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Medicinrådet

Baggrund for Medicinrådets anbefaling vedrørende tivozanib som mulig standardbehandling til nyrecellekarcinom

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	13. marts 2019
Ikrafttrædelsesdato	13. marts 2019
Dokumentnummer	43501
Versionsnummer	1.0

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Indhold

1 Lægemiddelinformationer

Lægemidlets oplysninger	
Handelsnavn	Fotivda
Generisk navn	Tivozanib
Firma	EUSA Pharma UK Ltd.
ATC-kode	L01XE34
Virkningsmekanisme	Vaskulær endotelial vækstfaktorreceptor (1, 2 og 3) inhibitor
Administration/dosis	1340 µg én gang dagligt i 21 dage efterfulgt af en pause på 7 dage. Behandlingen fortsættes til sygdomsprogression eller uacceptabel toxicitet.
EMA-indikation	1. linjebehandling af avanceret renalcellekarcinom til voksne patienter i god, intermediær eller dårlig prognosegruppe i henhold til IMCD's kriterier samt 2. linjebehandling til patienter, som er VEGFR- og mTOR-inhibitornaive og er progredieret efter én tidligere behandlingslinje med cytokinterapi.

2 Medicinrådets anbefaling

Medicinrådet **anbefaler** tivozanib som mulig standardbehandling til patienter med lokalavanceret inoperabel eller metastaserende nyrekræft (mRCC), der ikke tidligere har modtaget behandling.

Medicinrådet finder, at der er et rimeligt forhold mellem lægemidlets kliniske merværdi og omkostningerne ved behandling med tivozanib sammenlignet med sunitinib og pazopanib, som er dansk standardbehandling.

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

Hvad er den kliniske merværdi af tivozanib til voksne patienter med mRCC, der ikke tidligere har modtaget behandling?

3 Formål

Formålet med Baggrund for Medicinrådets anbefaling vedrørende tivozanib som mulig standardbehandling til patienter med lokalavanceret inoperabel eller metastaserende nyrekræft (mRCC), der ikke tidligere har modtaget behandling, er at skabe gennemsigtighed om det materiale, der ligger til grund for Medicinrådets anbefaling.

4 Baggrund

Renalcellekarcinom (RCC) er den mest almindelige form for nyrekræft og udgør ca. 85 % af alle tilfælde af kræft i nyrerne – og ca. 2 % af alle kræftformer i Danmark. Der diagnosticeres cirka 950 nye tilfælde årligt i Danmark. Cirka 20 % af de patienter, der opereres med helbredende sigte, får tilbagefald (lokalrecidiv) eller metastaser.

Patienter med mRCC inddeles i 3 prognosegrupper: god, intermediær og dårlig. Tivozanib er indiceret til 1. linjebehandling af voksne patienter med lokalavanceret inoperabel eller metastaserende nyrekræft (mRCC) og kan derfor anvendes til alle tre prognosegrupper. Årligt vil 150 patienter være kandidater til behandling med tivozanib.

Yderligere information findes i "Medicinrådets vurdering af klinisk merværdi for tivozanib til behandling af nyrecellekarcinom", bilag 4.

4.1 Sagsbehandlingstid og proces for Medicinrådets vurdering

Medicinrådet modtog den foreløbige ansøgning den 9. januar 2018, og protokollen blev sendt til ansøger den 14. april 2018.

Udkast til den endelige ansøgning blev modtaget den 11. september 2018, men ansøgningen blev af to omgange afvist pga. fejl og mangler. Ansøger sendte den version, der er godkendt som den endelige ansøgning, den 31. januar 2019. Medicinrådet har derfor gennemført vurderingen af tivozanib på 6 uger.

5 Medicinrådets vurdering af samlet klinisk merværdi

Medicinrådet vurderer, at tivozanib til patienter med lokalavanceret inoperabel eller metastaserende nyrekræft (mRCC), der ikke tidligere har modtaget behandling, giver en ikke-dokumenterbar klinisk merværdi sammenlignet med pazopanib og sunitinib (evidensens kvalitet er meget lav).

Medicinrådet tilslutter sig fagudvalgets vurdering af, at tivozanib, pazopanib og sunitinib forventes at være sammenlignelige, hvad angår effekt, sikkerhed og livskvalitet.

6 Høring

Ansøger har indsendt høringssvar den 26. februar 2019. Ansøger havde ikke bemærkninger til kategoriseringen af klinisk merværdi (Bilag 3).

7 Resumé af økonomisk beslutningsgrundlag

Behandling med tivozanib er forbundet med færre omkostninger sammenlignet med sunitinib og pazopanib, som er dansk standardbehandling (1. linjebehandling).

Ifølge AIP-priserne er der meromkostninger ved behandling med tivozanib. Amgros har indgået en aftale med ansøger om indkøb af tivozanib til en pris, der er lavere end AIP, og dermed er behandlingen med tivozanib forbundet med besparelser både sammenlignet med sunitinib og pazopanib.

Yderligere oplysninger vedrørende det økonomiske beslutningsgrundlag (Bilag 1 og 2).

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 nyrekræft

Formand	**Indstillet af**
Frede Donskov Professor, Overlæge, lektor, dr.med.	Lægevidenskabelige Selskaber og udpeget af Region Midtjylland
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Lennart Jønsson Patient/patientrepræsentant	Danske Patienter

Medicinrådets sekretariat

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Sekretariatets arbejdsgruppe Anne Sofie Gram (projekt- og metodeansvarlig) Pernille Koefod Arrevad (projektdeltager) Tina Klitmøller Sørensen Agander (projektdeltager) Ilse Linde (fagudvalgskoordinator) Jan Odgaard (biostatistiker) Kirsten Holdt Henningsen (teamleder)

10 Versionslog

Version	Dato	Ændring
1.0	13.03.2019	Godkendt af Medicinrådet.

11 Bilag

Bilagsliste:

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

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Beslutningsgrundlag til Medicinrådet

Dette dokument er Amgros' vurdering af tivozanib (Fotivda) som mulig standardbehandling til voksne patienter med lokalavanceret inoperabel eller metastaserende renalcellekarcinom (mRCC), der ikke tidligere har modtaget behandling. Vurderingen er baseret på lægemidlets gennemsnitlige inkrementelle omkostninger (baseret på SAIP) sammenholdt med Medicinrådets vurdering af den kliniske merværdi.

Dato for Medicinrådsbeslutning	13-03-2019
Firma	EUSA Pharma (ansøger)
Lægemiddel	Tivozanib (Fotivda)
Indikation	1. linje behandling af voksne patienter med lokalavanceret inoperabel eller metastaserende renalcellekarcinom (mRCC)

Amgros' vurdering

- Amgros vurderer at der **er** et rimeligt forhold mellem meromkostningerne og den kliniske merværdi for tivozanib (Fotivda) som mulig standardbehandling til voksne patienter med lokalavanceret inoperabel eller metastaserende renalcellekarcinom (mRCC) (1.linje behandling).

Overordnet konklusion

Medicinrådet har vurderet, at tivozanib (Fotivda) til patienter med mRCC (der ikke tidligere har modtaget behandling) sammenlignet med pazopanib (Votrient) og sunitinib (Sutent®) giver:

- Ikke-dokumenterbar klinisk merværdi

Fagudvalgets kliniske vurdering er, at tivozanib (Fotivda), pazopanib (Votrient) og sunitinib (Sutent®) er sammenlignelige, hvad angår effekt, sikkerhed og livskvalitet. Vurderingen er baseret på fagudvalgets kliniske erfaringer med lægemidlerne og lægemidlernes ens virkningsmekanisme (tyrosinkinasehæmmere).

Behandling med tivozanib (Fotivda) er ikke forbundet med meromkostninger sammenlignet med pazopanib (Votrient) og sunitinib (Sutent®). Amgros vurderer at forholdet mellem klinisk merværdi og omkostninger er acceptabelt.

Det skal dog bemærkes at omkostningerne er meget følsomme over for dosisjustering af lægemidlerne.

Amgros har indgået en aftale med EUSA Pharma om indkøb af tivozanib (Fotivda) til en SAIP, som er lavere end AIP. Konklusionen er baseret på SAIP for tivozanib (Fotivda).

Andre overvejelser

Amgros har indgået en aftale med EUSA Pharma, om køb af tivozanib (Fotivda) indtil 30-04-2019. Fra 01-05-2019 er der ny kontraktstart for tivozanib (Fotivda). Denne kontraktaftale kan forlænges indtil fagudvalget har udarbejdet en behandlingsvejledning indenfor området, hvor flere lægemidlers placering bliver beskrevet.

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
Patienter med lokalavanceret inoperabel eller metastaserende renalcellekarcinom (mRCC), der ikke tidligere har modtaget behandling.	Tivozanib (Fotivda)	Ikkedokumenterbar klinisk merværdi	Meget lav evidenskvalitet	Rimeligt

Supplerende informationer (resumé af resultaterne fra afrapporteringen)

Konklusion på omkostnings- og budgetkonsekvensanalyserne

Amgros' afrapportering af omkostnings- og budgetkonsekvensanalyser er baseret på AIP for tivozanib (Fotivda). Fortages analyserne på baggrund af SAIP og ikke på baggrund af AIP reduceres de inkrementelle omkostninger til fordel for tivozanib (Fotivda). 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 (AIP)

Behandling med tivozanib (Fotivda) er forbundet med meromkostninger (på AIP-niveau) sammenlignet med behandling med pazopanib (Votrient) og sunitinib (Sutent®) for patienter med lokalavanceret inoperabel eller metastaserende nyrekræft (mRCC), der ikke tidligere har modtaget behandling.

I nedenståe tabel 2 og 3 ses de inkrementelle omkostninger for tivozanib (Fotivda) og komparatorer for de to patientpopulationer.

Tabel 2: Gennemsnitlige behandlingsomkostninger for tivozanib (Fotivda) sammenlignet med pazopanib (Votrient), DKK, AIP.

	Fotivda (tivozanib)	Votrient (pazopanib)	Inkrementelle omkostninger
Lægemiddelomkostninger	297.586	212.173	**85.413**
Totale omkostninger	**297.586**	**212.173**	**85.413**

Tabel 3: Gennemsnitlige behandlingsomkostninger for tivozanib (Fotivda) sammenlignet med sunitinib (Sutent®), DKK, AIP.

	Fotivda (tivozanib)	Sutent® (Sunitinib)	Inkrementelle omkostninger
Lægemiddelomkostninger	297.586	253.459	**44.127**
Totale omkostninger	**297.586**	**253.459**	**44.127**

Amgros' afrapportering – Budgetkonsekvenser (AIP)

Amgros vurderer at anbefaling af tivozanib (Fotivda) som mulig standardbehandling vil resultere i budgetkonsekvenser på ca. 23 mio. DKK sammenlignet med komparatorerne.

TIVOZANIB (FOTIVDA)

RENALCELLEKARCINOM

AMGROS 19. februar 2019

AMGROS

OPSUMMERING

Baggrund

Tivozanib (Fotivda) er et lægemiddel, der er indiceret til 1.-linje behandling af voksne patienter med lokalavanceret inoperabel eller metastaserende renalcellekarcinom (mRCC). Ca. 300 nye patienter per år kandiderer til behandling af den ansøgte indikation i Danmark. Amgros' vurdering tager udgangspunkt i dokumentationen indsendt af EUSA Pharma.

Analyse

I analysen estimeres de gennemsnitlige omkostninger per patient og de samlede budgetkonsekvenser for regionerne forbundet med behandling med tivozanib (Fotivda) til patienter med lokalavanceret inoperabel eller metastaserende renalcellekarcinom (mRCC). I analyserne sammenlignes behandling med tivozanib (Fotivda) med behandling med pazopanib (Votrient) og sunitinib (Sutent®).

I analyserne i denne afrapportering anvendes AIP på tivozanib (Fotivda), sunitinib (Sutent®) og pazopanib (Votrient).

Inkrementelle omkostninger og budgetkonsekvenser

I det scenarie, som Amgros vurderer er mest sandsynligt er de gennemsnitlige meromkostninger pr. patient i behandling med tivozanib (Fotivda) sammenlignet med behandling med sunitinib (Sutent®) og pazopanib (Votrient) på hhv. 44.000 DKK og 85.000 DKK.

Analysens resultater påvirkes i altovervejende grad af omkostningerne forbundet med prisen på tivozanib (Fotivda). Resultaterne er derfor meget følsomme over for nuværende og fremtidige rabatter.

Amgros vurderer at budgetkonsekvenserne for regionerne per år ved anbefaling af tivozanib (Fotivda) som standardbehandling vil være ca. 23 mio. DKK per år.

Konklusion

Amgros kan konkludere, at behandling med tivozanib (Fotivda) er forbundet med meromkostninger sammenlignet med behandling med sunitinib (Sutent®) og pazopanib (Votrient). Meromkostningerne drives primært af prisen på tivozanib (Fotivda). Hvis der tages højde for dosisreduktion, vil meromkostningerne for tivozanib (Fotivda) øges.

Liste over forkortelser

AIP	Apotekernes indkøbpris
DKK	Danske kroner
DRG	Diagnose Relaterede Grupper
mRCC	Renalcellekarcinom
PFS	Progressionsfri overlevelse (progression free survival)

INDHOLD

LOG

Ansøgning	
Lægemiddelfirma:	EUSA Pharma
Handelsnavn:	Fotivda
Generisk navn:	Tivozanib
Indikation:	Renalcellekarcinom
ATC-kode:	L01XE34

Proces	
Ansøgning modtaget hos Amgros:	31-01-2019
Endelig rapport færdig:	20-02-2019
Sagsbehandlingstid fra endelig ansøgning:	20 dage
Arbejdsgruppe:	**Lianna Christensen** Line Brøns Louise Greve Dal Mark Friborg Pernille Winther Johansen

Priser

Alle lægemiddelpriser i denne afrapportering er på AIP-niveau. Amgros har ofte aftaler om rabatter på de analyserede lægemidler. Derfor vil analyser på AIP-niveau ikke altid afspejle regionernes faktiske omkostninger til anskaffelse af lægemidlerne. Da rabatterne varierer betragteligt på tværs af lægemidler, vil prisforskellene i afrapporteringen, ikke altid afspejle de faktiske prisforskelle.

Anbefalingerne i Amgros' beslutningsgrundlag, som sendes sammen med denne afrapportering, bygger på regionernes faktiske anskaffelsespriser (SAIP).

1 BAGGRUND

Tivozanib (Fotivda) er indiceret til 1.-linje behandling af voksne patienter med lokalavanceret inoperabel eller metastaserende renalcellekarcinom (mRCC). EUSA Pharma (herefter omtalt som ansøger) er markedsføringstilladelsesindehaver af tivozanib (Fotivda) og har den 31.01.2019 indsendt en ansøgning til Medicinrådet om anbefaling af tivozanib (Fotivda) 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 patienter med mRCC i form af de gennemsnitlige inkrementelle omkostninger pr. patient og de samlede budgetkonsekvenser for regionerne ved anbefaling af tivozanib (Fotivda) som standardbehandling. I analyserne sammenlignes behandling med tivozanib (Fotivda) med behandling med pazopanib (Votrient) og sunitinib (Sutent®).

1.2 Patientpopulation

Renalcellecarcinom (RCC) udgør omkring 85% af nyrekræfttilfælde i Danmark, og ca. 2 % af alle kræftformer (1). Ca. 900 patienter diagnosticeres årligt, hvoraf Medicinrådets fagudvalg vedrørende nyrekræft estimerer, at ca. 300 patienter med mRCC vil være egnet til behandling (2).

1.3 Behandling med tivozanib (Fotivda)

Nuværende 1.-linje førstevalgsbehandling af patienter med mRCC er pazopanib (Votrient), mens sunitnib (Sutent®) bør overvejes som 2. valg.

Indikation

Tivozanib (Fotivda) er indiceret til 1.-linje behandling af voksne patienter med metastaserende renalcellekarcinom (mRCC) (3) og til voksne patienter, som er VEGRF og mTOR pathway-hæmmernaive som følge af sygdomsprogression efter tidligere behandling af mRCC med cytokiner.

Virkningsmekanisme

Tivozanib er en tyrosin kinasehæmmer, som blokerer tre vaskulære endotelial vækstfaktorreceptorer (VEGFR-1, VEGFR-2 og VEGFR-3). VEGF øger celledeling og spiller en central rolle i dannelsen af nye blodkar i tumorvævet og blodkarrenes gennemtrængelighed. Tivozanib virker ved at blokere den VEGF-inducerede VEGFR-aktivering og dermed hæmme tumorvækst (4).

Dosering

Den anbefalede dosis tivozanib (Fotivda) er 1340 mikrogram én gang daglig i 21 dage efterfulgt af 7 dages pause. Behandlingen bør fortsættes, indtil patienten ikke længere har klinisk fordel af behandlingen, eller indtil der forekommer uacceptabel toksicitet. Når dosisreduktion er nødvendig, anbefales det at reducere til 890 mikrogram dagligt med samme behandlingsfrekvens - 21 dage efterfulgt af 7 dages pause (5).

1.3.1 Komparator

Medicinrådet har defineret pazopanib (Votrient) og sunitinib (Sutent®) som relevante komparatorer for tivozanib (Fotivda).

Den anbefalede dosis af sunitinib (Sutent) er 50 mg én gang dagligt indtaget oralt i 4 på hinanden følgende uger og derefter 2 ugers pause.

Den anbefalede dosis af pazopanib (Votrient) er 800 mg én gang daglig.

1.4 Medicinrådets kliniske spørgsmål

Medicinrådet har vurderet den kliniske merværdi for tivozanib til behandling af renalcellekarcinom (mRCC) sammenlignet med pazopanib (Votrient) og sunitinib (Sutent®) for følgende populationer:

- Voksne patienter med lokalavanceret inoperabel eller metastaserende renalcellekarcinom (mRCC)

2 VURDERING AF INDSENDT ØKONOMISK ANALYSE

I analysen af gennemsnitlige behandlingsomkostninger per patient sammenlignes behandling med tivozanib (Fotivda) med behandling med pazopanib (Votrient) og sunitinib (Sutent®) til voksne patienter med lokalavanceret inoperabel eller metastaserende renalcellekarcinom (mRCC)

2.1 Model, metode og forudsætninger

2.1.1 Modelbeskrivelse

Ansøger har indsendt en model for behandling af patienter i den nævnte population.

Der foreligger ingen studier, der direkte sammenligner tivozanib (Fotivda) med hhv. pazopanib (Votrient) og sunitinib (Sutent®). I modellen antages det, at effekten af tivozanib (Fotivda), pazopanib (Votrient) og sunitinib (Sutent®) er ens og at der ikke er nogen statistisk signifikant forskel i PFS. På baggrund af dette har ansøger udarbejdet en simpel sammenligning af de omkostninger, der er forbundet med behandlingen.

Amgros' vurdering

Ansøger har udarbejdet en analyse, hvor der ikke er forskel i behandlingslængden mellem tivozanib (Fotivda), pazopanib (Votrient) og sunitinib (Sutent®). Amgros har været i dialog med relevante regionsudpegede klinikere og fået verificeret, at denne antagelse virker plausibel. Amgros mener derfor, at ansøgers tilgang er rimelig.

Amgros vurderer, at modellen er acceptabel.

2.1.2 Analyseperspektiv

Analysen anvender et begrænset samfundsperspektiv. Tidshorisonten i analysen er sat til 12 måneder, da ansøger ikke finder forskel i behandlingslængden mellem lægemidlerne og vurderer at en længere tidshorisont kun vil have en mindre effekt på de inkrementelle omkostninger.

