, hvilket afspejler den lave overlevelse for denne patientgruppe. Etårsoverlevelsen er således 37 % for mænd og 40 % for kvinder, mens femårsoverlevelsen kun er 9 % for mænd og 11 % for kvinder [1].

2.1 Nuværende behandling

HCC udgør et sygdomskontinuum, hvor Barcelona Clinic Liver Cancer (BCLC) stadiesystemet ofte bruges til stadieinddeling og ligeledes til at beslutte, hvilken behandling patienten har gavn af. Stadierne inddeles efter tumorstadie, leverfunktionsstatus, fysisk status og kræftrelaterede symptomer. Overordnet opdeles HCC-patienter i de med tidlig HCC, som har mulighed for kurativ terapi, de med intermediær og fremskreden sygdom, som har gavn af palliative behandlinger, og endeligt patienter der har terminal sygdom som tilbydes symptomatisk behandling [3].

Patienter med tidlig sygdom (BCLC A) vurderes med henblik på kirurgisk fjernelse af tumor, levertransplantation eller perkutan ablation (destruktion af kræftceller ved hjælp af kemiske substanser eller hyper-/hypotermi, hvor især radiofrekvensbehandling (RFA) har vundet indpas i Danmark) med mulighed for helbredelse og en femårsoverlevelse omkring 50-75 % afhængigt af behandlingen [3].

I Intermediærstadiet (BCLC stadie B) har patienterne store eller flere levertumorer og leverfunktion svarende til Child-Pugh A eller B, men de har ikke kræftrelaterede symptomer og har ikke makrovaskulær invasion eller ekstrahepatisk spredning. Patienter med sygdom i dette stadie vurderes med henblik på lokal kemoterapi i leveren (transarteriel kemoembolisering) [3].

I det fremskredne stadie (BCLC stadie C) har patienter stadig leverfunktion svarende til Child-Pugh A eller B, men kandiderer ikke længere til lokal behandling idet de har kræftsymptomer og/eller vaskulær invasion eller ekstrahepatisk spredning [3]. De vurderes således med henblik på 1. linje systemisk behandling med multikinaseinhibitoren sorafenib. Det anslås, at ca. 40 patienter behandles med sorafenib om året [4].

Den 30. januar 2018 anbefalede Medicinrådet regorafenib som mulig standardbehandling til 2. linje systemisk behandling til patienter med HCC, med performancestadie 0-1 og leverfunktion svarende til Child-Pugh A, som tidligere er behandlet med og har tolereret sorafenib [5].

Patienter med ekstensiv tumorinvolvering førende til dårlig alment helbred og/eller har leverfunktion svarende til Child-Pugh C behandles symptomatisk [3].

2.2 Lenvatinib

Lenvatinib er indiceret til behandling af patienter med HCC i fremskredent stadie eller patienter med inoperabel HCC, som ikke tidligere er behandlet systemisk.

Lenvatinib er en multi-receptortyrosinkinase inhibitor, der hæmmer vækstfaktorreceptorerne VEGF receptor 1-3, FGF receptor 1-4 og PDGF receptor α samt proto-onkogenerne RET og KIT, som alle er centrale for kræftudvikling.

Lenvatinib administreres peroralt som tabletter. Dosis er 8 mg (ved kropsvægt < 60 kg) eller 12 mg (ved kropsvægt ≥ 60 kg) en gang dagligt. Fagudvalget vurderer, at hovedparten at de danske HCC patienter vejer mere end 60 kg. Lenvatinib administreres så længe klinisk fordel observeres, eller indtil der opstår uacceptable bivirkninger.

Lenvatinib er i forvejen indiceret som monoterapi til behandling af voksne patienter med differentieret thyreoideakarcinom refraktært over for radioaktivt jod og i kombination med everolimus til behandling af voksne patienter med fremskreden nyrecellekarcinom efter én forudgående behandling rettet mod vaskulær endothelvækstfaktor [6,7].

3 Kliniske spørgsmål

De kliniske spørgsmål skal indeholde specifikation af patientgruppen, interventionen, alternativet/-erne til interventionen og effektmål.

3.1 Klinisk spørgsmål 1

1. *Hvad er den kliniske merværdi af lenvatinib til voksne patienter med fremskredent eller inoperabelt hepatocellulært karcinom, som er kandidater til systemisk behandling, sammenlignet med sorafenib?*

Population
Voksne patienter med HCC i fremskredent stadie og voksne patienter med inoperabel HCC. Patienterne har performance status 0-1 og bevaret leverfunktion svarende til Child-Pugh A og B(7).