Amgros' vurdering

Amgros har været i dialog med relevante regionsudpegede klinikere og fået verificeret, at antagelsen om en behandlingslængde på ca. 12 måneder virker plausibel.

Amgros godtager analysens perspektiv og tidshorisont.

2.1.3 Omkostninger

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

Lægemiddelomkostninger

Alle lægemiddelpriser er hentet fra medicinpriser.dk og anvendes på AIP-niveau. Ressourceforbrug (dosering) er hentet fra de respektive SPC'er for de tre lægemidler. Tabel 1 illustrerer de lægemiddelpriser, som anvendes i analysen.

Tabel 1 Anvendte lægemiddelpriser, AIP (august 2018)

Lægemiddel	Styrke	Pakningsstørrelse	Pris (DKK)	Kilde
Sutent® (Sunitinib)	50 mg	28 stk.	31.682	Medicinpriser.dk
Votrient (pazopanib)	400 mg	60 stk.	18.944	Medicinpriser.dk
Fotivda (tivozanib)	1.340 mg	21 stk.	24.799	EUSA Pharma

Ansøger har kun medtaget styrker og pakningsstørrelser, der anvendes til startdosis og har derfor ikke taget højde for dosisreduktion. Alle tre lægemidler kan dosisreduceres ved uacceptable bivirkninger.
Ansøger antager at patienter i behandling behandles i alle 12 måneder og antager derfor 100 % compliance.

Andre omkostninger

Da alle tre lægemidler administreres af patienten selv har ansøger antaget, at der ikke er nogen forskel i administrations- og monitoreringsomkostninger mellem lægemidlerne.

Ansøger er bevidst om forskelle i bivirkninger mellem lægemidlerne, men angiver, at omkostninger til bivirkninger kun vil have en lille betydning på de inkrementelle omkostninger og disse er derfor udeladt af analysen.

På baggrund af dette har ansøger kun medtaget lægemiddelomkostninger i deres analyse.

Amgros' vurdering

Lægemiddelomkostninger

Amgros har været i dialog med klinikere og det vurderes at dosisjustering ofte anvendes i klinisk praksis. Amgros udarbejder derfor en følsomhedsanalyse hvor dosisjustering medtages.

Andre omkostninger

Amgros noterer sig, at flere patienter i behandling med tivozanib (Fotivda) oplever hypertension end med pazopanib (Votrient) og sunitinib (Sutent). Til gengæld har patienter i behandling med tivozanib (Fotivda) væsentlig mindre diarre, træthed og tilfælde af hånd- og fod-syndrom end patienterne i behandling med henholdsvis pazopanib (Votrient) og sunitinib (Sutent).

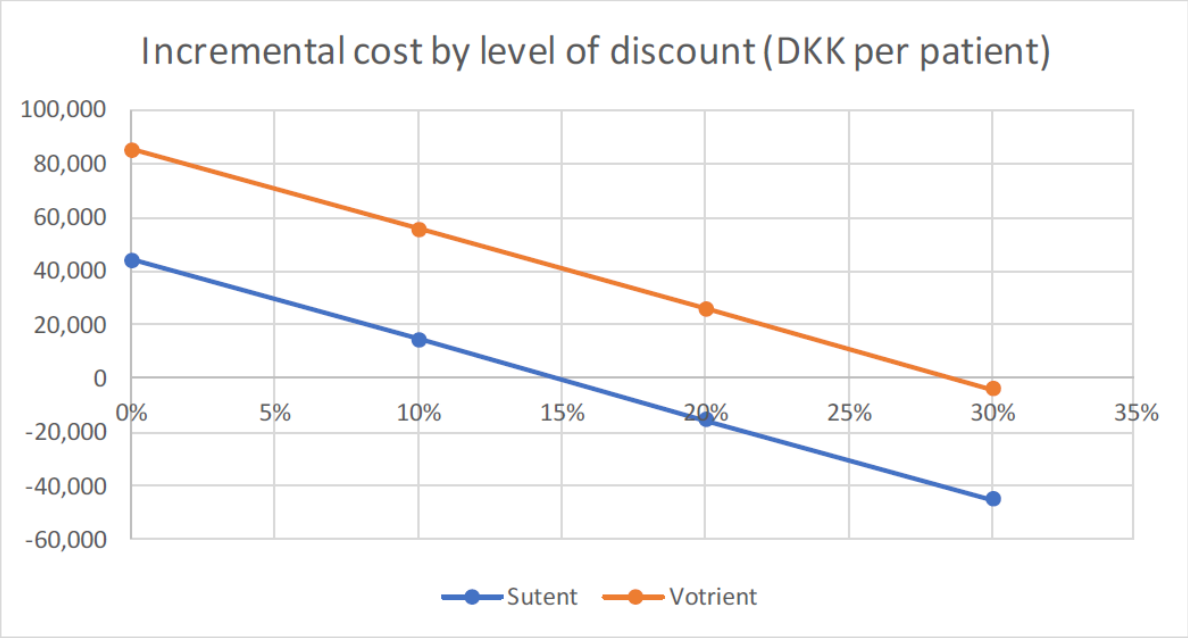
Amgros har været i dialog med regionsudpegede klinikere om de behandlingsrelaterede bivirkninger og det vurderes at der ikke er betydelige forskelle i ressourcetræk og omkostninger.

Amgros accepterer tilgangen.

2.2 Følsomhedsanalyser

Ansøger har udarbejdet én følsomhedsanalyse, hvor AIP-prisen på tivozanib (Fotivda) varieres. Således kan man se hvilken effekt prisen har på de inkrementelle omkostninger ved forskellige prisniveauer.

Figur 1: Inkrementelle omkostninger ved forskellige rabatniveauer



Amgros' vurdering

Amgros vurderer at følsomhedsanalysen er relevant, men mener at ansøger burde have inkluderet en følsomhedsanalyse, der illustrer forskelle i omkostninger ved dosisreduktion.

Amgros udarbejder derfor egen følsomhedsanalyse.

3 RESULTATER

3.1 Ansøgers hovedanalyse

Ansøgers hovedanalyse resulterer i gennemsnitlige meromkostninger per patient på ca. 85.000 DKK sammenlignet med pazopanib (Votrient) og ca. 44.000 DKK sammenlignet med sunitinib (Sutent).

Resultaterne fra ansøgers hovedanalyse præsenteres i tabel 2 og tabel 3.

Tabel 2 Resultat af ansøgers hovedanalyse, gns. omkostninger per patient, DKK, AIP

	Fotivda (tivozanib)	Votrient (pazopanib)	Inkrementelle omkostninger
Lægemiddelomkostninger	297.586	212.173	**85.413**
Totale omkostninger	**297.586**	**212.173**	**85.413**

Tabel 3 Resultat af ansøgers hovedanalyse, gns. omkostninger per patient, DKK, AIP

	Fotivda (tivozanib)	Sutent (Sunitinib)	Inkrementelle omkostninger
Lægemiddelomkostninger	297.586	253.459	**44.127**
Totale omkostninger	**297.586**	**253.459**	**44.127**

Amgros' vurdering

Amgros mener at ansøgers model er en stærk forsimpling af behandlingsforløbet med tivozanib (Fotivda) og komparatorerne, men accepterer ansøgers hovedanalyse, da de antagelser ansøger har valgt virker plausible. Ansøgers hovedanalyse afspejler derfor Amgros' hovedanalyse.

3.1.2 Amgros' følsomhedsanalyser

Amgros har udarbejdet følsomhedsanalyser, der belyser betydningen af dosisreduktion på AIP.

Eftersom det har betydning for resultatet, hvor stor en andel af patienterne der får dosisjustering, har Amgros undersøgt betydningen af denne parameter. Amgros har udarbejdet en følsomhedsanalyse, hvor andelen af patienter der kræver dosisreduktion antages at være hhv. 10 % og 30 %. Disse antagelser er fastsat i samarbejde med relevante klinikere.

Følsomhedsanalysen viser at dosisreduktion kun har betydning for omkostningerne for pazopanib (Votrient) og sunitinib (Sutent), da lægemidlerne på AIP-niveau har forskellig pris på pakningsstørrelser. Dette er ikke tilfældet for tivozanib (Fotivda) på AIP-niveau. Amgros har illustreret resultaterne i nedenstående tabel 4 og 5.

Tabel 4 Resultat af Amgros' følsomhedsanalyser, DKK

	Fotivda (tivozanib)	Votrient (pazopanib)	Meromkostninger ved Fotivda (tivozanib)
Hovedanalyse	**297.586**	**212.173**	**85.413**
Dosisreduktion 10 %	297.586	196.260	**101.326**
Dosisreduktion 30 %	297.586	164.434	**133.152**

Tabel 5 Resultat af Amgros' følsomhedsanalyser, DKK

	Fotivda (tivozanib)	Sutent (Sunitinib)	Meromkostninger ved Fotivda (tivozanib)
Hovedanalyse	**297.586**	**253.459**	**44.127**
Dosisreduktion 10 %	297.586	247.123	**50.463**
Dosisreduktion 30 %	297.586	234.450	**63.136**

Som det fremgår af tabel af tabel 4 og 5, så har det betydning for resultatet, hvorvidt patienter får dosisjustering, samt hvor stor en andel af patienterne der får dosisjustering. Tivozanib (fotivda) er på AIP-niveau forbundet med meromkostninger per patient sammenlignet med pazopanib (Votrient) og Sunitinib (Sutent) og meromkostningen stiger jo højere andelen af patienter der modtager dosisjustering.

4 BUDGETKONSEKVENSER

Budgetkonsekvenserne per år er baseret på antagelsen om, at tivozanib (Fotivda) vil blive anbefalet som standardbehandling. Man ser derfor på to scenarier:

A. Tivozanib (Fotivda) bliver anbefalet som standardbehandling af Medicinrådet til indikationen, som denne analyse omhandler
B. Tivozanib (Fotivda) bliver ikke anbefalet som standardbehandling

Budgetkonsekvenserne bliver differencen mellem budgetkonsekvenserne i de to scenarier.

4.1 Ansøgers estimater

4.1.1 Patientpopulation og markedsandel

Medicinrådet har i protokollen for vurdering af den kliniske merværdi af tivozanib (Fotivda) til behandling af nyrecellekarcinom estimeret, at ca. 300 patienter er kandidater til behandlingen per år. Ansøger har brugt dette estimat i deres ansøgning. Det antages, at hvis tivozanib (Fotivda) ikke anbefales som standardbehandling vil 20 % af patienterne behandles med sunitinib (Sutent) og 80 % af patienterne behandles med pazopanib (Votrient).

Tabel 6 Ansøgers estimat af antal nye patienter per år

	Anbefales som standardbehandling						Anbefales IKKE som standardbehandling				
	År 1	År 2	År 3	År 4	År 5		År 1	År 2	År 3	År 4	År 5
Tivozanib (Fotivda)	300	300	300	300	300		0	0	0	0	0
Sunitinib (Sutent)	0	0	0	0	0		60	60	60	60	60
Pazopanib (Votrient)	0	0	0	0	0		240	240	240	240	240

Amgros' vurdering af estimeret patientantal

Ansøger har anvendt patientestimaterne fra protokollen. Antagelsen omkring fordelingen af markedsandelene, hvis tivozanib (Fotivda) ikke anbefales som standardbehandling virker rimelige, da nuværende 1.-linje førstevalgsbehandling af patienter med mRCC er pazopanib (Votrient), mens sunitnib (Sutent®) bør overvejes som 2. valg.

4.1.2 Estimat af budgetkonsekvenser

Ansøger har inkluderet de samme omkostninger i budgetkonsekvensanalysen, som der er inkluderet i omkostningsanalysen. Med de indlagte antagelser estimerer ansøger, at anvendelse af tivozanib (Fotivda) vil resultere i budgetkonsekvenser på ca. 23 mio. DKK per år.

Ansøgers estimat af budgetkonsekvenserne fremgår af nedenstående tabel 7.

Tabel 7 Ansøgers hovedanalyse for totale budgetkonsekvenser, MIO. DKK, ikke-diskonterede tal

	År 1	År 2	År 3	År 4	År 5
Anbefales	89	89	89	89	89
Anbefales ikke	66	66	66	66	66
Totale budgetkonsekvenser	**23**	**23**	**23**	**23**	**23**

5 DISKUSSION

Amgros vurderer, at behandling med tivozanib (Fotivda) er forbundet med meromkostninger sammenlignet med behandling med pazopanib (Votrient) og Sunitinib (Sutent). Evidensens kvalitet er meget lav.

Meromkostningerne er primært drevet af prisen på tivozanib (Fotivda) og meromkostningerne er derfor også følsomme over for behandlingslængden. Meromkostningerne er desuden følsomme overfor dosisreduktion.

6 REFERENCER

1. Engholm G, Ferlay J, Christensen N, Hansen HL, Hertzum-Larsen R, Johannesen TB, Kejs AMT, Khan S, Ólafsdóttir E, Petersen T, Schmidt LKH VA and SH. Kræftstatistik: Nøgletal og figurer Danmark – Nyre NORDCAN: Cancer Incidence, Mortality, Prevalence and Survival in the Nordic Countries. 2017. Tilgængelig fra: https://www.ancr.nu/

2. Medicinrådet. Protokol for vurdering af den kliniske merværdi af tivozanib til behandling af nyrecellekarcinom

3. European Medicines Agency EMA. Produktresumé. Tivozanib (Fotivda) 2017. Tilgængelig fra: http://www.ema.europa.eu/docs/da_DK/document_library/EPAR_-_Product_Information/human/004131/WC500239033.pdf

4. Medicinrådet. Protokol for vurdering af den kliniske merværdi af tivozanib til behandling af nyrecellekarcinom

5. European Medicines Agency EMA. Produktresumé. Tivozanib (Fotivda) 2017. Tilgængelig fra: http://www.ema.europa.eu/docs/da_DK/document_library/EPAR_-_Product_Information/human/004131/WC500239033.pdf

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Høringssvar fra ansøger

Fra: Lars K Langkilde <ll@wlpharma.com>
Sendt: 26. februar 2019 12:15
Til: Anne Sofie Gram <ASG@medicinraadet.dk>
Cc: Imran Ladha <Imran.Ladha@eusapharma.com>
Emne: RE: Medicinrådets vurdering af klinisk merværdi for tivozanib til behandling af nyrecellekarcinom

Kære Anne Sofie,
Jeg skriver på vegne af EUSA Pharma vedrørende Medicinrådets vurdering af klinisk merværdi for Fotivda i mRCC.

EUSA Pharma har ingen kommentarer til den fremsendte vurdering og imødeser Medicinrådet endelige beslutning.

Med venlig hilsen

Lars K. Langkilde, Ph.D.
Wickstrøm & Langkilde ApS

Medicinrådet

Medicinrådets vurdering af klinisk merværdi for tivozanib til behandling af nyrecellekarcinom

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 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 vurderingen af klinisk merværdi

Vurderingen af klinisk merværdi er Medicinrådets vurdering af, hvor effektiv og sikkert lægemidlet er i forhold til andre lægemidler til den samme gruppe patienter.

Vurderingen af klinisk merværdi indgår, når Medicinrådet skal beslutte, om lægemidlet anbefales som mulig standardbehandling.

Se Medicinrådets metodehåndbog for yderligere information.

Dokumentoplysninger	
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Versionsnummer	1.0

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Udgivet af Medicinrådet, 20. februar 2019

Indhold

1 Lægemiddelinformationer

Lægemidlets oplysninger	
Handelsnavn	Fotivda
Generisk navn	Tivozanib
Firma	EUSA Pharma UK Ltd.
ATC-kode	L01XE34
Virkningsmekanisme	Vaskulær endotelial vækstfaktorreceptor (1, 2 og 3) inhibitor
Administration/dosis	1340 µg én gang dagligt i 21 dage efterfulgt af en pause på 7 dage. Behandlingen fortsættes til sygdomsprogression eller uacceptabel toxicitet.
EMA-indikation	1. linjebehandling af avanceret renalcellekarcinom til voksne patienter i god, intermediær eller dårlig prognosegruppe i henhold til IMCD's kriterier samt 2. linjebehandling til patienter, som er VEGFR- og mTOR-inhibitornaive og er progredieret efter én tidligere behandlingslinje med cytokinterapi.

2 Medicinrådets konklusion vedrørende klinisk merværdi

Medicinrådet vurderer, at tivozanib til patienter med lokalavanceret inoperabel eller metastaserende nyrekræft (mRCC), der ikke tidligere har modtaget behandling, giver en **ikke-dokumenterbar klinisk merværdi** sammenlignet med pazopanib og sunitinib (evidensens kvalitet er meget lav).

Medicinrådet kategoriserer lægemidlers 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.

3 Forkortelser

ACR:	Antagede hændelsesrater (*assumed control group rates*)
AXL:	Anexelekto (GAS6-receptor)
CI:	Konfidensinterval
DOR:	Responsvarighed (*duration of response)*
EMA:	Det Europæiske Lægemiddelagentur (*European Medicines Agency)*
EPAR:	*European Public Assessment Report*
GRADE:	System til vurdering af evidens (*Grading of Recommendations Assessment, Development and Evaluation*)
HR:	Hazard ratio
IMDC:	Redskab til prognosegruppeallokering (*International Metastatic Renal Cell Carcinoma Database Consortium)*
MET:	Hepatocyt vækstfaktor-receptorprotein
mRCC:	Lokalavanceret inoperabelt eller metastatisk nyrekræft
mTOR:	Proliferative signalhæmmere (*mammalian target of rapamycin*)
OR:	Odds ratio
ORR:	Objektiv responsrate
OS:	Samlet overlevelse (*overall survival*)
PFS:	Progressionsfri overlevelse (*progression free survival*)
PICO:	Fokuseret forskningsspørgsmål *(Population, Intervention, Comparator, Outcome)*
PS:	*Performance status*
RADS:	Rådet for Anvendelse af Dyr Sygehusmedicin
RCC:	Nyrecellekarcinom
RR:	Relativ risiko
SAE:	Alvorlig uønsket hændelse (s*erious adverse event*)
SAR:	Alvorlig bivirkning (s*erious adverse reaction*)
TKI:	Tyrosinkinasehæmmer (*inhibitor)*
VEGF:	Vaskulær endotelial vækstfaktor
VEGFR:	Vaskulær endotelial vækstfaktorreceptor

4 Formål

Formålet med Medicinrådets vurdering af klinisk merværdi af tivozanib til lokalavanceret inoperabel eller metastaserende nyrekræft (mRCC) 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 tivozanib anbefales som mulig standardbehandling.

5 Baggrund

Nyrekræft

Nyrecellekarcinom (RCC) er den mest almindelige form for nyrekræft og udgør ca. 85 % af alle tilfælde af kræft i nyrerne - og ca. 2 % af alle kræftformer i Danmark [1]. Der diagnosticeres cirka 950 nye tilfælde årligt i Danmark [4]. Sygdommen debuterer hyppigst i 60-70-årsalderen og sjældent hos personer under 40 år. Fordelingen mellem mænd og kvinder er ca. 2:1 [4].

RCC opstår i/udgår fra nyreepitelet, og tumorvævet har et højt indhold af blodkar. Den høje forekomst af blodkar i tumorvævet skyldes en øget produktion af vaskulær endotelial vækstfaktor (VEGF) [2]. RCC opdeles i forskellige subtyper. De fire mest almindelige subtyper er: clearcelle, papillært, kromofobt- og samlerørsrenalcellekarcinomer. Af disse er clearcellekarcinom den mest almindelige og udgør ca. 70-85 % af alle RCC-tilfælde [3].

Omkring halvdelen af tumorerne opdages ofte tilfældigt ved udredning af anden sygdom, og ca. 20 % af patienterne har fjernmetastaser på diagnosetidspunktet. Cirka 20 % af de patienter, der opereres med helbredende sigte, får tilbagefald (lokalrecidiv) eller metastaser [4]. Fagudvalget vurderer derfor, at der årligt er ca. 300 nye patienter med mRCC, som vil være egnede til behandling. Patienter med mRCC inddeles i 3 prognosegrupper: god, intermediær eller dårlig. Fagudvalget anslår, at ca. 240 danske patienter årligt er i intermediær eller dårlig prognosegruppe. Fagudvalget vurderer heraf, at 2 ud af 3 patienter er kandidater til behandling med tivozanib, svarende til 150 patienter årligt.

Prognosen for RCC er væsentligt forbedret de sidste 15 år, og 5-års overlevelsen var i 2016 ca. 60 % mod ca. 43 % tidligere [4]. Forbedringen skyldes hovedsageligt flere tilfældigt fundne lokaliserede tilfælde af RCC, forbedrede kirurgiske teknikker og løbende introduktion af nye targetterede lægemidler siden 2006, herunder tyrosinkinasehæmmere (TKI) og proliferative signalhæmmere (mTOR) [5].

Nuværende behandling

Patienter med solitære metastaser tilbydes i udgangspunktet kurativ intenderet behandling med kirurgi. Patienter med multiple metastaser tilbydes medicinsk onkologisk behandling.

Opstart af medicinsk behandling sker ved hjælp af det prognostiske stratificeringsredskab International Metastatic RCC Database Consortium (IMDC). IMDC anvendes som standard i Danmark og opdeler på baggrund af seks risikofaktorer patienterne i tre prognosegrupper: god, intermediær og dårlig.

Risikofaktorerne for prognosestratificering er, som følger:

- Karnofsky performance status < 80
- Mindre end et år fra diagnose til opstart af onkologisk behandling
- Hæmoglobin < laveste normalgrænse

- Hyperkalcæmi (korrigeret kalcium koncentration > øverste normalgrænse)
- Neutrofil antal > øverste normalgrænse
- Blodplade antal > øverste normalgrænse.

Patienterne allokeres til prognosegrupperne på baggrund af forekomst af ovennævnte risikofaktorer:

- 0 risikofaktorer: **god prognosegruppe**
- 1-2 risikofaktorer: **intermediær prognosegruppe**
- ≥ 3 risikofaktorer: **dårlig prognosegruppe.**

Den nuværende behandling i Danmark er i henhold til RADS' behandlingsvejledning fra 2016 [5]:

I *1. linjebehandling* af patienter med mRCC (god/intermediær og dårlig prognosegruppe) er pazopanib førstevalg, mens sunitinib bør overvejes som andetvalg til alle tre prognosegrupper. Derudover bør temsirolimus overvejes som andetvalg til patienter i dårlig prognosegruppe. Pazopanib anbefales som førstevalg fremfor sunitinib, da pazopanib vurderes at have en tendens til mere favorabel bivirkningsprofil samt en mere favorabel livskvalitet, men med hensyn til effekt vurderes pazopanib og sunitinib at være ligeværdige. Fagudvalget vurderer, trods indplacering af pazopanib som førstevalg i RADS' behandlingsvejledning, at det er relevant at angive både pazopanib og sunitinib som komparatorer.

I *2. linjebehandling* af patienter med mRCC (god/intermediær og dårlig prognosegruppe) er nivolumab førstevalg for alle prognosegrupper, mens cabozantinib bør overvejes som andetvalg til alle tre prognosegrupper. Derudover bør axitinib overvejes som andetvalg til patienter i dårlig prognosegruppe.

Anvendelse af det nye lægemiddel

Vurderingen af tivozanib omfatter 1. linjebehandling af patienter i god, intermediær eller dårlig prognosegruppe. Tivozanib er en tyrosinkinasehæmmer, som blokerer tre vaskulære endotelial vækstfaktorreceptorer (VEGFR-1, VEGFR-2 og VEGFR-3). VEGF øger celledeling og spiller en central rolle i dannelsen af nye blodkar i tumorvævet og blodkarrenes gennemtrængelighed. Tivozanib virker ved at blokere den VEGF-inducerede VEGFR-aktivering og dermed hæmme tumorvækst.

Tivozanib er formuleret som oral kapselbehandling i styrkerne 1340 mikrogram og 890 mikrogram. Anbefalet dosis er 1340 mikrogram én gang om dagen i 21 dage efterfulgt af en pause på 7 dage. Ved behov for dosisreduktion kan tivozanib reduceres til 890 mikrogram én gang om dagen i henhold til det normale behandlingsskema med dosering i 21 dage og en pause på 7 dage. Behandlingen forsættes til sygdomsprogression eller uacceptabel toksicitet.

Tivozanib har indikation til 1. linjebehandling af voksne patienter med mRCC, som er VEGRF og mTOR pathway-hæmmernaive som følge af sygdomsprogression efter tidligere behandling af mRCC med cytokiner. Danske patienter behandles ikke længere med cytokinterapi i 1. linje. Fagudvalget vurderer derfor, at det i dansk behandlingsregi ikke er relevant at vurdere den kliniske merværdi af 2. linjebehandling med targeterede lægemidler efter én cytokinbehandling. Behandling med tivozanib vil derfor kun blive vurderet i henhold til indikationen for 1. linjebehandling.

6 Metode

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

Ansøgers ansøgning opfylder den præspecificerede protokol, der blev godkendt i Medicinrådet den 14. april 2018. Sekretariatet har dog følgende bemærkninger:

- Ansøger har indsendt en narrativ gennemgang af data for tivozanib sammenlignet med hhv. pazopanib og sunitinib. Sekretariatet er enige i, at det tilgængelige datagrundlag ikke tillader en indirekte sammenlignende analyse af tivozanib og de to komparatorer (pazopanib og sunitinib). (jf. afsnit 5)

- Ansøger har ikke opgjort data separat for patienter i hhv. god, intermediær og dårlig prognosegruppe. Fagudvalget ønskede (jf. protokollen) at orientere sig i disse. Ansøger argumenterer for, at prognosegrupperne er svære at opgøre data for, idet de behandlingsnaive patienter allerede udgør en subgruppe i de inkluderede studier. Fagudvalget er enige i, at yderligere inddeling i subgrupper vil svække datagrundlaget.

- Ansøger har ikke rapporteret samlet overlevelse (OS) ved 12 og 24 måneder, men rapporteret OS med længst mulig opfølgningstid (minimum 24 måneder).

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.

7 Litteratursøgning

Ansøger har udført en systematisk litteratursøgning som anført i protokollen.
Ansøger har inkluderet data fra fire studier: VEG105192, Motzer 2007, COMPARZ og TIVO-1. De enkelte studier beskrives yderligere i afsnit 6.1.1. Derudover vil fagudvalget orientere sig i data fra EMAs European Public Assessment Report (EPAR) for tivozanib [6].

Følgende kliniske studier indgår i Medicinrådets vurdering af tivozanib til patienter med mRCC:

Tabel 1: Inkluderede studier

Reference	Titel	Klinisk studie
Sternberg et al. (2010)	*Pazopanib in locally advanced or metastatic renal cell carcinoma: results of a randomized phase III trial.*	**VEG105192**
Motzer et al. (2007)	*Sunitinib versus interferon alfa in metastatic renal-cell carcinoma.*	**Motzer 2007**
Motzer et al. (2013)	*Pazopanib versus sunitinib in metastatic renal-cell carcinoma.*	**COMPARZ**
Motzer (2013)	*Tivozanib versus sorafenib as initial targeted therapy for patients with metastatic renal cell carcinoma: results from a phase III trial.*	**TIVO-1**

8 Databehandling

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

Det tilgængelige datagrundlag tillader ikke en indirekte sammenligning mellem tivozanib og de to komparatorer (pazopanib og sunitinib). Ansøger har derfor foretaget og indsendt en narrativ gennemgang af de inkluderede studier. Derudover er der i det primære studie af tivozanib (TIVO-1) ikke proportionale hazards (relativ risiko konstant over tid), hvilket er meget tydeligt for overlevelsesdata. Brud på antagelsen om, at der er proportionale hazards vil ikke udgøre et troværdigt statistisk grundlag i vurderingen af den kliniske merværdi af tivozanib, hvorfor fagudvalget accepterer, at data i stedet vil blive vurderet i en narrativ gennemgang.

9 Klinisk merværdi

9.1 Konklusion klinisk spørgsmål

Hvad er den kliniske merværdi af tivozanib til voksne patienter med mRCC, der ikke tidligere har modtaget behandling?

Fagudvalget vurderer, at tivozanib til patienter med mRCC, der ikke tidligere har modtaget behandling, giver en **ikke-dokumenterbar klinisk merværdi** sammenlignet med pazopanib og sunitinib (evidensens kvalitet er meget lav).

9.1.1 Gennemgang af studier

Karakteristika

COMPARZ

COMPARZ er et ublindet, randomiseret kontrolleret fase 3-studie, hvor pazopanib sammenlignes med sunitinib hos patienter med mRCC [8]. Der er i studiet anvendt dosering svarende til dansk klinisk praksis. Mellem år 2011 og 2013 blev 1110 patienter randomiseret i blokke af fire i en 1:1 ratio til behandling med pazopanib (n = 55) eller sunitinib (n = 55). Data for respons blev evalueret af en uafhængig reviewkomité. Randomiseringen er stratificeret efter Karnofsky performancestatus (70 eller 80 versus 90 eller 100).

Inklusionskriterierne omfatter voksne patienter (≥ 18 år) med mRCC, som ikke har modtaget tidligere behandling, Karnofsky performancestatus score på minimum 70 og normal organfunktion.

Studiet er et non-inferioritetsstudie af pazopanib overfor sunitinib med PFS som primært endepunkt. Sekundære endepunkter omfatter ORR, OS, bivirkninger og livskvalitet. Median opfølgningstid er ikke angivet, men den endelige overlevelsesanalyse blev foretaget med data cut-off i september 2013 (24 måneder efter inklusion af den sidste patient) [8,9].

TVIO-1

TIVO-1 er et ublindet, randomiseret kontrolleret fase 3-studie, hvor tivozanib sammenlignes med sorafenib hos patienter med mRCC (tilbagevendende eller metastatisk). Mellem februar og august 2010 blev 517 patienter randomiseret 1:1 til behandling med enten tivozanib eller sorafenib. Randomiseringen blev stratificeret efter geografi, antal tidligere behandlinger for metastatisk sygdom og antal af metastaser fordelt på involverede organer. Inklusionskriterierne omfattede: voksne patienter (≥ 18 år), tidligere nefrektomi, med mRCC, målbar sygdom ved Response Evaluation Criteria in Solid Tumors (RECIST) kriterier og ECOG performance status 0-1. Patienter kunne enten være behandlingsnaive eller være patienter, som ikke havde modtaget tidligere systemisk behandling (immunterapi, kemoterapi eller hormonelbehandling) mere end én gang for mRCC. Postoperativ eller adjuverende systemisk behandling talte ikke som tidligere behandling (medmindre tilbagefald observeredes inden for seks måneder efter behandlingsafslutning, og dermed blev talt med som tidligere behandling for metastatisk sygdom). Tidligere VEGF- eller mTOR-målrettet behandling var ikke tilladt.

Dosis af tivozanib var 1,5 mg én gang dagligt i tre uger efterfulgt af én uges pause, og dosis af sorafenib var 400 mg to gange dagligt. Begge behandlinger blev givet som oral behandling. Behandlingen skulle fortsætte indtil sygdomsprogression, uacceptabel toksicitet eller død. Patienter med ≥ 3 bivirkninger kunne få dosisreduktion til 1 mg dagligt for tivozanib og til 400 mg en gang dagligt og 400 mg hver anden dag for sorafenib.

Patienter i sorafenibbehandling, som af en investigator blev vurderet til at have RECIST-defineret progressiv sygdom, blev tilbudt at skifte til behandling med tivozanib i en separat protokol.

Studiets primære endepunkt var PFS, som blev defineret som tidsintervallet mellem tidspunkt for randomisering og tidspunkt for sygdomsprogression eller død. De sekundære effektmål var OS, objektiv responsrate (ORR, komplet plus partielt respons), sikkerhed, nyrespecifikke symptomer og livskvalitet (HRQoL). Vurdering af tumorer blev foretaget i et uafhængigt radiologisk blindet review.

Supplerende litteratur

Fagudvalget vurderer, at COMPARZ og TIVO-1 udgør det primære datagrundlag. Baselinekarakteristika for patienter i studierne VEG105192 og Motzer 2007 fremgår af bilag 2 og indgår kun som supplerende data i vurderingen af tivozanib.

Motzer 2007 er et randomiseret fase 3-studie, som sammenligner sunitinib med IFN-α 1:1 hos 750 patienter med RCC. Det primære endepunkt var PFS, og de sekundære endepunkter var ORR, OS, HRQoL og sikkerhed. I 2009 blev der publiceret en opdateret analyse for OS.

VEG105192 er et placebokontrolleret, randomiseret, dobbeltblindet multicenter fase 3-studie af pazopanib til behandling af mRCC i 1. linje [7]. Studiet omfatter behandlingsnaive patienter samt patienter, der har modtaget cytokinterapi men med subgruppeanalyser for hver enkelt gruppe. Studiet inkluderes i denne vurdering, da resultater for effekt og sikkerhed for de behandlingsnaive patienter er anvendt som estimater for effekt af pazopanib og dermed anvendes i den narrative sammenligning af tivozanib og pazopanib.

Population

Af tabel 1 og 2 nedenfor fremgår baselinekarakteristika for patienter i de inkluderede studier, som er anvendt til at besvare det kliniske spørgsmål. Baselinekarakteristika er opgjort for den samlede population og for hver enkelt prognosegruppe i henhold til IMDC's kriterier i de tilfælde, hvor data herfor foreligger. Nedenfor er udelukkende anført baselinekarakteristika for tivozanib vs. sorafenib (TIVO-1) og for non-inferioritetsstudiet af de to komparatorer, pazopanib og sunitinib (COMPARZ), da fagudvalget vurderer, at disse data udgør det primære datagrundlag. Baselinekarakteristika for VEG105192 og Motzer 2007 fremgår af bilag 2 og indgår primært som supplerende data.

Tabel 1: Baselinekarakteristika for TIVO-1

Behandlingsnaive subpopulation		
	Tivozanib (N = 170) *70 % af totale population*	*Sorafenib (N = 181)* *70 % af totale population*
Median alder, år (range)	*59 (23-83)*	*59 (23-85)*
Mænd, n (%)	*134 (74)*	*135 (75)*
ECOG Performance Status, n (%)		
0	*85 (47)*	*94 (52)*
1	*96 (53)*	*87 (48)*
2	-	-
MSKCC prognosegruppe, n (%)		
Favorabel *Intermediær*	*48 (27)* *121 (67)*	*60 (33)* *112 (62)*
Dårlig	*12 (7)*	*9 (5)*
Antal organer med metastase, n (%) *1* *≥ 2*	 *53 (29)* *128 (71)*	 *65 (36)* *116 (64)*

Tabel 2: Baselinekarakteristika for COMPARZ

Total population		
	Pazopanib (n = 557)	*Sunitinib (n = 553)*
Median alder, år (range)	*61 (18-88)*	*62 (23-86)*
Mænd, n (%)	*398 (71)*	*415 (75)*
Karnofsky Performance Status, n (%) *70 eller 80* *90 eller 100*	 *141 (25)* *416 (75)*	 *130 (24)* *465 (84)*
Knoglemetastaser, n (%)	*7 (47)*	*8 (53)*
Tidligere nefrektomi, n (%)	*459 (82)*	*465 (84)*
Tidligere strålebehandlet, n (%)	*46 (8)*	*42 (8)*
IMDC prognosegruppe, n (%) *God* *Intermediær* *Dårlig* *Ukendt*	 *142 (25)* *299 (54)* *106 (19)* *10 (2)*	 *137 (25)* *308 (56)* *94 (17)* *14 (3)*

Fagudvalget vurderer, at de behandlingsnaive patienter i TIVO-1 og COMPARZ er sammenlignelige med hensyn til alder, performancestatus, knoglemetastaser og tidligere nefrektomi. I TIVO-1 og COMPARZ er der inkluderet patienter i god, intermediær og dårlig prognosegruppe. Fagudvalget vurderer, at patienterne i de to studier er repræsentative for den danske patientpopulation.

9.1.2 Resultater og vurdering

Resultater og vurdering af de effektmål, som fagudvalget har præspecificeret som hhv. kritiske og vigtige, følger nedenfor. Jf. afsnit 5 vurderes den kliniske merværdi af tivozanib narrativt ift. både pazopanib og sunitinib.

- *Hvad er den kliniske merværdi af tivozanib til voksne patienter med mRCC, der ikke tidligere har modtaget behandling?*

Samlet overlevelse (kritisk)

Medianen for samlet overlevelse (OS) belyser, hvor lang tid der går, inden halvdelen af patienterne er døde. OS-raten er derimod et estimat for, hvor mange der er i live efter hhv. 12 og 24 måneder. Jf. afsnit 3 har ansøger kun indsendt data for median overlevelse ved længst mulig opfølgning og ingen resultater for OS-rate.

Resultaterne for samlet overlevelse på tværs af de fire inkluderede studier kan ses af tabel 3. Den mindste klinisk relevante forskel var 3 måneder.

Tabel 3: Resultater for samlet overlevelse (OS) for behandlingsnaive patienter i de fire inkluderede studier

Studie	Studiearm	N	Median OS (måneder)	95 % CI	Forskel	HR	95 % CI
Sternberg 2010*	Pazopanib	155	22,9	17,6-25,4	-0,6	1,01	0,72-1,42
	Placebo	78	23,5	12,0-32,9			
Motzer 2007	Sunitinib	375	26,4	23,0-32,9	4,6	0,821	0,673-1,001
	IFN-α	375	21,8	17,9-26,9			
Comparz	Pazopanib	557	28,3	26,0-35,5	-0,8	0,92	0,79-1,06
	Sunitinib	553	29,1	25,4-33,1			
TIVO-1*	Tivozanib	181	27,1	NR	-2,4	1,14	0,860-1,532
	Sorafenib	181	29,5	NR			
Evidensens kvalitet	Meget lav						

* Baseret på behandlingsnaiv subgruppe

Forbedret OS er vist for sunitinib sammenlignet med IFN-α men ikke sammenlignet med pazopanib. Pazopanib viser en numerisk lavere overlevelse sammenlignet med placebo hos behandlingsnaive, og tivozanib viser en numerisk lavere overlevelse sammenlignet med sorafenib. Fagudvalget bemærker, at resultaterne for overlevelse i begge studier er påvirket af overkrydsning (cross-over) til interventionen efter progression. Studiet af Sternberg et. al viser således betydningen af tidlig versus forsinket behandlingsstart med pazopanib, og ikke reelt effekten ved placebo, da dette vil være uetisk at foretage på mennesker med metastatisk sygdom. Data i tabellen er uden korrektion for overkrydsning, og effekten af både pazopanib og tivozanib i TIVO-1 og Sternberg 2010 er derfor sandsynligvis underestimeret.