Intervention
Lenvatinib som beskrevet i pkt. 2.2.

Komparator
400 mg sorafenib to gange dagligt så længe klinisk fordel observeres eller indtil der opstår uacceptable bivirkninger. Administreres peroralt som tabletter af 200 mg (2 tabletter 2 gange dagligt)

Effektmål
De valgte effektmål kan ses i tabel 1.

3.2 Valg af effektmål

Tabel 1 summerer de valgte effektmål, deres vigtighed, mindste klinisk relevante forskel og kategori.
For alle effektmål ønskes både absolutte og relative værdier, jævnfør ansøgningsskemaet. For de relative værdier vurderes den klinisk relevans (merværdi), jævnfør væsentlighedskriterierne beskrevet i Medicinrådets metodehåndbog for vurdering af nye lægemidler. De relative effektestimater kan angives i relativ risiko (RR), odds ratio (OR) eller hazard ratio (HR). Det skal begrundes i ansøgningen, hvis der afviges fra de ønskede effektmål.

Tabel 1. Oversigt over valgte effektmål. For hvert effektmål er angivet deres vigtighed. For kritiske og vigtige effektmål er desuden angivet den mindste klinisk relevante forskel samt indplacering i de fire kategorier (overlevelse, alvorlige symptomer og bivirkninger, livskvalitet og ikkealvorlige symptomer og bivirkninger).

Effektmål*	**Vigtighed**	**Kategori**	**Måleenhed**	**Mindste klinisk relevante forskelle (absolutte værdier)**
Samlet overlevelse Overall survival (OS)	Kritisk	Dødelighed	Median overlevelse (antal måneder)	3 måneder
			12 måneders overlevelse - Andel af patienter, der overlever i 12 måneder	8 procentpoint
			24 måneders overlevelse - Andel af patienter, der overlever i 24 måneder	4 procentpoint
Bivirkninger	Kritisk	Alvorlige symptomer og bivirkninger	Andel af patienter, der ophører behandlingen pga. bivirkninger	5 procentpoint
			Antal grad 3-5 bivirkninger pr. 100 patient-år	10 procent relativ forøgelse eller reduktion
			Kvalitativ gennemgang af bivirkningstyperne med henblik på at vurdere alvorlighed, håndterbarhed og hyppighed af bivirkningerne	Narrativ vurdering
			Andel af patienter der dosisreduceres	10 procentpoint
Progressionsfri overlevelse (PFS)	Vigtig	Alvorlige symptomer og bivirkninger	Median (antal måneder)	3 måneder

Livskvalitet	Vigtig	Helbredsrelateret livskvalitet	EORTC QLQ-C30 Summary score målt ved 1, 2 og 3 måneder samt en beskrivelse af hvilke domæner der driver en evt. forskel.	0,5 SD

*Hvis andet ikke er angivet ønskes data for effektmål med længst mulig opfølgningstid.

Hvis andet ikke er angivet, er de mindste kliniske relevante forskelle fastsat for en tidshorisont på 27,7 måneder svarende til den mediane opfølgningstid i REFLECT studiet, som forventes at danne basis for den samlede kliniske merværdi [8].

Kritiske effektmål

Samlet overlevelse (overall survival, OS)

Overlevelse er guldstandarden for at demonstrere klinisk effekt i cancerstudier, herunder HCC. Det er et patientrelevant effektmål, der belyser patienternes levetid efter en fast opfølgningstid. Overlevelse defineres som tiden fra randomisering eller opstart af behandling til død uanset årsag. Fagudvalget ønsker effektmålet opgjort som median overlevelse samt overlevelsesrater ved 12 og 24 måneder.

Median overlevelse

Fagudvalget vurderer, at 3 måneder er klinisk relevant. Referencen for dette er ESMO Magnitude of Clinical Benefit Scale [9], hvor en gevinst på ≥3 svarer til en grad 4 kategorisering. Denne skala er et redskab til at vurdere størrelsen af den kliniske værdi for kræftlægemidler, som er livsforlængende og ikke kurative, hvor grad 1 svarer til en triviel klinisk betydende effekt, og grad 4 er en væsentlig klinisk betydende effekt. Den valgte tærskelværdi er baseret på populationens forventede korte livslængde, som også er påvirket af underliggende komorbiditet, idet størstedelen af patienterne har levercirrose.