Resultaterne for median OS viser, at overlevelsen for tivozanib er 27,1 måneder vs. varierende overlevelse i studierne på 22,9-28,3 måneder for pazopanib og 26,4-29,1 måneder for sunitinib. Resultaterne indikerer ikke, at den mindste klinisk relevante forskel i median overlevelse på 3 måneder er opnået. Da datagrundlaget for sammenligningen samtidig er usikkert, vurderer fagudvalget, at tivozanib har en **ikke-dokumenterbar klinisk merværdi** sammenlignet med sunitinib og pazopanib for behandlingsnaive patienter for effektmålet samlet overlevelse. Evidensens kvalitet er meget lav.

Progressionsfri overlevelse (kritisk)

PFS anvendes til vurdering af sygdomskontrol og er en ofte anvendt surrogatmarkør for overlevelse i onkologiske studier. I modsætning til OS påvirkes PFS ikke af akkumulerede effekter af efterfølgende behandlinger, hvorfor fagudvalget betragter PFS, herunder median PFS samt PFS-rate ved henholdsvis 12 og 24 måneder, som et kritisk effektmål i vurderingen af den kliniske merværdi af tivozanib.

Tabel 4: Resultater for progressionsfri overlevelse (PFS) hos behandlingsnaive patienter i de fire inkluderede studier

Studie	Studiearm	N	Median PFS (måneder)	95 % CI	Forskel	HR	95 % CI
Sternberg 2018*	Pazopanib	155	11,1	NR	8,3	0,40	0,27-0,60
	Placebo	78	2,8	NR			
Motzer 2007	Sunitinib	375	11	10-12	6	0,42	0,32-0,54
	IFN-α	375	5	4-6			
Comparz	Pazopanib	557	8,4	8,3-10,9	-1,1	1,05	0,90-1,22
	Sunitinib	553	9,5	8,3-11,1			
TIVO-1*	Tivozanib	181	12,7	9,1-15,0	3,6	0,756	0,580-0,985
	Sorafenib	181	9,1	7,3-10,8			
Evidensens kvalitet	Meget lav						

* Baseret på behandlingsnaiv subgruppe

Median PFS for tivozanib er 12,7 måneder sammenlignet med 9,5-11 måneder for sunitinib og 8,4-11 måneder for pazopanib. Resultaterne for median PFS indikerer, at den mindste klinisk relevante forskel på 3 måneder ikke er opnået.

Da datagrundlaget for sammenligningen samtidig er usikkert, vurderer fagudvalget, at tivozanib har en **ikke-dokumenterbar klinisk merværdi** sammenlignet med sunitinib og pazopanib for behandlingsnaive patienter. Evidensens kvalitet er meget lav.

Livskvalitet (kritisk)

Livskvalitet blev undersøgt og afrapporteret forskelligt i de inkluderede studier. Data er for utilstrækkeligt rapporteret i publikationerne til at kunne sammenlignes ved hjælp af standardiserede ændringer fra baseline. Derudover findes resultaterne for TIVO-1 kun for den samlede population (behandlingsnaive og tidligere behandlede). Fagudvalget vurderer på den baggrund, at tivozanib har en **ikke-dokumenterbar klinisk merværdi** for effektmålet livskvalitet. Evidensens kvalitet er meget lav.

Alvorlige uønskede hændelser (uønskede hændelser af grad 3-4) (vigtig)

Forekomst af alvorlige bivirkninger grad 3-4 er et udtryk for alvorlig, men ikke fatal toksicitet af lægemidlet defineret ved European Organisation for Research and Treatment of Cancer – Common Terminology Criteria for Adverse Events [10].

Tabel 5: Resultater for uønskede hændelser grad 3-4 for behandlingsnaive patienter i de inkluderede studier**

Studie	Studiearm	N	Frekvens	Forskel	Risiko ratio	95 % CI
Sternberg 2010*	Pazopanib	NA	NA	NA	NA	NA
	Placebo	NA	NA			
Motzer 2007	Sunitinib	375	50 %	0,24	RR: 1,92	1,57-2,35
	IFN-α	360	26 %			
Comparz	Pazopanib	554	74 %	0,00	RR: 1,00	0,93-1,07
	Sunitinib	548	74 %			
TIVO-1*	Tivozanib	181	62 %	-0,08	RR: 0,89	0,76-1,03
	Sorafenib	181	70 %			
Evidensens kvalitet	Meget lav					

* Baseret på behandlingsnaiv subgruppe. ** For den behandlingsnaive population i TIVO-1 er der kun rapporteret uønskede hændelser ≥ grad 3.

62 % af patienterne i den behandlingsnaive population, der fik tivozanib i TIVO-1, oplevede alvorlige uønskede hændelser. Til sammenligning oplevede 74 % af patienterne, der fik sunitinib eller pazopanib i COMPARZ-studiet, uønskede hændelser af grad 3-4.

Tabel 6: Andel af de hyppigste ikke-hæmatologiske bivirkninger i TIVO-1 (behandlingsnaive) og COMPARZ

	Tivozanib	Sorafenib	Sunitinib	Pazopanib
	≥ grad 3	≥ grad 3	Grad 3-4	Grad 3-4
Diarre	2 %	7 %	7 %	9 %
Træthed	5 %	4 %	17 %	10 %
Hånd og fod-syndrom (Palmar-plantar erytro-dysæstesi syndrom)	2 %	16 %	11 %	6 %
Forhøjet blodtryk	25 %	18 %	15 %	15 %
Vægttab	3 %	2 %	< 1 %	1 %
Kvalme	1 %	1 %	2 %	2 %
Nedsat appetit	11 %	9 %	3 %	1 %

Af de bivirkninger, der er fremhævet i tabel 6, bemærker fagudvalget, at flere patienter i behandling med tivozanib end de øvrige tre lægemidler oplever hypertension. Hypertension vurderes dog at være en håndterbar bivirkning i klinikken. Derudover bemærker fagudvalget, at patienter i behandling med tivozanib har væsentlig mindre diarre, træthed og tilfælde af hånd- og fod-syndrom end patienterne i behandling med henholdsvis sunitinib og pazopanib. Fagudvalget antager, at den lavere forekomst af bivirkninger har betydning for patienternes livskvalitet.

Resultaterne for effektmålet alvorlige uønskede hændelser indikerer ikke tydeligt, om den mindste klinisk relevante forskel, en absolut reduktion på 10 % i forhold til pazopanib og sunitinib, er opnået. Sammenholdt med den kvalitative gennemgang af de uønskede hændelser vurderer fagudvalget, at der er en tendens til, at tivozanib medfører færre alvorlige uønskede hændelser sammenlignet med sunitinib og pazopanib. Fagudvalget bemærker også, at bivirkningsprofilen for alle tre lægemidler er håndterbar.

Fagudvalget vurderer, at tivozanib for effektmålet alvorlige uønskede hændelser har en **ikke-dokumenterbar klinisk merværdi** sammenlignet med sunitinib og pazopanib for behandlingsnaive patienter. Evidensens kvalitet er meget lav.

Objektiv responsrate (vigtig)

Objektiv responsrate (ORR) anvendes til belysning af behandlingsrespons. Komplet respons (CR) svarer til, at patienten er radiologisk kræftfri. Partielt respons (PR) indikerer som minimum en 30 % reduktion af tumorlæsioner sammenlignet med baseline. Objektivt respons opnås for en patient, hvis vedkommende er klassificeret som CR eller PR, og ORR defineres som CR + PR delt med det samlede patientantal.

Tabel 7: Resultater for objektiv responsrate hos behandlingsnaive patienter i de inkluderede studier

Studie	Studiearm	N	ORR (95 % CI)	Forskel	P-værdi	Rate ratio**	95 % CI**
Sternberg 2018*	Pazopanib	155	NA	NA	NA	NA	NA
	Placebo	78	NA	NA			
Motzer 2007	Sunitinib	375	31 % (26 %-36 %)	0,25	< 0,001	5,17	3,37-7,93
	IFN-α	375	6 % (4 %-9 %)				
Comparz	Pazopanib	557	31 % (26,9 %-34,5 %)	0,06	0,03	1,24	1,03-1,50
	Sunitinib	553	25 % (21,2 %-28,4 %)				
TIVO-1*	Tivozanib	181	34,2 % (27 %-42 %)	0,09	0,038	1,41	1,01-1,95
	Sorafenib	181	24,3 % (18 %-31 %)				
Evidensens kvalitet	Meget lav						

*Baseret på behandlingsnaiv subgruppe.

Andelen af patienter, der oplever objektivt respons ved behandling med tivozanib var 34,2 %, hvilket er højere end for patienterne i behandling med pazopanib (31 %) og sunitinib (25 %) i COMPARZ og for patienterne, der blev behandlet med sunitinib i Motzer 2007 (31 %).
Resultaterne for ORR indikerer dog ikke, at den mindste klinisk relevante forskel på 10 % i absolut forbedring er opnået. Da datagrundlaget for sammenligningen samtidig er usikkert, vurderer fagudvalget, at tivozanib har **ikke-dokumenterbar klinisk merværdi** sammenlignet med sunitinib og pazopanib for behandlingsnaive patienter. Evidensens kvalitet er meget lav.

Responsvarighed (vigtig)

Responsvarighed (DOR) er defineret som tiden fra opnåelse af respons til progression. DOR blev ikke rapporteret tilstrækkeligt i alle studier, hvorfor der ikke er grundlag for en sammenligning af data for effektmålet. Fagudvalget vurderer på den baggrund, at tivozanib har **ikke-dokumenterbar klinisk merværdi** sammenlignet med sunitinib og pazopanib for behandlingsnaive patienter for effektmålet responsvarighed. Evidensens kvalitet er meget lav.

9.1.3 Evidensens kvalitet

Evidensens kvalitet for tivozanib sammenlignet med sunitinib og pazopanib til patienter med mRCC, der ikke tidligere har modtaget behandling, er samlet set **meget lav.**

Fagudvalget har nedgraderet et niveau for inkonsistens, fordi den narrative sammenligning ikke tillader at estimere relative effektforskelle mellem studierne eller usikkerheder relateret til estimaterne. Der er yderligere nedgraderet to niveauer for alle effektmål for indirekte evidens, da der er tale om en narrativ sammenligning, og da interventionerne er administreret forskelligt i studierne. For effektmålene OS, PFS og ORR er der nedgraderet et niveau for upræcist estimat, da relative effekter og dertilhørende konfidensintervaller ikke kan estimeres. For SAE's har fagudvalget nedgraderet et niveau for upræcist estimat, da SAE's er rapporteret og opgjort forskelligt i de to studier. Der er ikke nedgraderet for risiko for bias. Overvejelser vedrørende evidensens kvalitet kan ses i bilag 1.

9.1.4 Konklusion

Fagudvalget vurderer, at tivozanib giver en **ikke-dokumenterbar klinisk merværdi** for patienter med lokalavanceret inoperabel eller metastaserende nyrekræft (mRCC), der ikke tidligere har modtaget behandling sammenlignet med pazopanib og sunitinib (meget lav evidenskvalitet).

Af tabel 8 fremgår fagudvalgets vurdering af den kliniske merværdi for de seks effektmål, som ligger til grund for den samlede vurdering af tivozanib.

Tabel 8. Klinisk merværdi for alle effektmål

Effektmål	**Vigtighed**	**Klinisk merværdi ved tivozanib sammenlignet med:**	
		pazopanib	**sunitinib**
Samlet overlevelse	Kritisk	Ikke-dokumenterbar	Ikke-dokumenterbar
Progressionsfri overlevelse	Kritisk	Ikke-dokumenterbar	Ikke-dokumenterbar
Livskvalitet	Kritisk	Ikke-dokumenterbar	Ikke-dokumenterbar
Alvorlige bivirkninger (SAE eller bivirkninger af grad 3-4)	Vigtig	Ikke-dokumenterbar	Ikke-dokumenterbar
Objektiv responsrate	Vigtig	Ikke-dokumenterbar	Ikke-dokumenterbar
Responsvarighed	Vigtig	Ikke-dokumenterbar	Ikke-dokumenterbar
Samlet vurdering		**Ikke-dokumenterbar**	**Ikke-dokumenterbar**

I den samlede vurdering af den kliniske merværdi lægger fagudvalget vægt på manglen på en direkte eller indirekte sammenligning af data. Datagrundlaget er usikkert, og derfor vurderer fagudvalget, at der er en **ikke-dokumenterbar klinisk merværdi** for alle effektmål i sammenligningen med begge komparatorer.

Fagudvalgets kliniske vurdering er, at tivozanib, pazopanib og sunitinib er sammenlignelige, hvad angår effekt, sikkerhed og livskvalitet. Vurderingen er baseret på fagudvalgets kliniske erfaringer med lægemidlerne og lægemidlernes ens virkningsmekanisme (tyrosinkinasehæmmere).

10 Andre overvejelser

Datagrundlaget alene er for usikkert til, at fagudvalget kan estimere relative effektforskelle mellem tivozanib, pazopanib og sunitinib. På baggrund af fagudvalgets kliniske erfaring med lægemidlerne, og fordi lægemidlerne har samme virkningsmekanisme (tyrosinkinasehæmmere) vurderer fagudvalget, at tivozanib ikke er dårligere end pazopanib og sunitinib.
Indtil der foreligger en behandlingsvejledning fra Medicinrådet finder fagudvalget, at tivozanib, sunitinib og pazopanib kan ligestilles til behandlingsnaive patienter med lokalavanceret inoperabel eller metastaserende nyrekræft (mRCC).

11 Fagudvalgets vurdering af samlet klinisk merværdi og samlet evidensniveau

Fagudvalget vurderer, at tivozanib giver en **ikke-dokumenterbar klinisk merværdi** for patienter med mRCC, der ikke tidligere har modtaget behandling sammenlignet med pazopanib og sunitinib (evidensens kvalitet er meget lav).

Datagrundlaget alene er for usikkert til, at fagudvalget kan estimere relative effektforskelle mellem tivozanib, pazopanib og sunitinib. Fagudvalget forventer, at tivozanib, pazopanib og sunitinib er sammenlignelige, hvad angår effekt, sikkerhed og livskvalitet. Denne vurdering er baseret på fagudvalgets kliniske erfaringer med lægemidlerne, og at lægemidlerne har samme virkningsmekanisme (tyrosinkinasehæmmere). Fagudvalget vurderer, at tivozanib ikke er dårligere end pazopanib og sunitinib.

12 Rådets vurdering af samlet klinisk merværdi og samlet evidensniveau

Medicinrådet vurderer, at tivozanib til patienter med mRCC, der ikke tidligere har modtaget behandling, giver en **ikke-dokumenterbar klinisk merværdi** sammenlignet med pazopanib og sunitinib (evidensens kvalitet er meget lav).

Medicinrådet er enig i fagudvalgets kliniske vurdering af, at tivozanib, pazopanib og sunitinib forventes at være sammenlignelige, hvad angår effekt, sikkerhed og livskvalitet

13 Relation til eksisterende behandlingsvejledning

Der foreligger en behandlingsvejledning fra RADS fra 2016 [5]. Såfremt tivozanib anbefales som mulig standardbehandling, vurderer fagudvalget, at behandlingen kan anvendes som mulig 1. linjebehandling under hensyntagen til den godkendte population og indikation. Cabozantinib blev i 2018 vurderet i Medicinrådet til samme indikation som tivozanib (1. linjebehandling til mRCC). Et yderligere lægemiddel (nivolumab/ipilimumab) er også under behandling til samme indikation.

Medicinrådet vil i 2019 udarbejde en opdateret behandlingsvejledning for nyrekræft, hvor de nye lægemidler vil blive indplaceret i forhold til hinanden.

14 Referencer

1. Engholm G, Ferlay J, Christensen N, Hansen HL, Hertzum-Larsen R, Johannesen TB, Kejs AMT, Khan S, Ólafsdóttir E, Petersen T, Schmidt LKH VA and SH. Kræftstatistik : Nøgletal og figurer Danmark − Nyre Ordforklaringer til Kræftstatistik Incidens (antal nye tilfælde) [internet]. NORDCAN: Cancer Incidence, Mortality, Prevalence and Survival in the Nordic Countries. 2017 [citeret 2. august 2018]. s. Version 8.0 (20.12.2017). Tilgængelig fra: www.ancr.nu
2. Lægehåndbogen. Nyrekræft [internet]. 2017. Tilgængelig fra: https://www.sundhed.dk/sundhedsfaglig/laegehaandbogen/nyrer-og-urinveje/tilstande-og-sygdomme/nyresygdomme/nyrekraeft/
3. Retningslinier K. NYRECANCER. 2013;
4. DaRenCa. Årsrapport 2016. 2017.
5. Rådet for Anvendelse af Dyr Sygehusmedicin (RADS). RADS Baggrundsnotat for behandling af metastaserende nyrekræft Side 1 af 68. 2017;1–68.
6. European Medicines Agency EMA. Fotivda : EPAR - Public assessment report [internet]. EMA. 2017. Tilgængelig fra: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/004131/WC500239035.pdf
7. Sternberg CN, Davis ID, Mardiak J, Szczylik C, Lee E, Wagstaff J, et al. Pazopanib in locally advanced or metastatic renal cell carcinoma: results of a randomized phase III trial. J Clin Oncol [internet]. 2010;28(6):1061–8. Tilgængelig fra: http://www.ncbi.nlm.nih.gov/pubmed/20100962
8. Motzer RJ, Hutson TE, Cella D, Reeves J, Hawkins R, Guo J, et al. Pazopanib versus Sunitinib in Metastatic Renal-Cell Carcinoma. N Engl J Med [internet]. 2013;369(8):722–31. Tilgængelig fra: http://www.ncbi.nlm.nih.gov/pubmed/23964934
9. Motzer RJ, Hutson TE, McCann L, Deen K, Choueiri TK. Overall survival in renal-cell carcinoma with pazopanib versus sunitinib. N Engl J Med [internet]. 2014;370(18):1769–70. Tilgængelig fra: http://www.ncbi.nlm.nih.gov/pubmed/24785224
10. National Institute of Cancer. Common Terminology Criteria for Adverse Events (CTCAE). NIH Publ [internet]. 2010;2009:0–71. Tilgængelig fra: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf

15 Sammensætning af fagudvalg og kontaktinformation til Medicinrådet

Medicinrådets fagudvalg vedrørende nyrekræft

Formand	**Indstillet af**
Frede Donskov Overlæge, lektor, dr.med.	Lægevidenskabelige Selskaber og udpeget af Region Midtjylland
Medlemmer	**Udpeget af**
Andreas Carus Overlæge, lektor, ph.d.	Region Nordjylland
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Lars Lund Professor, overlæge, dr.med.	Dansk Renal Cancer Gruppe
Ib Henneberg Patient/patientrepræsentant	Danske Patienter
Lennart Jønsson 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 Anne Sofie Gram (projekt- og metodeansvarlig) Pernille Koefod Arrevad (projektdeltager) Tina Klitmøller Sørensen Agander (projektdeltager) Ilse Linde (fagudvalgskoordinator) Jan Odgaard (biostatistiker) Kirsten Holdt Henningsen (teamleder)

16 Versionslog

Version	Dato	Ændring
1.0	20. februar 2019	Godkendt af Medicinrådet.

17 Bilag 1: GRADE-evidensprofiler

17.1 Cochrane Risk of Bias

TIVO-1:

Bias	Risk of bias	Elaboration
Selection bias		
Random sequence generation	**Some concerns**	Patients were randomly assigned 1:1 to either tivozanib or sorafenib as their initial targeted therapy. Random assignment of patients was stratified by geographic region, number of prior treatments for metastatic disease, and number of metastatic sites/organs involved.
Allocation concealment	**High**	The trial was open-label, which means that the allocation was not concealed, posing a high risk of bias.
Performance bias: blinding of participants and personnel. Assessment made for class of outcomes.		
Objective outcomes: ORR, OS, PFS	**Low**	As the outcomes were either objective by definition (OS, PFS) or based on independent review committee, there is a low risk of bias regarding the performance bias.
Subjective outcome: Quality of life (FKSI-19 questionnaire)	**Some concerns**	Due to the nature of the measurement (a questionnaire), there are some concerns of bias.
Detection bias: blinding of outcome assessment. Assessment made for class of outcomes.		
Objective outcomes: ORR, OS, PFS,	**Low**	All imaging scans were evaluated by independent radiology review blinded to study treatment. Tumor response was evaluated according to RECIST version 1.0. Patients with radiologic evidence of PD, as assessed by the investigator, had confirmation by blinded independent radiology review within 48 hours. This independent review to confirm investigator-called PD was a separate process from the third-party review of response performed by the core imaging laboratory to assess the primary end point. Confirmation of PD was not required if significant clinical deterioration, appearance of new lesions, or > 50% increase in measurable disease per RECIST was noted by the investigator. The data was analyzed in collaboration of the pharmaceutical company and the authors. There are some concerns regarding the detection bias due to the study being open-label.
Safety and tolerability	**Low**	AEs were collected throughout the patients' participation, including a period of 30 days after the last dose of study drug. AEs were graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events version 3.0. There are some concerns regarding the detection bias due to the study being open-label
Subjective outcome: Quality of life (FACT-G, FKSI-DRS and EuroQol-5D questionnaire)	**Some concerns**	As the quality of life was measured via a questionnaire, there are by definition some concerns of bias. There are some concerns regarding the detection bias due to the study being open-label
Attrition bias: incomplete outcome data. Assessment made for class of outcomes.	**Low**	All randomized patients (minus one in the tivozanib group) in both groups received study treatment.

Reporting bias: selective reporting outcome data.	**Some concerns**	Results of duration of response is not reported in the publication.
Other bias	**Low**	No other concern regarding potential risk of bias.
Overall bias	**Some concerns**	There some concerns of bias due to the selection, detection and performance bias. The overall risk of bias is perceived as 'Some concerns'.

COMPARZ:

Bias	Risk of bias	Elaboration
Selection bias		
Random sequence generation	**Low risk**	Patients were randomly assigned to one of the two study drugs in a 1:1 ratio in permuted blocks of four. Randomization was stratified according to Karnofsky performance-status score (70 or 80 vs. 90 or 100), level of lac- tate dehydrogenase (>1.5 vs. ≤1.5 times the upper limit of the normal range), and nephrectomy (yes vs. no).
Allocation concealment	**High**	The trial was open-label, which means that the allocation was not concealed, posing a high risk of bias.
Performance bias: blinding of participants and personnel. Assessment made for class of outcomes.		
Objective outcomes: ORR, OS, PFS	**Low**	As the outcomes were either objective by definition (OS, PFS) or based on independent review committee, there is a low risk of bias regarding the performance bias.
Subjective outcome: Quality of life (FKSI-19 questionnaire)	**Some concerns**	Due to the nature of the measurement (a questionnaire), there are some concerns of bias.
Detection bias: blinding of outcome assessment. Assessment made for class of outcomes.		
Objective outcomes: ORR, OS, PFS,	**Low**	We performed disease assessments with the use of computed tomography or magnetic resonance imaging at baseline, every 6 weeks until week 24, and every 12 weeks thereafter until progression of disease. Imaging data were reevaluated by an independent review committee whose members were unaware of the treatment assignments to assess the primary end point and tumor response according to RECIST, version 1.0. Patient follow- up continued until death or withdrawal from the study.
Safety and tolerability	**Low**	Adverse events were graded according to the Common Terminology Criteria for Adverse Events of the National Cancer Institute, version 3.0.11 Cardiac function was monitored on echocardiograms or multigated ac- quisition scans obtained every three cycles. There are some concerns regarding the detection bias due to the study being open-label
Subjective outcome: Quality of life (FACT-G, FKSI-DRS and EuroQol-5D questionnaire)	**Some concerns**	As the quality of life was measured via a questionnaire, there are by definition some concerns of bias. There are some concerns regarding the detection bias due to the study being open-label
Attrition bias: incomplete outcome data. Assessment made for class of outcomes.	**Low**	A total of 8 patients (3 patients in the pazopanib group and 5 in the sunitinib group) did not receive any study therapy for vari- ous reasons, including withdrawal of consent. Efficacy data were analyzed in the intention-to-treat population (all patients who underwent randomization).

Reporting bias: selective reporting outcome data.	**Some concerns**	Intention-to-treat analysis are performed and data were reported for all prespecified primary (PFS) and secondary pitcomes (ORR, OS, safety). Data for time to response and duration of response are not reported as prespecified in the study protocol.
Other bias	**Low**	No other concern regarding potential risk of bias.
Overall bias	**Some concerns**	There some concerns of bias due to the selection, detection, performance and reporting bias. The overall risk of bias is perceived as 'Some concerns'.

17.2 GRADE-evaluering evidenskvaliteten til vurdering af den kliniske merværdi af tivozanib sammenlignet med pazopanib og sunitinib

Question: Tivozanib compared to sunitinib for 1L mRCC

Bibliography: TIVO-1, COMPARZ. Supplementary data: Motzer 2007.

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Overall survival									
2	observational studies	not serious	serious [a]	very serious [b,c]	serious [a]	none	OS for tivozanib in the TIVO-1 study: 27.1 months, OS for sunitinib in COMPARZ: 29.1 months. MCID is not reached.	⊕◯◯◯ VERY LOW	CRITICAL
Progression free survival									
2	observational studies	not serious	serious [a]	very serious [b,c]	serious [a]	none	PFS for tivozanib in TIVO-1: 12.7 months. PFS for sunitinib in COMPARZ: 9.5 months. For pazopanib PFS variates in the supplementary data material with a range of 9,5-11 months (Motzer et al. 2007). MCID is not reached.	⊕◯◯◯ VERY LOW	CRITICAL
Objective response rate									
2	observational studies	not serious	serious [a]	very serious [b,c]	serious [a]	none	ORR for tivozanib in TIVO-1 was: 34.2%. ORR for sunitinib in COMPARZ was 25%. MCID of 10% was not reached.	⊕◯◯◯ VERY LOW	IMPORTANT
SAE's (grade III-IV)									
2	observational studies	not serious	serious [a]	very serious [b,c]	serious [d]	none	SAE's grade >3 for tivozanib in TIVO-1 was 62%. SAE's grade 3-4 for sunitinib in COMPARZ was 74%. It is uncertain whether MCID is reached due to inconsistency in the assessment of SAE's.	⊕◯◯◯ VERY LOW	IMPORTANT

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Quality of life - not reported									
-	-	-	-	-	-	-	Not reported	-	CRITICAL
Duration of response - not reported									
-	-	-	-	-	-	-	Not reported	-	IMPORTANT

CI: Confidence interval

Explanations

a. The naive indirect comparison does not allow estimates of relative effect. Confidence limits cannot be estimated and the estimate of effect is considered very uncertain.
b. Naive indirect comparison.
c. The interventions were administered in different settings.
d. SAE's were not assessed equally in the two studies.

Question: Tivozanib compared to pazopanib for 1L mRCC

Bibliography: TIVO-1, COMPARZ. Supplementary material: Sternberg 2010.

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Overall survival									
2	observational studies	not serious	serious [a]	very serious [b,c]	serious [a]	none	OS for tivozanib in the TIVO-1 study: 27.1 months, OS for pazopanib in COMPARZ: 28.3. MCID is not reached.	⊕◯◯◯ VERY LOW	CRITICAL
Progression free survival									

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
2	observational studies	not serious	serious [a]	very serious [b,c]	serious [a]	none	PFS for tivozanib in TIVO-1: 12.7 months. PFS for pazopanib in COMPARZ: 8.4 months. For pazopanib PFS variates within a range of 8,4-11.1 months (Sternberg et al. 2010). MCID is not reached.	⊕◯◯◯ VERY LOW	CRITICAL
Objective response rate									
2	observational studies	not serious	serious [a]	very serious [b,c]	serious [a]	none	ORR for tivozanib in TIVO-1 was: 34.2%. ORR for pazopanib in COMPARZ was 31%. MCID of 10% was not reached.	⊕◯◯◯ VERY LOW	IMPORTANT
SAE's (grade III-IV)									
2	observational studies	not serious	serious [a]	very serious [b,c]	serious [d]	none	SAE's grade >3 for tivozanib in TIVO-1 was 62%. SAE's grade 3-4 for pazopanib in COMPARZ was 74%. It is uncertain whether MCID is reached due to inconsistency in the assessment of SAE's.	⊕◯◯◯ VERY LOW	IMPORTANT
Quality of life - not reported									
-	-	-	-	-	-	-	Not reported	-	CRITICAL
Duration of response - not reported									
-	-	-	-	-	-	-	Not reported	-	IMPORTANT

CI: Confidence interval

Explanations

a. The naive indirect comparison does not allow estimates of relative effect. Confidence limits cannot be estimated and the estimate of effect is considered very uncertain.
b. Naive indirect comparison.
c. The interventions were administered in different settings.
d. SAE's were not reported equally in the two studies.

18 Bilag 2: Baselinekarakteristika

I tabellen nedenfor fremgår baselinekarakteristika for VEG105192 og Motzer 2007, som refererer til de to komparatorer sunitinib og pazopanib sammenlignet med TNF-a og placebo.

VEG105192

Baselinekarakteristika (Total population)		
	Pazopanib (n=290)	*Placebo (n=145)*
Median alder, år (range)	*59 (28-85)*	*60 (25-81)*
Mænd, n (%)	*198 (68)*	*109 (75)*
Hyppigste metastaser, n (%) - *Lunge* - *Lymfeknuder* - *Knogle* - *Lever* - *Nyre*	 *214 (74)* *157 (54)* *81 (28)* *75 (26)* *66 (23)*	 *106 (73)* *86 (59)* *38 (26)* *32 (22)* *36 (25)*
Tidligere nefrektomi, n (%)	*258 (89)*	*127 (88)*
ECOG performance status - *0* - *1*	 *123 (42)* *167 (58)*	 *60 (41)* *85 (59)*
MSKCC prognosegruppe, n (%) *God* *Intermediær* *Dårlig* *Ukendt*	 *113 (39)* *159 (55)* *9 (3)* *9 (3)*	 *57 (39)* *77 (53)* *5 (3)* *6 (4)*
Tidligere systemisk behandling - *Behandlingsnaive* - *Cytokinbehandlede*	 *155 (53)* *135 (47)*	 *78 (54)* *67 (46)*

Motzer 2007

Baselinekarakteristika (Total population)		
	Sunitinib (n=375)	*Placebo (n=375)*
Median alder, år (range)	*62 (27-87)*	*59 (34-85)*
Mænd, n (%)	*267 (71)*	*269 (72)*
Hyppigste metastaser, n (%) - *Lunge* - *Lymfeknuder* - *Knogle* - *Lever*	 *292 (78)* *218 (58)* *112 (30)* *99 (26)*	 *298 (79)* *198 (53)* *112 (30)* *90 (24)*
Tidligere nefrektomi, n (%)	*340 (91)*	*355 (89)*

ECOG performance status - *0* - *1*	 *231 (62)* *144 (38)*	 *229 (61)* *146 (39)*
MSKCC prognosegruppe, n (%) *God* *Intermediær* *Dårlig*	 *143 (38)* *209 (56)* *23 (6)*	 *121 (34)* *212 (59)* *25 (7)*

Application for the assessment of clinically added value of Fotivda (tivozanib) for advanced renal cell carcinoma

2019-01-24

Contents

1 Basic information

Contact information

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Overview of the pharmaceutical

Proprietary name	Fotivda
Generic name	Tivozanib
Marketing authorization holder in Denmark	EUSA Pharma (UK) Limited Breakspear Park, Breakspear Way Hemel Hempstead, HP2 4TZ Great Britain
ATC code	L01XE34
Pharmacotherapeutic group	Antineoplastic agents
Active substance(s)	Tivozanib hydrochloride monohydrate
Pharmaceutical form(s)	Hard capsules
Mechanism of action	Tivozanib potently and selectively blocks all 3 Vascular Endothelial Growth Factor receptors (VEGFR) and has been shown to block various VEGF-induced biochemical and biologic responses in vitro, including VEGF-ligand-induced phosphorylation of all three VEGFR 1, 2 and 3, and proliferation of human endothelial cells. The next most potently inhibited kinase is c-kit which is 8-fold less sensitive to inhibition by tivozanib compared to VEGFR 1, 2 and 3. VEGF is a potent mitogenic factor that plays a central role in angiogenesis and vascular permeability of tumour tissues. By blocking VEGF-induced VEGFR activation, tivozanib inhibits angiogenesis and vascular permeability in tumour tissues, leading to inhibition of tumour *growth in vivo*.
Dosage regimen	The recommended dose of tivozanib is 1340 microgram once daily for 21 days, followed by a 7-day rest period to comprise one complete treatment cycle of 4 weeks. This treatment schedule should be continued until disease progression or unacceptable toxicity.
Therapeutic indication relevant for assessment (as defined by the European Medicines Agency, EMA)	Fotivda is indicated for the first line treatment of adult patients with advanced renal cell carcinoma (RCC) and for adult patients who are VEGFR and mTOR pathway inhibitor-naïve following disease progression after one prior treatment with cytokine therapy for advanced RCC.
Other approved therapeutic indications	None
Will dispensing be restricted to hospitals?	Yes
Combination therapy and/or co-medication	Not applicable
Packaging – types, sizes/number of units, and concentrations	Bottle, 21 capsules, 890 micrograms Bottle, 21 capsules, 1 340 micrograms
Orphan drug designation	Not applicable

2 Abbreviations

DOR	Duration of response
ECOG	Eastern cooperative oncology group performance status
EORTC-QLQ	European Organisation for Research and Treatment of Cancer Quality of Life Questionaire
EPAR	European Public Assessment Report
EQ-5D	European Quality of Life-5 Dimensions
FACIT-G	Functional Assessment of Cancer Therapy – General
FACIT-F	Functional Assessment of Cancer Therapy – Fatique
FKSI	Functional Assessment Of Cancer Therapy- Kidney Symptom Index
HFS	Hand foot syndrom
HR	Hazard ratio
HRQoL	health related quality of life
IFN	Interferon
IRC	Idependent review committee
ITT	Intention to treat
KM	Kaplan-Meier
MAIC	Matched adjusted indirect comparison
MMSKCC	Modified MSKCC
mRCC	Metastatic RCC
MSKCC	Memorial Sloan-Kettering Cancer Center score
MTC	Mixed treatment comparison
mTOR	Mammalian target of rapamycin
NICE	National institute of Clinical Excellence
NMA	Network Meta-analysis
OR	Odds ratio
ORR	Objective response rate
OS	Overall survival
PD	Progressed disease
PFS	Progression free survial
RCC	Renal cell carcinoma
RCT	Randomised controlled trial
RECIST	Response Evaluation Criteria in Solid Tumors
SD	Standard deviation
SLR	Systemic literature review
SMC	Scottish Medicine Consortium
TKI	Tyrosin kinase inhibitorer
VEGF	Vascular endothelial growth factor

3 Summary

This document reports on the assessment of treatment outcomes associated with treatment of metastatic renal cell carcinoma (mRCC) in treatment naïve patients. The research was based on the Danish Medicine Council protocol for Fotivda (tivozanib). The purpose of the assessment is to compare tivozanib to pazopanib and sunitinib with respect to efficacy, health related quality of life (HRQoL) and safety.

Four randomized controlled trials with parallel group designs were identified. All the pivotal trials included analogous populations with advanced or metastatic RCC. All patient groups across trials were of similar median age (59-60 years), most commonly males on equal ECOG performance status with lung or lymph nodes metastasis. For most participants their prognostic risk was intermediate, and the majority were treatment naïve.

Tivozanib efficacy outcomes in terms of overall survival (OS), progression free survival (PFS), objective response rate (ORR) in the TIVO-1 pivotal trials were at comparable level to those observed in sunitinib and pazopanib trials.

HRQoL was not consistently measured, analyzed or reported across the trials. None of the three tyrosin kinase inhibitorers (TKIs) have shown a treatment effect using the generic HRQoL instruments EQ-5D or EORTC compared to other TKIs. Statistically significant and clinical meaningful differences have only been reported for pazopanib compared to sunitinib using the fatigue symptom-specific instrument FACIT-F. FKSI instruments in different versions have been applied in several trials but mean scores or change from baseline scores cannot be compared across studies due to differences in reporting. For this reason, no quantitative indirect comparison of HRQoL was attempted.

Overall no evidence exists to suggest an added value of tivozanib (positive or negative) in comparison to pazopanib or sunitinib.

Safety as measured by the frequency of grade 3-4 adverse events were comparable across treatments, although the distribution of type of AE may vary. There was a tendency for a higher frequency of hypertension observed in patients treated with tivozanib compared to pazopanib and sunitinib and a tendency to higher frequencies of hand-foot syndrome (HFS) being reported for pazopanib and sunitinib. Tolerability of tivozanib is further supported by the low rates of discontinuation, dose reduction and dose interruptions due to AE observed in the TIVO-1 trial.

The evidence indicates that tivozanib offers patients an alternative treatment option to existing first line treatments of mRCC in Denmark - with an efficacy of the same magnitude as existing pazopanib and sunitinib. Evidence also suggest, that tivozanib has a tolerability profile comparable to existing treatments with a low need for dose reduction or interruptions, and a low frequency of discontinuation due to side-effects.

4 Literature search

The literature search was made in two databases: the PubMed Central database and the Cochrane Central Register of Controlled Trials (CENTRAL) database. The search was conducted on January 4, 2019 and was designed to identify phase III clinical trials in parallel group designs. The search strategy included search terms to identify the relevant study population, study design, interventions, comparators, outcomes, and analyses performed according to the eligibility criteria listed in Appendix A. The search was restricted to English full-text publication.

In total 451 records were screened, 34 articles were assessed for eligibility. 8 articles reporting results from 4 studies were included for narrative synthesis (see Table 3). Appendix A provides full information of the search strategy, search terms, search results, excluded and included records / full text articles. The 4 clinical studies selected for the synthesis included the three pivotal trials for each of the TKIs and a direct comparison of pazopanib and sunitinib.

The evidence network (see section 4.1) do not include any common comparator that would allow meta-analysis of data for any of the TKIs or quantitative indirect comparison across TKIs. The pivotal studies and the direct comparison of sunitinib and pazopanib were included in a narrative comparison (section 5.1). In addition, one study compared combination of nivolumab and ipilimumab to sunitinib in first line treatment of clear cell advanced/ metastatic renal cell cancer (NCT02231749. Motzer et al. N Engl J Med. 2018;378(14):1277-90.) The comparison of biologic treatment to sunitinib was excluded after consultation with the Medicine Council secretariat. This approach was taken because inclusion of the trial would not add new options for meta-analysis of the sunitinib data nor new options for quantitative indirect comparison.