Overlevelsesrate 12 og 24 måneder

Fagudvalget vurderer, at en opgørelse over 12 måneders overlevelse er relevant, idet patienter, som lever efter 12 måneder, må betragtes som langtidsoverlevere. Den mindste klinisk relevante forskel vurderes at være 8 % og er derved sat lidt lavere end ESMO Magnitude of Clinical Benefit Scale. Dette skyldes, at hovedparten af patienterne også har levercirrose. Ligeledes ønskes data for overlevelse efter 24 måneder, og den mindste klinisk relevante forskel er sat til 4 %

Bivirkninger

Bivirkninger har betydning for den enkelte patients livskvalitet og kompliance. Fagudvalget ønsker bivirkninger ved lenvatinib belyst, ved andelen af patienter der ophører behandling pga. bivirkninger, og antallet af bivirkninger grad 3-5. Dernæst ønsker fagudvalget også at foretage en kvalitativ vurdering af bivirkningsprofilerne. Beskrivelser af de enkelte effektmål følger nedenfor.

Behandlingsophør pga. bivirkninger

Behandlingsophør på grund af bivirkninger ønskes belyst, idet dette er et mål for, hvor stor en del af patienterne, som oplever så alvorlige eller generende bivirkninger, at de må stoppe behandlingen og dermed muligvis ikke har fået gavn af at modtage lægemidlet. Fagudvalget vurderer, at der som regel skal meget til, før patienter ophører behandling, og at dette effektmål derfor er et mål for, hvor tålelig

behandlingen er. Fagudvalget vurderer, at en forskel på 5 procentpoint i andel af patienter, som ophører grundet bivirkninger, er klinisk relevant.

Fagudvalget ønsker desuden, at ansøger leverer data over hvilke 5 bivirkninger, som hyppigst giver anledning til ophør for både sorafenib og lenvatinib.

Antal grad 3-5 bivirkninger pr. 100 patient-år
Antallet af grad 3-5 bivirkninger vurderes at være relevant for vurderingen. Fagudvalget ønsker dette opgjort pr. 100 patient-år, ud fra den observation, at den mediane tid i behandling varierer væsentligt mellem de to arme i REFLECT studiet. Den mindste klinisk relevante forskel vurderes at være 10 procent relativ forøgelse eller reduktion sammenlignet med komparator. Mildere bivirkninger forventes at blive opfanget af livskvalitetsmål og vurderes ikke at være vigtigt for vurderingen af klinisk merværdi for effektmålet bivirkninger.

Kvalitativ gennemgang af bivirkninger
Fagudvalget vil desuden foretage en kvalitativ gennemgang af bivirkningstyperne med henblik på at vurdere, om der er forskel i bivirkningsprofilerne mht. alvorlighed, håndterbarhed og hyppighed af bivirkningerne. Ansøger bedes derfor bidrage med produktresumeet for lægemidlet.

Andelen af patienter hvor dosis reduceres
Dosis for både lenvatinib og sorafenib kan reduceres i tilfælde af lægemiddel-relateret toksicitet. Effektmålet er derfor et mål for sikkerhed af behandlingen, og fagudvalget vurderer, at det er et vigtigt effektmål. Det vurderes, at 10 procentpoint er en klinisk relevant forskel.

Vigtige effektmål

Progressionsfri overlevelse (PFS)
Progressionsfri overlevelse defineres som tiden fra randomisering til radiologisk eller klinisk progression eller død. Fagudvalget betragter PFS som et supplement til overlevelsesdata. Effektmålet er relevant, da det måler effekten af førstelinjebehandling, uanset hvilken andenlinjebehandling patienten modtager, hvorimod OS afspejler effekten af både første- og evt. andenlinjebehandling. Fagudvalget vurderer, at 3 måneder er den mindste klinisk relevante forskel.

Livskvalitet
Livskvalitet har stor betydning for den enkelte patient og er derfor et patientnært effektmål, der her vurderes at være af vigtig betydning, idet behandlingen er livsforlængende og ikke kurativ. Ligeledes forventes dette effektmål også at kunne give en indikation af, om bivirkningerne ved produktet påvirker patienternes livskvalitet. Fagudvalget ønsker at belyse livskvalitet med følgende værktøj; European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30).