EPARs of the interventions was consulted for cross-checking and for completeness on the relevant outcomes. Furthermore, data from TIVO-1 not previously published in peer-reviewed publication was used in order for the dossier to be specific for the treatment naïve population defined in the Medicine Council protocol. These data have previously been presented at the ASCO 2013 conference (appendix D). Further data on the TIVO-1 subgroup including previously unpublished data is presented in appendix C.

4.1 Relevant studies

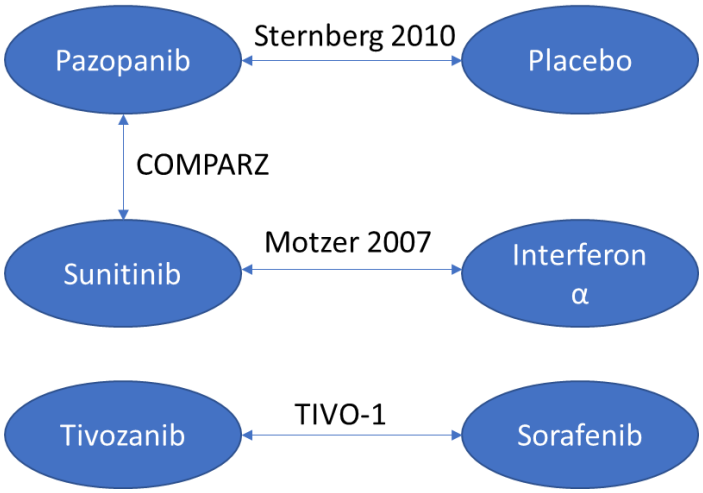
TABLE 3 RELEVANT STUDIES INCLUDED IN THE ASSESSMENT

Reference (title, author, journal, year)	Trial name (or name used for reference in this document)	NCT number	Dates of study (start and expected completion date)
Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. Motzer et al. N Engl J Med. 2007;356(2):115-24.	Motzer 2007	NCT00083889 and NCT00098657	August 2004 to September 2008
Overall survival and updated results for sunitinib compared with interferon alfa in patients with metastatic renal cell carcinoma. Motzer et al. J Clin Oncol. 2009;27(22):3584-90.	Motzer 2007	NCT00083889 and NCT00098657	August 2004 to September 2008
Health-related quality of life in patients with metastatic renal cell carcinoma treated with sunitinib vs interferon-alpha in a phase III trial: final results and geographical analysis. Cella et al. Br J Cancer. 2010;102(4):658-64.	Motzer 2007	NCT00083889 and NCT00098657	August 2004 to September 2008
Pazopanib in locally advanced or metastatic renal cell carcinoma: results of a randomized phase III trial. Sternberg et al. J Clin Oncol. 2010;28(6):1061-8.	Sternberg 2010	NCT00334282	April 2006 to December 2014
A randomised, double-blind phase III study of pazopanib in patients with advanced and/or metastatic renal cell carcinoma: final overall survival results and safety update. Sternberg et al. Eur J Cancer. 2013;49(6):1287-96.	Sternberg 2010	NCT00334282	April 2006 to December 2014

Pazopanib versus sunitinib in metastatic renal-cell carcinoma. Motzer et al. New England journal of medicine. 2013;369(8):722-731.	COMPARZ	NCT00720941	August 2008 to June 2019
Overall survival in renal-cell carcinoma with pazopanib versus sunitinib. Motzer et al. New England journal of medicine. 2014;370(18):1769-70.	COMPARZ	NCT00720941	August 2008 to June 2019
Tivozanib versus sorafenib as initial targeted therapy for patients with metastatic renal cell carcinoma: results from a phase III trial. Motzer et al. J Clin Oncol. 2013;31(30):3791-9.	TIVO-1	NCT01030783	December 2009 to June 2013

Figure 1 shows the resulting evidence net-work of studies included in the main narrative comparative analysis.

FIGURE 1 EVIDENCE NETWORK



Sources (primary publication)

Sternberg 2010: [1]; Motzer 2007: [2]; COMPARZ: [3]; TIVO-1:[4]

Sternberg 2010 (NCT00334282)

This randomized controlled phase III trial compared pazopanib to placebo in patient with clear cell RCC and good, intermediate and poor MSKCC prognosis. Two-third of the included patients had not received systemic treatment (66.6%) and one-third were previously treated (33.4%). A total of 435 patients were randomized (2:1) to pazopanib or placebo [1].

Motzer 2007 (NCT00098657 and NCT00083889)

A randomized phase III study compared sunitinib to IFN-a in clear cell patients with good, intermediate, and poor MSKCC prognosis, whom have not received systematic treatment previously[2]. An update by OS was published in 2009[5]. The study includes 750 patients who were randomized 1:1 to either sunitinib or IFN-a.

90% of the patients was previously treated with nephrectomy. The study primarily investigated PFS, and secondarily ORR, OS, HRQoL, and safety [2].

COMPARZ (NCT00720941)

COMPARZ is an open-label phase III randomized non-inferiority trial comparing pazopanib to sunitinib in patients with clear cell RCC with good to intermediate MSKCC prognosis, who had not previously received systemic treatment. The study pooled data from two trials; NCT00720941 (N:927) conducted North America, Europe, and Australia and NCT01147822 (N:183) conducted in China, Taiwan, and South Korea. A total of 1110 patients were included and randomized 1:1 to pazopanib (n=557) or sunitinib (n=553). The proportion of patients in good or intermediate MSKCC prognosis was 27 % and 59 % respectively. 83 % of patients where previously treated with nephrectomy. The primary endpoint in the trial was PFS. Secondary endpoints included ORR, OS, HRQoL and safety [3].

TIVO-1 (NCT01030783)

Study TIVO-1 was a 2-year pivotal Phase 3, Randomized, Controlled, Multicentre, Open-label Study to Compare Tivozanib Hydrochloride (AV-951) to Sorafenib in Patients with recurrent or metastatic RCC with a clear cell component who had undergone prior nephrectomy (complete or partial) for excision of the primary tumor. Patients had no prior therapy or no more than 1 prior systemic therapy for metastatic RCC (prior systemic therapy could include immunotherapy, chemotherapy, hormonal therapy or an investigational agent, but prior VEGF-directed therapy and prior therapy with an agent targeting the mammalian target of rapamycin [mTOR] pathway were prohibited).

Patients in the sorafenib arm of who experienced radiographic evidence of progression were given the option to cross over to receive tivozanib, while patients randomized to tivozanib were discontinued from the study once progression was confirmed and continued treatment with standard of care as per local availability of therapy in their particular country.

The primary endpoint was PFS and secondary endpoints included OS, ORR (based on RECIST criteria), safety and tolerability, and HRQoL.

70% of patients had no prior systemic treatment [4].

4.2 Main characteristics of included studies

An overview is provided in section 5.1.1. A detailed presentation of each study characteristics is available in Appendix A tables A2a-d.

5 Clinical questions

5.1 What is the added clinical value of tivozanib in treatment-naïve, adult mRCC patients?

5.1.1 Presentation of relevant studies

Table 1 list the design of the pivotal trials of sunitinib, pazopanib, and tivozanib. Comparing baseline characteristics of the studied populations (Table 2), all pivotal trials included analogous populations with advanced or metastatic RCC. All patient groups across trials were of similar median age (59-60 years), most commonly males on equal ECOG performance status [either fully active (ECOG = 0) or restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (ECOG = 1)] with lung or lymph nodes metastasis. For most participants their prognostic risk was intermediate, and the majority were treatment naïve.

TABLE 1 PIVOTAL CLINICAL TRIALS FOR SUNITINIB, PAZOPANIB, AND TIVOZANIB

Reference	Study design	Studied drugs	Population charactristics, n	% treatment naïve	Primary study endpoint	Secondary study endpoints
Sternberg CN et al, 2010 [1] Sternberg et al 2013 **[6]**	Randomized, double-blind, placebo-controlled, multi-centre, phase III clinical trial	Pazopanib, placebo	Treatment-naive and cytokine-pretreated patients with advanced RCC, 435	Pazo: 67 PBO: 67	PFS	ORR OS HRQoL Adverse events
Motzer RJ et al, 2007[2] Motzer RJ et al, 2009[5] Cella et al, 2010[7]	Randomized, open label, one-way cross over phase III, multi-centre, clinical trial	Sunitinib, IFN-α	Treatment-naïve patients with metastatic clear cell RCC, 750	Suni: 100 IFN: 100	PFS (superiority of sunitinib over IFN-α as first-line treatment)	OS ORR HRQoL Adverse events
COMPARZ: Motzer RJ et al, 2013[3] Motzer et al. 2014 **[8]**	Randomized, open-label, phase 3, multi-centre, trial	Pazopanib, sunitinib	Treatment-naïve patients with advanced or metastatic clear cell RCC, 1110	Pazo: 100 Suni: 100	PFS	OS ORR HRQoL Adverse events Medical resource utilization
TIVO-I Motzer JR et al, 2013[4] Sternberg et al. 2013[9] Appendix C Tivozanib EPAR	Randomized, open label, one-way cross over, multi-centre, phase III clinical trial	Tivozanib, sorafenib	Patients with metastatic RCC, 0 or 1 prior therapies,517	Tivo: 70 Sora: 70	PFS	OS ORR HRQoL Adverse events

PFS: progression free survival; OS: overall survival; ORR: objective response rate; HRQoL: health-related Quality of Life; Suni: sunitinib; Pazo: pazopanib; Tivo: tivozanib; sora: sorafenib; PBO: placebo; IFN/IFN-α: interferon alfa; RCC: renal cell carcinoma; EMA: European Medicines Association; RCC: Renal Cell Carcinoma; SmPc: Summary Product Characteristics; EPAR: European Public Assessment Report

TABLE 2. BASELINE CHARACTERISTICS OF PATIENTS IN THE PIVOTAL CLINICAL TRIALS OF SUNITINIB, PAZOPANIB AND TIVOZANIB

Reference	Age (median, years)	Gender male,%	First two most common sites of metastasis (%)	ECOG or Karnovsky PS, %		MMSKCC prognostic group, %	
				0	1	Favorable	Intermediate
Motzer RJ et al, 2007[2] Motzer RJ et al, 2009[5] Cella et al, 2010[7]	Sunitinib vs. IFN-α						
	Suni: 62 IFN: 59	Suni: 71 IFN: 72	**Lung** Suni: 78 IFN: 79 **Lymph nodes** Suni: 58 IFN: 53	Suni: 62 IFN: 61	Suni: 38 IFN: 39	Suni: 38 IFN: 34	Suni: 56 IFN: 59
Sternberg CN et al, 2010 [1] Sternberg et al 2013 **[6]**	Pazopanib vs. Placebo						
	Pazo: 59 PBO: 60	Pazo: 68 PBO: 75	**Lung** Pazo: 74 PBO: 73 **Lymph nodes** Pazo: 54 PBO: 59	Pazo: 42 PBO: 41	Pazo: 58 PBO: 59	Pazo: 39 PBO: 39	Pazo: 55 PBO: 53
Motzer RJ et al, 2013[3] (COMPARZ); Motzer et al. 2014 **[8]**	Pazopanib vs. Sunitinib						
	Pazo: 61 Suni: 62	Pazo: 71 Suni: 75	**Lung** Pazo: 76 Suni: 77 **Lymph nodes** Pazo: 40 Suni: 45	Pazo: 75 Suni: 76	Pazo: 25 Suni: 24	Pazo: 27 Suni: 27	Pazo: 58 Suni: 59
Motzer RJ et al, 2013[4] (TIVO-I) Sternberg et al. 2013[9] Tivozanib EPAR; Appendix C	Tivozanib vs Sorafenib						
	Tivo: 59 Sora: 59	Tivo: 71 Suni: 74	**Lung** Tivo: 82 Sora: 79 **Lymph nodes** Tivo: 70 Sora: 65	Tivo: 45 Suni: 54	Tivo: 55 Sora:46	Tivo: 27 Sora: 34	Tivo: 67 Sora: 62

Suni: sunitinib; Pazo: pazopanib; Tivo: tivozanib; sora: sorafenib; PBO: placebo; IFN/IFN-α: interferon alfa; RCC: renal cell carcinoma; EMA: European Medicines Association; ECOG PS: Eastern Cooperative Oncology Group performance status; MSKCC, Memorial Sloan-Kettering Cancer Center; RCC: Renal Cell Carcinoma; SmPc: Summary Product Characteristics; EPAR: European Public Assessment Report

5.1.2 Results per study

Data extraction tables are available in appendix A (table A3a-d). In the following sections the results are described for the ITT/ full safety population and – if applicable – for the population of treatment naïve (population of interest according to the scientific questions). The findings for each outcome in the treatment naïve population are summarized in the beginning of each section.

Sternberg 2010 (pazopanib vs placebo)

Summary results for treatment naïve subgroup

Sternberg 2010	
Data reported here	Treatment naïve subgroup (pazopanib N:155; placebo N: 78) of study population (290 vs 145)
Overall survival	
Median (95% CI), Hazard ratio (95% CI)	Median (months): 22.9 (17.6–25.4) vs 23.5 (12.0–34.3). Difference -0.6 (own calculation) [6] HR: 1.01 (0.72–1.42) ITT analysis[6] KM curve not reported
PFS	
Median (95% CI), Hazard ratio (95% CI)	Median (months): PFS 11.1 vs 2.8 months (CI not reported). Difference 8.3 (own calculation) [1] HR: 0.40 (0.27 to 0.60) [1] KM curve available [1]
HRQoL	
Generic instruments	EORTC QLQ-C30 and EQ-5D collected. Results not reported for subgroup
Other	Not reported
Grade 3-4 AE	
Frequency Relative risk (95% CI)	Not reported
ORR	
ORR rate (95% CI)	Pazopanib:32% (24.3% - 38.9%) vs placebo 4% (0.0 - 8.1%) [1]. Difference 28% points*. Rate ratio (RR): 8.0 (2.63-24.3)*
Duration of response	
	Not reported

* Own calculation. 95% CI for Rate ratio calculated using normal approximation to log-RR distribution

Overall survival

For the treatment naïve sub-population, the ITT analysis revealed a HR of 1.01 (95% CI: 0.72–1.42) while the exploratory analysis with cross-over censoring revealed a HR of 0.64 (95% CI: 0.266-1.248) [10]

In the total patient population, median OS was 22.9 months (95%CI: 19.9-25.4) for pazopanib and 20.5 months (95% CI: 15.6-27.6) for placebo. The difference was not statistically significant (HR:0.91 (95% CI: 0.71-1.16 [p=0.224]). Overall survival was confounded by the fact that 54% of patients in the placebo arm crossed over to pazopanib after progression. In exploratory analyses, OS data was censored at cross-over. In the overall study population, a statistically significant risk reduction was observed in pazopanib treated patients compared to placebo (HR: 0.50 (95% CI: 0.315-0.762)[1]

PFS

Median PFS in the sub-group of treatment naïve was 11.1 months (pazopanib) compared to 2.8 months (placebo) resulting in a HR of 0.40 (95% CI: 0.27-0,60 [p<0,0001]) [1]

HRQoL

The study found no significant effect on HRQoL (EORTC QLQ-C30 and EQ-5D)[1]. Difference in average change from baseline in each score were reported by week of observation. Base-line averages and variability not reported.

Grade 3-4 adverse events

Adverse events were not reported for the treatment-naïve subgroup. In the total patient population, the frequency of grade 3-4 treatment emergent adverse events occurred in 21% of subjects given pazopanib, and in 7% of patients treated with placebo.

According to the authors, the side effect profiles were comparable for both groups; treatment naïve, and those previously treated with cytokines. The most occurring grade 3-4 side effects for pazopanib were hypertension and diarrhea [1].

Response rate

ORR in treatment naïve patients treated with pazopanib was 32% compared to 4% (difference of 28%-points; RR: 8.0 (95%CI: 2.63-24.3). [1]

The study found an ORR at 88 (30%) for pazopanib and 5(3%) for placebo in the overall population.

Response duration

Response duration not reported for treatment naïve subgroup.

The median duration of response in the pazopanib group was 58.7 weeks (95% CI, 52.1 to 68.1 weeks) as per IRC review [11] equivalent to 13.5 months (95% CI, 12.0 to 15.7) when assuming 30.44 days per month (365.25:12).

Motzer 2007 (sunitinib vs interferon alpha)

Summary results

Motzer 2007	
Data reported here	Full study population. All treatment naïve (sunitinib N: 375; IFN N:375)
Overall survival	
Median (95% CI), Hazard ratio (95% CI)	Median (months) 26.4 months (23.0-32.9) vs 21.8 months (17.9-26.9). Difference: 4.6 (own calculation) HR: 0.821 (0.673-1.001) KM curve available [5]
PFS	
Median (95% CI), Hazard ratio (95% CI)	Median (months): 11 months (10-12) vs 5 months (4-6). Difference 6 (own calculation), HR of 0.42 (0.32-0.54) KM curve available[2].
HRQoL	
Generic instruments	FACT-G total score 82.89 vs 73.88. Difference 6.62 p<0.0001. (N not reported, CI not reported, SD not reported, Base-line score not reported) [7] FKSI-DRS score 29.90 vs 27.53. Difference 3.56 p<0.0001. (N not reported, CI not reported, SD not reported, Base-line score not reported) [7] EQ-5D index 0.75 vs 0.69. Difference 0.05 p=0.0078 (N not reported, CI not reported, SD not reported, Base-line score not reported) [7] For all instruments, total score refers to the least-square means for each treatment group estimated using data from all post-randomization assessments. The overall differences between the two treatment groups were estimated and tested using repeated-measures mixed-effects models controlling for the assessment time, treatment-by-time interaction and the baseline score.[7]
Other	None reported
Grade 3-4 AE	
Frequency Relative risk (95% CI)	Grade 3-4 AEs: 50.0% vs 26.0% RR: 1.92 (1.57-2.35)*
ORR	
ORR rate (95% CI)	31% (26%-36%) vs 6% (4%-9%) No relative measure reported
Duration of response	
	Not reported

* Own calculation. 95% CI for Risk Ratio calculated using normal approximation to log-RR distribution

Overall survival

The study found no significant difference in median OS for all participants, with a median OS for sunitinib at 26.4 months (95% CI: 23.0-32.9) and 21.8 months (95% CI: 17.9-26.9) for IFN-a, which amounts to an HR at 0.821 (95% CI: 0.673-1.001 [p=0.051]) [5].

In an explorative analysis which censored 25 patients, who switched from IFN-a treatment to sunitinib treatment, the study found a median OS 26.4 months (95% CI: 23.0-32.9) and 20.0 months (95% CI: 17.8-26.9), which amounted to an HR at 0.808 (95% CI: 0.661-0.987 [p=0.036])[5].

PFS

The study found a median PFS for sunitinib at 11 months (95% CI:10-12) and for IFN-a at 5 months PFS (95% CI: 4-6), amounting to a HR of 0.42 (95% CI: 0.32-0.54 [p<0.001]) [2].

HRQol

The study found a FACT-G mean total score in post-randomization assessments at 82.89 for sunitinib, and 73.88 for IFN-a (difference 6.62; p<0.001) [7].

A mean FACT-kidney Symptom Index (FKSI-DRS) score at 29.90 and 27.53 (difference 3.56; <0.001) was reported. [7]

The mean EQ-5D index in the post-randomization period was 0.75 for sunitib vs 0.69 for INF-a (difference 0.05 p=0.0078) [7]

No data on statistical variation or change from base-line was reported for either endpoint.

Grade 3-4 adverse events

The frequency of grade 3-4 AEs were at 26.0% for IFN-α and 50.0% for sunitinib [2].

Response rate

The study found a higher ORR for sunitinib of 31% (95% CI, 26%-36%) and 6% in the INF-α group (95% CI, 4%-9%). The difference was statistically significant (P<0.001) [2].

Duration of response

Not reported

COMPARZ (pazopanib vs sunitinib)

Summary results

COMPARZ	
Data reported here	Full study population. All treatment naïve (pazopanib: 557; sunitinib: 553)
Overall survival	
Median (95% CI), Hazard ratio (95% CI)	Median (months) 28.3 months (26.0-35.5) vs 29.1 months (25.4-33.1) [8] Difference: -0.8* HR: 0.92 (0.79-1.06) [8] KM curve available [8]
PFS	
Median (95% CI), Hazard ratio (95% CI)	Median (months): 8.4 months (8.3-10.9) vs 9.5 months (8.3-11.1). [3] Difference -1.1* HR of 1.05 (0.90-1.22) KM curve available[3]
HRQoL	
Generic instruments	FKSI-19: Patients in the pazopanib arm reported a 1.41 point higher change compared to patients in the sunitinib arm (p=0.02). The change standardized by the pooled standard deviation at base-line measurement was 0.14 SD[3]
Other	FACIT-F. The average change from baseline was 2.32 point higher for pazopanib compared to sunitinib (p<0.001) equivalent to a 0.24 pooled standard deviations for base line FACIT-F[3]
Grade 3-4 AE	
Frequency Relative risk (95% CI)	Treatment-Emergent Adverse Event (reported in more than 10% of patients in either arm) of grade 3 or grade 4: 74% vs 74%* [3] RR: 1.0 (0.93-1.07)**
ORR	
ORR rate (95% CI) Rate ratio (95% CI)	31 % (26.9-34.5) vs 25 % (21.2-28.4). Difference 6% (0.7-11.2) [3] No relative measure reported (p=0.03, Fischers exact test) [3] Rate ratio: 1.24 (1.03-1.50)**
Duration of response	
	Not reported

* Own calculation.

** Own calculation. 95% CI for Risk/ Rate Ratio calculated using normal approximation to log-RR distribution

Overall survival

The final analysis of OS was conducted in 2013 after 60% of events had occurred and confirmed the initial results; overall median OS for pazopanib was 28.3 months (95 % CI: 26.0-35.5) and 29.1 months (95 % CI:

25.4-33.1) for sunitinib. The relative mortality was not statistically significant (HR:0.92 (95 % CI: 0.76-1.06) [p=0.24 by a stratified log-rank test] [8].

PFS

Median PFS was 8.4 month (95 % CI: 8.3-10.9) for pazopanib and 9.5 months (95 % CI: 8.3-11.1) for sunitinib. The resulting HR was 1.05 (95 % CI: 0.90-1.22) based on which non-inferiority of pazopanib compared to sunitinib was concluded (predefined non-inferiority criteria at upper CI for HR at 1.25)[3].

HRQoL

Patients in the pazopanib arm reported a 1.41 point higher change in the FKSI-19 instrument compared to patients in the sunitinib arm (p=0.02). The change standardized by the pooled standard deviation at base-line measurement was 0.14 SD[3].

A statistically significant difference was observed on the FACIT-F instrument in favour of pazopanib compared to sunitinib. The average change from baseline was 2.32 point higher for pazopanib compared to sunitinib (p<0.001) equivalent to 0.24 standard deviations for base line FACIT-F[3].

Base line mean score was not reported for either instrument and therefore it is not possible to calculate standardized changes from baseline for the separate treatments.

Grade 3-4 adverse events

Treatment-Emergent Adverse Event (reported in more than 10% of patients in either arm) of grade 3 or grade 4 was reported in 74% of patients treated with pazopanib and 74% of patients treated with sunitinib[3] (own calculation). The relative risk was calculated at 1.0 (95% CI 0.93-1.07) (own calculation).

Response rate

ORR was 31 % for pazopanib and 25 % for sunitinib (p=0.03)[3]

Duration of response

Not reported

TIVO-1 (tivozanib vs sorafenib)

Summary results

TIVO-1	
Data reported here	Subgroup of treatment naïve (tivozanib N: 181; sorafenib N: 181) of total population (260 vs 257)
Overall survival	
Median (95% CI), Hazard ratio (95% CI)	Median (months) 27.1 vs 29.5 (CI not reported). Difference: -2.4 (own calculation) (appendix C) (HR 1.14; 95% CI 0.8599 to 1.532) (appendix C) KM curve available (appendix C)
PFS	
Median (95% CI), Hazard ratio (95% CI)	Median (months):12.7 months (9.1-15.0) vs 9.1 months (7.3-10.8) (appendix C). Difference 3.6 (own calculation) HR: 0.756 (0.580-0.985) (appendix C) KM curve available. Appendix C
HRQoL	
Generic instruments	Not reported in subgroup of treatment naïve
Other	Not reported in subgroup of treatment naïve
Grade ≥3 AE	
Frequency Relative risk (95% CI)	Treatment-Emergent Adverse Event (reported in more than 10% of patients in either arm) of **grade 3 or higher**: 62% vs 70% (appendix C) RR: 0.89 (0.76-1.03) (own calculation)
ORR	
ORR rate (95% CI) Rate ratio (95% CI)	34.2% (27%-42%) vs 24.3% (18%-31%)[9]. Difference 0.09 (own calculation) Rate ratio: 1.42 (1.01-1.95) (own calculation)
Duration of response	
	Not reported

Overall survival

The final OS analysis in the overall study population (ITT) showed a trend toward longer survival on the sorafenib arm than on the tivozanib arm (median, 29.3 v 28.8 months; HR, 1.245; 95% CI, 0.954 to 1.624; P=0.105). A greater proportion of patients in the sorafenib arm received a next-line targeted therapy for RCC (63% in the sorafenib arm v 13% in the tivozanib arm). Almost all of the patients in the sorafenib arm who received a next-line targeted agent (156 of 162) received tivozanib. Compared with patients from Central/Eastern Europe, patients from North America/Western Europe on the tivozanib arm received more next-line therapy, including next-line targeted therapy. A trend toward longer OS in the tivozanib arm (HR: 0.503; 95% CI: 0.174 to 1.451; p =0.195) was observed in the stratum of patients from North America/Western Europe (N:40)[4].

OS for the treatment-naïve population is not available in published literature, therefore a post-hoc KM curve was produced from individual patient data for the purpose of health technology assessments. Median OS was estimated at 27.1 months for tivozanib versus 29.5 months for sorafenib (HR 1.14; 95% CI 0.8599 to 1.532, p=ns) in line with the results in the total population (unpublished data, Appendix C).

PFS

Median PFS in the treatment naïve population was 12.7 month (95 % CI: 9.1-15.0) for tivozanib and 9.1 months (95 % CI: 7.3-10.8) for sorafenib. The resulting HR was 0.756 (95 % CI: 0.580-0.985 [p=0.037])[4, 9].

HRQoL

In the overall study population, HRQoL was maintained at a level comparable to the baseline level during the first 12 months of treatment in both arms for all three instruments used (FACT-G, FSKI-DRS, and EQ-5D). The standardized change from base-line to 12 months in the EQ-5D utility index was -0.2 standard deviations (a decline of 7% of base-line value) in patients treated with tivozanib compared to -0.23 standard deviations or 8% decline in patients treated with sorafenib. No data is available for sub-groups by previously treatment[4].

Grade 3-4 adverse events

Grade ≥3 AEs were reported in 338 patients (61%) overall: 159 (61%) in the tivozanib arm versus 179 (70%) in the sorafenib arm[4]. Grade 3-4 events were reported in 61% vs 70% (own calculation)

Safety data from the treatment naïve-subpopulation has been presented at ASCO 2013. AE of grade 3 or above were reported by 62% in the tivozanib arm and 70% in the sorafenib arm [9] from which a relative risk (RR) of 0.89 (95% CI: 0.76-1.03)) was calculated. These rates were similar to those seen in the overall TIVO-1 population [9]

Response rate

The confirmed ORR for tivozanib, based on blinded independent radiology review of tumor response, was 33.1% (95% CI, 27.4% to 39.2%) versus 23.3% (95% CI, 18.3% to 29.0%) for sorafenib (p=0.014) [4].

ORR for the treatment-naïve subpopulation has been presented at ASCO 2013. The ORR was significantly higher with tivozanib compared with sorafenib: 34.2% versus 24.3%, (OR 1.62, 95% CI 1.03 to 2.56, p=0.038) (see appendix C). The rate ratio was calculated at 1.41 (1.01-1.95) (own calculation).

Duration of response

Median duration of response (DOR) has not been reported for the subgroup of treatment-naïve. In the full patient, ITT population, DOR by independent radiological review was 15.0 months for tivozanib compared to 12.9 months for sorafenib. The hazard ratio was 0.823 (90% CI: 0.488, 1.388). When investigator assessed, including the extension study data, the difference in median duration of response was further increased: 24.3 months for tivozanib vs. 12.5 months for sorafenib [12].

5.1.3 Comparative analyses

There are no direct comparisons of tivozanib to either sunitinib or pazopanib. Furthermore, no common comparator is available to allow for a quantitative, indirect comparison (see section 4.1). Below a narrative synthesis of the available trials are provided. Design and base-line characteristic of the clinical trial is presented in section 5.1.1). Further information on base-line characteristics of patients in the TIVO-1 subgroup of treatment naïve patients is presented in appendix C. All pivotal trials included analogous populations with advanced or metastatic RCC. All patient groups across trials were of similar median age (59-60 years), most commonly males on equal ECOG performance status (ECOG 0-1) with lung or lymph nodes metastasis. For most participants their prognostic risk was intermediate.

OS and PFS

Improved OS has been shown for sunitinib compared to IFN-alpha, but not in comparison to pazopanib (Table 3). Pazopanib showed numerical lower survival compared to placebo in treatment naïve, and tivozanib show numerical lower survival compared to sorafenib (Table 3). In both trials the OS results are

confounded by cross-over to investigational drug after progression [2, 4, 12]. Data in Table 3 are with-out correction for cross-over.

Pazopanib demonstrated improved PFS compared to placebo, sunitinib compared to IFN-alpha, and tivozanib compared to sorafenib (Table 4). In COMPARZ non-inferiority of pazopanib vs sunitinib on PFS was demonstrated.

TABLE 3 COMPARISON OF OS IN TREATMENT NAÏVE PATIENTS BY STUDY

Study	Study arm	N	Median OS (months)	95% CI	Difference	Hazard ratio	95% CI
Sternberg 2010*	Pazopanib	155	22.9	17.6–25.4	-0.6	1.01	0.72–1.42
	Placebo	78	23.5	12.0–34.3			
Motzer 2007	Sunitinib	375	26.4	23.0-32.9	4.6	0.821	0.673-1.001
	IFN-α	375	21.8	17.9-26.9			
COMPARZ	Pazopanib	557	28.3	26.0–35.5	-0.8	0.92	0.79-1.06
	Sunitinib	553	29.1	25.4–33.1			
TIVO-1*	Tivozanib	181	27.1	not reported	-2.4	1.14	0.860- 1.532
	Sorafenib	181	29.5	not reported			

* Based on subgroup

Sources: Sternberg 2010: [1, 6]; Motzer 2007: [2], COMPARZ: [3], TIVO-1:[4, 9], Appendix C

TABLE 4 COMPARISON OF PFS IN TREATMENT NAÏVE PATIENTS BY STUDY

Study	Study arm	N	Median PFS (months)	95% CI	Difference	Hazard ratio	95% CI
Sternberg 2010*	Pazopanib	155	11.1	not reported	8.3	0.40	0.27-0.60
	Placebo	78	2.8	not reported			
Motzer 2007	Sunitinib	375	11	10-12	6	0.42	0.32-0.54
	IFN-α	375	5	4-6			
COMPARZ	Pazopanib	557	8.4	8.3–10.9	-1.1	1.05	0.90-1.22
	Sunitinib	553	9.5	8.3–11.1			
TIVO-1*	Tivozanib	181	12.7	9.1-15.0	3.6	0.756	0.580-0.985
	Sorafenib	181	9.1	7.3-10.8			

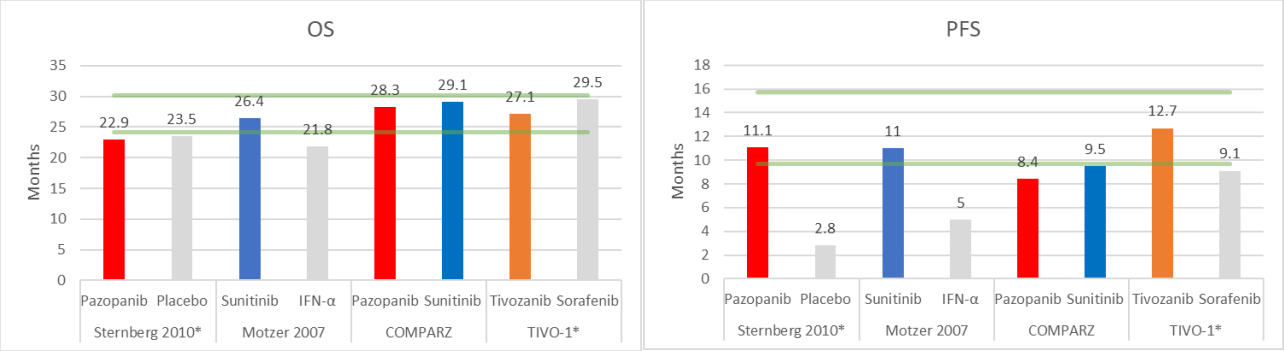
* Based on subgroup

Sources: Sternberg 2010: [1, 6]; Motzer 2007: [2], COMPARZ: [3], TIVO-1:[4, 9], Appendix C

Figure 2 show the level of median PFS and median OS observed in the sub-group of treatment-naïve in the clinical trials. Horizontal lines (Figure 2) show the range of median survival with in the MCID of ±3 months difference from the median survival observed for tivozanib in the treatment naïve subgroup.

Overall, these figures suggest results in terms of PFS and OS for the three products at the same level and that they are broadly similar. Based on these results, sunitinib, pazopanib and tivozanib have shown comparable efficacy in their pivotal clinical trials.

FIGURE 2 MEDIAN OS AND PFS IN SUB-GROUP OF TREATMENT-NAÏVE MRCC PATIENTS



* Based on subgroup; Horizontal lines mark the results for tivozanib ±3 month (MCID)

Sources: Sternberg 2010: [1, 6]; Motzer 2007: [2], COMPARZ: [3], TIVO-1:[4, 9], Appendix C

HRQoL

HrQoL was studied using different instruments. Furthermore, results were insufficiently reported in the publications to compare outcomes using standardized change from base-line.

None of the interventions has shown significant and clinically relevant differences in EORTC or EQ-5D relative to other TKIs. This includes tivozanib compared to sorafenib (EQ-5D), however, results from this trial were only available for the full population of treatment-naïve and previously treated.

In treatment naïve populations, pazopanib has shown statistical superiority to sunitinib using the symptom-specific FACIT-F instrument in the COMPARZ trial and a statistical significant improvement of 1 point on the FKSI-10 instrument (not evaluated as clinically significant by the authors) [3]. Sunitinib demonstrated statistically significant improvement on the mean FKSI-DRS (2.56 points higher) and FACT-G (6.62 points higher) in comparison to INF-α[2].

No differences in FACT-G or FKSI-DRS change from base-line were found between tivozanib and sorafenib in the TIVO-1 trial[4]. Data in the subgroup of treatment naïve subpopulation are not available.

Magnitude of FKSI and FACT-G across trials cannot be compared due to different analysis methods and insufficient reporting.

Safety

Table 5 show the comparison of AE grade 3-4 (for TIVO-1 grade ≥ 3) in the population of treatment naïve. Sunitinib was associated with a risk grade 3-4 AE in the Motzer 2007 trial compare to interferon alpha[2], however at absolute levels lower than observed in COMPARZ [3]. A trend towards lower levels of AE grade ≥ 3 was observed in tivozanib treated patients compared to sorafenib in TIVO-1 (appendix C) with a risk ratio of 0.89 (95% CI: 0.76-1.03).

TABLE 5 COMPARISON OF AE GRADE 3-4** IN TREATMENT NAÏVE PATIENTS ACROSS TRIALS

Study	Study arm	N	Frequency	Difference	Risk ratio	95% CI
Sternberg 2010*	Pazopanib	Data not available for treatment naïve sub-group				
	Placebo					
Motzer 2007	Sunitinib	375	50%	0.24	RR: 1.92	1.57-2.35
	IFN-α	360	26%			
COMPARZ	Pazopanib	554	74%	0.00	RR: 1.00	0.93-1.07
	Sunitinib	548	74%			
TIVO-1*,**	Tivozanib	181	62%	-0.08	RR: 0.89	0.76-1.03
	Sorafenib	181	70%			

* Subgroup of study population

** For TIVO-1 treatment naïve subgroup only AE grade ≥ 3 is reported

Sources: Sternberg 2010: [1, 6]; Motzer 2007: [2], COMPARZ: [3], TIVO-1:[4, 9], Appendix C

Response

ORR in treatment naïve patients is compared across studies in Table 6 and Figure 3. ORR for tivozanib was reported as 34% in the treatment naïve subgroup and significantly higher than sorafenib 24% (p=0.038) in treatment naïve[9], with a ARR of 0.10 this difference meet the criteria for being clinically relevant. The level of response compares with the range of ORR found for the other RCTs (25% to 31%). In the COMPARZ trial pazopanib had a significantly higher response compared to sunitinib (31% vs 25%; p=0.03)[3] reaching an ARR of 0.06. Sunitinib has shown significantly higher response rates (31% vs 6%; p<0.001) compared to interferon-alpha. Overall the levels of response seem to similar for the three TKIs in treatment naïve patients and the observed levels are within the MCID limits of ±0.10 (Figure 3)

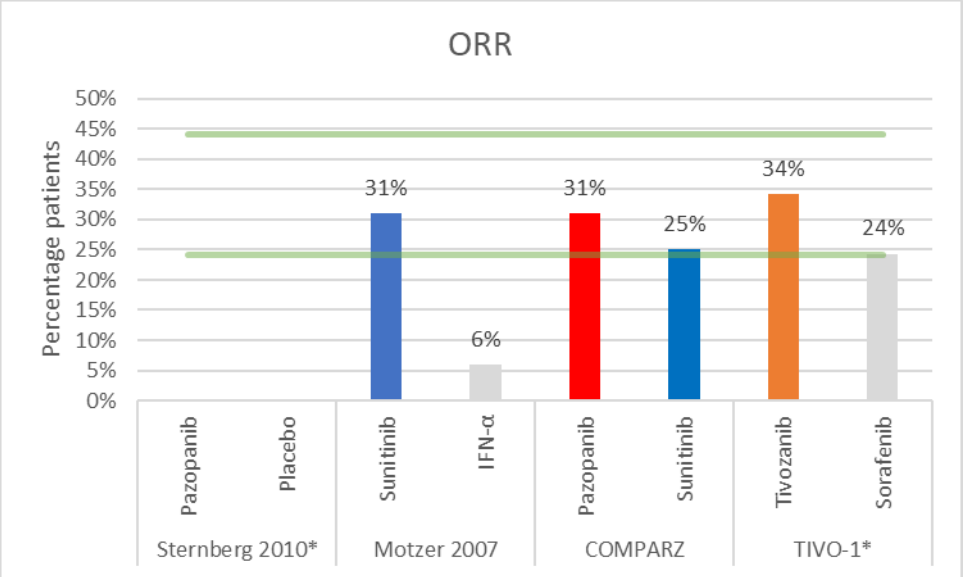
TABLE 6 ORR IN TREATMENT NAÏVE PATIENTS WITH ABSOLUTE AND RELATIVE RATE CHANGES

Study	Study arm	N	ORR (95% CI)	Difference	P value	Rate ratio**	95% CI**
Sternberg 2010*	Pazopanib	155	Data not available for treatment naïve sub-group				
	Placebo	78					
Motzer 2007	Sunitinib	375	31% (26%-36%)	0.25	<0.001	5.17	3.37-7.93
	IFN-α	375	6% (4%-9%)				
COMPARZ	Pazopanib	557	31% (26.9-34.5)	0.06	0.03	1.24	1.03-1.50
	Sunitinib	553	25% (21.2-28.4)				
TIVO-1*	Tivozanib	181	34.2% (27%-42%)	0.09	0.038	1.41	1.01-1.95
	Sorafenib	181	24.3% (18%-31%)				

* Subgroup of treatment naïve; ** own calculation

Sources: Sunitinib, IFN-α: Motzer 2007 [2], Tivozanib, Sorafenib: TIVO-1[4, 9], appendix C. Pazopanib, Sunitinib: COMPARZ [3]

FIGURE 3 ORR IN TREATMENT NAÏVE PATIENTS ACROSS STUDIES



* Based on subgroup; Horizontal lines mark the results for tivozanib ± 0.01 (MCID)

Sources: Sternberg 2010: [1, 6]; Motzer 2007: [2], COMPARZ: [3], TIVO-1:[4, 9], Appendix C

Duration of response was insufficiently reported and do not allow for indirect comparison. In the overall population in TIVO-1, the median duration of response in tivozanib was 15.0 months (not statistically different from that of sorafenib 12.9 months)[12] and on level with that of pazopanib in one placebo-controlled trial (13.5 months)[11].