EORTC QLQ-C30
EORTC QLQ-C30 er udviklet til at måle livskvaliteten hos patienter med kræft. EORTC QLQ-C30 er et spørgeskema med 30 spørgsmål, og i alt 15 outcomes herunder fem funktionsskalaer, tre symptomskalaer, seks enkeltstående symptomer/omstændigheder og en ”global” livskvalitetsskala [10]. Der anvendes en scoringsskala fra 0-100. Der findes også en opsummerings-score som er gennemsnittet af alle de ovenstående domæner bortset fra den ”globale” livskvalitetsscore og ”financial difficulties” [11]. Fagudvalget ønsker at se data for opsummerings-scoren (”summary score”). Fagudvalget er opmærksom på, at EORTC quality of life gruppen anbefaler at benytte summaryscoren som supplement til de øvrige 15

domæner. Såfremt der er en forskel på summaryscoren mellem komparator og intervention på de valgte tidspunkter, ønsker fagudvalget derfor en narrativ gennemgang af, hvilke domæner der driver forskellen. Et studie har vist, at for hver af de 15 domæner er en klinisk signifikant forskel omtrent svarende til 0,5 SD fra baselineværdien [12]. Desuden har en systematisk litteraturgennemgang vist at på flere af livskvalitetsskalaerne er en ændring i 0,5 SD fra baseline en klinisk relevant forskel [13]. Derfor fastsætter fagudvalget den mindste klinisk relevante forskel til 0,5 SD baseret på poolede data (for de to studiearme) ved baseline. Fagudvalget ønsker at se en opgørelse for livskvalitet ved 1, 2 og 3 måneder. Fagudvalget forventer, at bivirkninger som kan påvirke livskvaliteten, vil vise sig i starten af behandlingsforløbet. Dertil er den mediane behandlingstid i REFLECT-studiet relativ kort.

4 Litteratursøgning

Databaser for søgningen

Relevant litteratur søges i databaserne MEDLINE (via PubMed eller Ovid) og CENTRAL (via Cochrane Library).

Derudover skal EMAs European public assessment reports (EPAR) konsulteres for både det aktuelle lægemiddel og dets komparator(er).

Søgetermer

Søgningen skal inkludere det generiske navn og handelsnavnet for det aktuelle lægemiddel, som kombineres med termer for indikationen.

Søgningen skal som minimum indeholde termer, som er beskrivende for de områder, der angivet i tabellen herunder. Både indekseret (f.eks. Medical Subject Headings, MeSH) og fritekstsøgning skal anvendes.

Lægemiddel	**Indikation**
Lenvatinib	*Hepatocellular carcinoma*

I ansøgers foreløbige ansøgning beskrives en direkte sammenligning mellem lenvatinib og sorafenib. Fagudvalget finder det derfor kun relevant at gennemføre en systematisk søgning på lenvatinib.

De anvendte søgetermer, og hvordan de er blevet kombineret, dokumenteres separat for hver af de to databaser.

Kriterier for udvælgelse af litteratur

Der ekskluderes først på titel- og abstractniveau, dernæst ved gennemlæsning af fuldtekstartikler. Artikler, der ekskluderes ved fuldtekstlæsning, skal fremgå med forfatter, årstal og titel i en eksklusionsliste, hvor eksklusionen begrundes kort. Den samlede udvælgelsesproces skal afrapporteres ved brug af et PRISMA-flowdiagram (http://prisma-statement.org/PRISMAStatement/FlowDiagram.aspx).

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

Inklusions- og eksklusionskriterier:

Studier som ikke er randomiserede kliniske forsøg ekskluderes. Ligeledes ekskluderes fase 1 forsøg. Studier med anden population end den valgte ekskluderes. Studier, som ikke rapporterer mindst et af de kritiske eller vigtige effektmål ekskluderes.

Vurderingen af klinisk merværdi baseres på data fra publicerede fuldtekstartikler og data fra EMAs EPAR – Public assessment report. Data skal derudover stemme overens med protokollens beskrivelser. Upublicerede data og data fra f.eks. abstracts kan fremsendes og vil indgå i vurderingen, såfremt Medicinrådet finder, at de er nødvendige for at sikre en fair sammenligning. Data skal i så fald stamme fra de forsøg, hovedpublikationerne rapporterer fra, og ansøger skal acceptere, at Medicinrådet offentliggør dem i ansøgningsskemaet og i rapporten vedr. klinisk merværdi.

5 Databehandling/analyse

De inkluderede studier og baselinekarakteristikken af studiepopulationerne beskrives i Medicinrådets ansøgningsskema. Det skal angives, hvilke studier der benyttes til at besvare hvilke kliniske spørgsmål.

Al relevant data skal som udgangspunkt ekstraheres ved brug af Medicinrådets ansøgningsskema. Der skal udføres en komparativ analyse for hvert enkelt effektmål på baggrund af relevant data fra inkluderede studier. For hvert effektmål og studie angives analysepopulation (f.eks. intention-to-treat (ITT), per-protocol) samt metode. Resultater for ITT-populationen skal angives, hvis muligt, hvis komparative analyser ikke i udgangspunktet er baseret på denne population. Alle ekstraherede data skal krydstjekkes med de resultater, der beskrives i EPAR'en. Findes uoverensstemmelser, gives en mulig grund herfor.

Hvis ekstraherede data afviger fra de forhåndsdefinerede PICO-beskrivelser, specielt i forhold til præspecificeret population og effektmål, begrundes dette.

Hvis data for et effektmål ikke er tilgængelig for alle deltagere i et studie, skal der ikke gøres forsøg på at erstatte manglende data med en meningsfuld værdi. Det vil sige, at alle analyser udelukkende baseres på tilgængelige data på individniveau.

For effektmål (ORR, SAE, behandlingsstop pga. bivirkninger og ikkealvorlige bivirkninger), hvor det er naturligt at beregne både absolut og relativ forskel, vil den relative forskel være basis for statistiske analyser. Den absolutte forskel skal derefter beregnes, baseret på den estimerede relative forskel for et antaget niveau på hændelsesraten i komparatorgruppen. Det antagne niveau vil afspejle det forventede niveau i Danmark ved behandling med komparator (hvis relativ risiko (RR) = 0,5 og antaget andel med hændelse i komparatorgruppen er 30 %, da er den absolutte risiko reduktion (ARR) = 30 – 30 x 0,5 = 15 %-point).

Hvis der er mere end et sammenlignende studie, skal der foretages en metaanalyse for de effektmål, hvor det er metodemæssigt forsvarligt. Hvis der ikke foreligger sammenlignende studier, kan data eventuelt syntetiseres indirekte (evt. i form af formelle netværksmetaanalyser eller ved brug af Buchers metode), hvis intervention og komparator er sammenlignet med samme alternative komparator i separate studier. Medicinrådet forbeholder sig retten til at foretage sensitivitets- og subgruppeanalyser på baggrund af studiernes validitet og relevans.

For effektmål, hvor forskellige måleinstrumenter er brugt på tværs af de inkluderede studier, skal eventuelle metaanalyser baseres på standardized mean difference (SMD). Den estimerede SMD skal

omregnes til den foretrukne skala for effektmålet. Til dette formål anvendes medianen af de observerede standardafvigelser i de inkluderede studier.

Hvis det ikke er en mulighed at udarbejde metaanalyser (herunder netværksmetaanalyser), syntetiseres data narrativt. Studie- og patientkarakteristika samt resultater fra de inkluderede studier beskrives narrativt og i tabelform med angivelse af resultater pr. effektmål for både intervention og komparator(er). Forskelle i patientkarakteristika og studiekontekst (f.eks. geografi og årstal) mellem studier skal beskrives og vurderes for at afgøre, hvorvidt resultaterne er sammenlignelige.

Valget af syntesemetode (metaanalyse eller narrativ beskrivelse) begrundes, og specifikke analysevalg truffet i forhold til metoden skal fremgå tydeligt.

6 Andre overvejelser

Ligestilling

Fagudvalget vil i forbindelse med vurderingen af lenvatinib tage stilling til, om det er muligt at ligestille de to 1.linjebehandlingsmuligheder sorafenib og lenvatinib.

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8 Sammensætning af fagudvalg og kontaktinformation til Medicinrådet

Medicinrådets fagudvalg vedrørende leverkræft

Formand	*Indstillet af*
Britta Weber *Afdelingslæge*	Lægevidenskabelige Selskaber
Medlemmer	*Udpeget af*
Gerda Elisabeth Villadsen *Overlæge, ph.d., Klinisk lektor*	Udpeget af Region Midtjylland og inviteret af formanden
Aleksander Krag *Professor*	Udpeget af Region Syddanmark
Kirsten Kjeldgaard Vistisen *Overlæge*	Udpeget af Region Hovedstaden
Har ikke udpeget	Region Sjælland
Har ikke udpeget	Region Nordjylland
Mette Skalshøi Kjær *Overlæge, klinisk lektor*	Udpeget af Dansk Selskab for Gastroenterologi og Hepatologi
Mette Kudsk Brink *Farmaceut*	Udpeget af Dansk Selskab for Sygehusapoteksledelse
Amy Daugaard Asmussen *Kvalitetskoordinator, sygeplejerske, MHH*	Inviteret af formanden
Niels Jessen *Professor, overlæge*	Udpeget af Dansk Selskab for Klinisk Farmakologi
Tóra Haraldsen	Udpeget af Danske Patienter

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