6 Scientific discussion

Deviation from the protocol

Aspect	Discussion
Da der er stor variation i forventet overlevelse for de tre prognosegrupper (god, intermediær og dårlig) udtrykt ved en variation på 6-34 måneder afhængigt af prognosegruppe, ønsker fagudvalget at orientere sig i data opgjort for patienter i hver enkelt prognosegruppe.	The review has shown that comparable data by prognosis group is difficult to establish for the treatment naïve treatment population (in itself a subgroup in the TIVO-1 and Sternberg 2010 trials).
Den samlede kliniske merværdi af tivozanib baseres, med udgangspunkt i den indsendte foreløbige ansøgning, på en beregning af effekt ved 12 måneder og 24 måneder	Separate analyses were not performed by the 12 and 24 months follow-up. For OS the longest reported follow-up is used. Where KM curves for the treatment naïve population is available this noted (but due to copyright not included)

Comparative analyses

Given that head-to-head studies of tivozanib versus pazopanib or sunitinib have not been carried out and the only available RCT evidence is versus sorafenib, indirect comparison is the only way to gauge the relative efficacy of tivozanib versus pazopanib or sunitinib. Given the lack of common comparator in the set

of clinical studies (section 5.1.1) no quantitative analyses were performed. Based on the narrative synthesis the efficacy and safety seem to be at least comparable to both pazopanib and sunitinib.

Efficacy

The finding in the narrative synthesis above document that efficacy of the three TKIs are similar are supported by indirect comparisons included a broader range of comparators allowing for quantitative synthesis methods.

Iacovelli et al. (2016) compared PFS, OS, and ORR of newer targeted agents (TA) compared to sorafenib and performed a meta-analysis of trials with sorafenib as the common comparator[13]. Sorafenib was selected because it was the first TA to report significant benefit in a large phase III trial. Published data from sorafenib controlled phase II+III trials were available for sunitinib, tivozanib, axitinib, dovitinib, and temsirolimus. The authors concluded that the newer TA are more active in reducing the risk of progression than sorafenib (HR: 0.78; p<0.001) but no difference in terms of OS was observed (HR: 1.07; p = 0.18). ORR was improved by 48% (HR 1.48; p<0.001) when comparing the newer TAs to sorafenib. For all three outcomes there were no statistically significant heterogeneity between included trials.

Iacovelli et al. (2016) presented the Forest plots for PFS, OS, and ORR [13]. The HR for PFS of tivozanib compared to sorafenib (TIVO-1) is on level with the overall estimate for all newer TAs compared to sorafenib and comparable to the HR of sunitinib compared to sorafenib in phase II (CROSS-J-RCC) and phase III (SWITCH) trials[13].

The Forest plots for the ORR outcome also show that the relative risk of tivozanib compared to sorafenib observed in TIVO-1 is very close to the aggregated estimate across all TA compared to sorafenib. Based on the SWITCH trial, sunitinib is numerically performing slightly worse on the ORR outcome compared to sorafenib, but the CI is wide and crosses one[13].

Forest plots for the OS outcome showed that neither sunitinib nor tivozanib HRs were significantly different from 1 in the comparisons to sorafenib. The HR of sunitinib compared to sorafenib is exactly 1 but it should be noted that the SWITCH trial was a cross-over design in which patient randomized to sunitinib was switched to sorafenib on progression and vice versa[13]. Numerically tivozanib performed less well than sorafenib in reducing OS, however, this should be seen on the background of investigator-driven cross-over of patients randomized to sorafenib to tivozanib after progression[4, 12]

While the review conducted by Iacovelli et al. [13] only included trials that included sorafenib as comparator, Larkin et al. (2015) conducted a network meta-analysis (NMA) including pazopanib, sunitinib, and tivozanib[14] but included other intervention to form a wider evidence network and allow NMA to be performed. NMA uses a network of comparative trials to estimate relative treatment effects between any two interventions contributing data. The authors report the results of the estimated HR of sunitinib for PFS compared to seven treatment strategies in first line treatment of mRCC including sorafenib, tivozanib and pazopanib. The TIVO-1 trial was included in the analysis, but linked to sunitinib only through two or more linked intervention in the network; partly via a phase II trial of sorafenib compared to IFN-α [15] and a trial comparing sunitinib to IFN-α (Motzer 2009)[2]; partly via a small sub-group analysis of sorafenib compared to placebo [16], a placebo-controlled trial of pazopanib (Sternberg 2010) [1] and a non-interiority trial of pazopanib compared to sunitinib (COMPARZ)[3]. The authors conclude that the HR of sunitinib of PFS compared to pazopanib (HR: 0.94; 95%CI 0.8-1.08) and tivozanib (HR: 0.76; 95%CI 0.48-1.13) are numerical in favor of sunitinib but not statistically significant different from 1[14]. The numerical advantage of sunitinib compared to tivozanib disappears when the network is re-analyzed without assuming

proportional hazard in the sorafenib/ IFN-α link (HR: 1.03; 95%CI 0.63-1.59)[14]. The analysis was conducted by Pfizer employees. The published NMA using a wider evidence network did not support superiority of one of the interventions with respect to efficacy.

The conclusions from the published indirect comparison are supported by a recent HTA of tivozanib. In their decision on tivozanib in first-line treatment of mRCC, *Tandvårds- och Läkemedelförmånsnämnden* (TLV) concluded based on the clinical evidence for tivozanib and the two published indirect comparisons:

Det saknas direkt jämförande studier mellan Fotivda och dess jämförelsealternativ. Av indirekta metaanalyser gör TLV bedömningen att Fotivda har en jämförbar effekt med jämförelsealternativen Sutent och Votrient. [17]

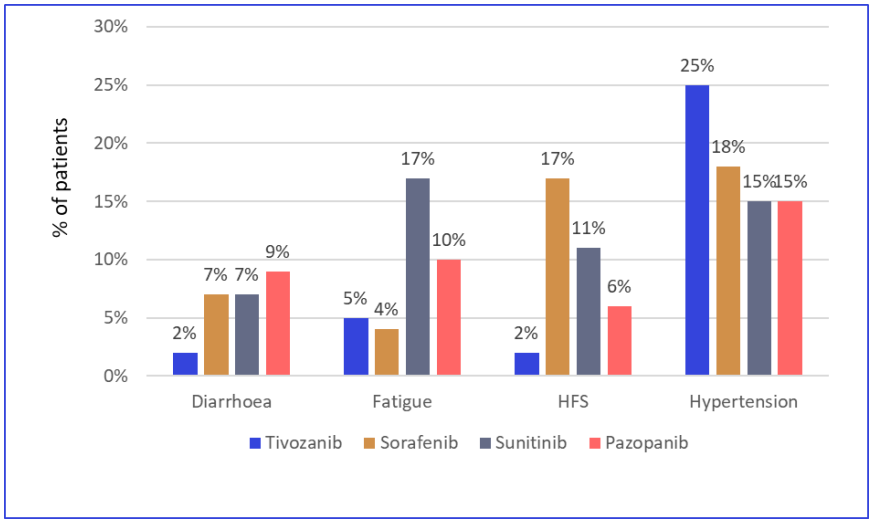
HRQoL and safety

The review of HRQoL reported in the RCTs suggest that generic instruments (such as EORTC-QLQ and EQ-5D) are insensitive to treatment effect with none of the intervention showing a significant effect over comparators. Significant and clinically relevant effects have been shown on the fatigue symptom specific scales, suggesting that treatment effects on HRQoL is closely linked to tolerability.

Incidence levels of high intensity AEs are at the same level across included studies, however differences in toxicity may exist. In the COMPARZ study which compared pazopanib and sunitinib, patients in both arms had a high incidence of adverse events with the most frequent of these events being fatigue, stomach problems, hand-foot syndrome and hypertension)[3].

Figure 4 compares the percent of patients reporting adverse events (occurring in at least 5% of patients) in the TIVO-1 (grade 3 or higher)[9] and COMPARZ trials (grade 3-4)[3]. Hypertension is the only single AE that appears more frequently in the tivozanib-arm compared to the other TKIs. Hypertension is a well-characterized adverse event common to all studied drugs linked to their inherent mechanism of action on vascular endothelial growth factor receptors (VEGFRs) 1,2 and 3[18, 19]. Although common, hypertension is routinely managed in clinical practice, and given the life expectancy of these patients, the occurrence of hypertension is unlikely to be factored into the choice of therapies for RCC.

FIGURE 4 GRADE 3-4 ADVERSE EVENTS* OCCURRING IN AT LEAST 5% OF PATIENTS: TIVO-1 AND COMPARZ



* For tivozanib and sorafenib grade 3-5 is reported

Sources: Tivozanib, Sorafenib: TIVO-1[4, 9], appendix C. Pazopanib, Sunitinib: COMPARZ [3]

Although a firm conclusion on HRQoL and safety is difficult to establish based on the available evidence, it should be noted that tivozanib was associated with less frequent dose reductions and treatment discontinuation compared to those reported with sunitinib and pazopanib (Table 7). In COMPARZ, treatment cessation due to adverse events was high across both groups (24% in the pazopanib group and 20% in the sunitinib group). Furthermore, a significant number of patients experienced a dose interruption or dose reduction. Despite pazopanib demonstrating improved safety and HRQoL over sunitinib, the incidence of quite substantive adverse events and the resulting impact on adherence to therapy remains high.

TABLE 7 FREQUENCY (%) OF DOSE REDUCTION, TREATMENT INTERRUPTION AND DISCONTINUATION WITH SUNITINIB, PAZOPANIB OR TIVOZANIB AS REPORTED IN TREATMENT NAÏVE PATIENTS (COMPARZ AND TIVO-1)

Reference	Dose reduction, treatment interruption, and discontinuation because of adverse events
Motzer RJ et al, 2013 (COMPARZ)[3]	**Pazopanib vs. Sunitinib**
	Dose reduction
	Pazo: 44% Suni: 51%
	Treatment interruption
	Pazo: 44% Suni: 49%
	Treatment discontinuation
	Pazo: 24% Suni: 20%
Motzer JR et al, 2013b (TIVO-I, treatment naïve)[9], appendix C	**Tivozanib vs Sorafenib**
	Dose reduction
	Tivo: 14% Sora: 41%
	Treatment interruption
	Tivo: 20% Sora: 36%
	Treatment discontinuation
	Tivo: 8% Sora: 8%

Suni: sunitinib; Pazo: pazopanib; Tivo: tivozanib; sora: sorafenib

7 References

1. Sternberg, C.N., et al., *Pazopanib in locally advanced or metastatic renal cell carcinoma: results of a randomized phase III trial.* J Clin Oncol, 2010. **28**(6): p. 1061-8.
2. Motzer, R.J., et al., *Sunitinib versus interferon alfa in metastatic renal-cell carcinoma.* New England Journal of Medicine, 2007. **356**(2): p. 115-124.
3. Motzer, R.J., et al., *Pazopanib versus sunitinib in metastatic renal-cell carcinoma.* N Engl J Med, 2013. **369**(8): p. 722-31.
4. Motzer, R.J., et al., *Tivozanib versus sorafenib as initial targeted therapy for patients with metastatic renal cell carcinoma: results from a phase III trial.* J Clin Oncol, 2013. **31**(30): p. 3791-9.
5. Motzer, R.J., et al., *Overall survival and updated results for sunitinib compared with interferon alfa in patients with metastatic renal cell carcinoma.* J Clin Oncol, 2009. **27**(22): p. 3584-90.
6. Sternberg, C.N., et al., *A randomised, double-blind phase III study of pazopanib in patients with advanced and/or metastatic renal cell carcinoma: final overall survival results and safety update.* Eur J Cancer, 2013. **49**(6): p. 1287-96.
7. Cella, D., et al., *Health-related quality of life in patients with metastatic renal cell carcinoma treated with sunitinib vs interferon-alpha in a phase III trial: final results and geographical analysis.* Br J Cancer, 2010. **102**(4): p. 658-64.
8. Motzer, R.J., et al. *Overall survival in renal-cell carcinoma with pazopanib versus sunitinib*. The New England journal of medicine, 2014. **370**, 1769-70 DOI: 10.1056/NEJMc1400731.
9. Sternberg, C.N., et al., *Tivozanib in patients treatment-naive for metastatic renal cell carcinoma: A subset analysis of the phase III TIVO-1 study.* Journal of Clinical Oncology, 2013. **31**(15).
10. Sternberg, C.N., et al., *A randomized, double-blind phase III study (VEG105192) of pazopanib (paz) versus placebo (pbo) in patients with advanced/metastatic renal cell carcinoma (mRCC): Updated safety results.* Journal of Clinical Oncology, 2011. **29**(7).
11. Agency, E.M., *CHMP assessment report. Votrient (EMEA/H/C/001141)*. 2010.
12. European Medicines Agency, *CHMP assessment report Fotivda (EMA/CHMP/15251/2017)*. 2017.
13. Iacovelli, R., et al., *Is there still a role for sorafenib in metastatic renal cell carcinoma? A systematic review and meta-analysis of the effectiveness of sorafenib over other targeted agents.* Crit Rev Oncol Hematol, 2016. **99**: p. 324-31.
14. Larkin, J., et al., *First-line treatment in the management of advanced renal cell carcinoma: systematic review and network meta-analysis.* Expert Opin Pharmacother, 2015. **16**(13): p. 1915-27.
15. Escudier, B., et al., *Randomized phase II trial of first-line treatment with sorafenib versus interferon Alfa-2a in patients with metastatic renal cell carcinoma.* J Clin Oncol, 2009. **27**(8): p. 1280-9.
16. Negrier, S., et al., *Efficacy and safety of sorafenib in patients with advanced renal cell carcinoma with and without prior cytokine therapy, a subanalysis of TARGET.* Med Oncol, 2010. **27**(3): p. 899-906.
17. TLV. *Fotivda. Ärende 1638/2018. Beslut*. 2018; Available from: https://tlv.se/download/18.703c117b1661eb30f7c84543/1538400825123/bes180927_fotivda.pdf.
18. Hamnvik, O.P., et al., *Clinical risk factors for the development of hypertension in patients treated with inhibitors of the VEGF signaling pathway.* Cancer, 2015. **121**(2): p. 311-9.
19. Rini, B.I., et al., *Hypertension as a biomarker of efficacy in patients with metastatic renal cell carcinoma treated with sunitinib.* J Natl Cancer Inst, 2011. **103**(9): p. 763-73.

8 Appendices

Appendix A. Systematic literature search

Table A3a-d. Data extraction tables (in separate document)

Appendix B. Excluded records with reason for exclusion

Appendix C. TIVO-1 Efficacy and Safety in treatment naïve population

Appendix D. Sternberg et al. TIVO-1 treatment naïve population results. ASCO poster

Appendix A Literature search

Application to the Danish Medicine Council. January 2019. Fotivda in advanced RCC

A.1 Literature search

The literature search was made in the following databases

Database / information source	Interface / URL
PubMed database	https://www.ncbi.nlm.nih.gov/pmc/
Cochrane Central Register of Controlled Trials (CENTRAL) database	https://www.cochranelibrary.com/central/about-central

The search was designed to identify phase III clinical trials in parallel group designs. The search strategy included search terms to identify the relevant study population, study design, interventions, comparators, outcomes, and analyses performed according to the eligibility criteria listed in Table A.1. The search was restricted to English full-text publication published 1980 and onwards. However, no filters were applied in either database search. The search was conducted on January 4, 2019. The full search terms for each of the two databases searched are presented in Figure A.1.

TABLE A.1 ELIGIBILITY CRITERIA

Clinical effectiveness	Inclusion criteria	Exclusion criteria
Population	Aged ≥ 18 years Any gender Any race Has renal cell carcinoma AND Has locally advanced, unresectable/advanced/metastatic/stage III/stage IV disease No prior TKI or mTOR therapy	No data reported on relevant population
Study design	Phase III randomized clinical trials with parallel group design	Other study design
Interventions	Sunitinib monotherapy Tivozanib monotherapy Pazopanib monotherapy	No data reported on relevant intervention
Comparators	Placebo Any interventional drug therapy, excluding vaccines	No data reported on relevant comparator
Outcomes	**Efficacy:** Overall survival Progression-free survival Overall response rate (complete + partial) Duration of response EORTC-QLQ-30 FACT-G EQ-5D FKSI (any version) **Safety:** Incidence and severity of adverse events	No data reported on relevant outcome
Analyses	Intervention versus comparator with statistical hypothesis testing Most recent pre-specified analysis if more than one analysis is reported on the same study and outcome	Analysis not relevant
Language restrictions	English full-text publication	Full text publication in other language
Publication restriction	Published 1980 onwards	Published outside relevant dates Full text publication not available Conference proceedings

FIGURE A.1: DETAILED SEARCH STRATEGIES

PubMed database search

Search	Query	Items found
#1	Search **("Carcinoma, Renal Cell"[mh] OR "Kidney Neoplasms"[mh] OR ((renal[tiab] OR kidney[tiab]) AND (cancer[tiab] OR carcinoma[tiab] OR adenocarcinoma[tiab] OR tumor[tiab] OR tumour[tiab])) OR MRCC[tiab] OR RCC[tiab])**	**131940**
#2	Search **((Tivozanib[nm] OR tivozanib[tiab] OR tivopath[tiab] OR Fotivda[tiab] OR AV-951[tiab] OR (Sunitinib[mh] OR sunitinib[tiab] OR sutent[tiab] OR SU11248[tiab] OR Pazopanib[nm] OR pazopanib[tiab] OR votrient[tiab])**	**6473**
#3	Search **(("Randomized Controlled Trial"[pt] OR "Controlled Clinical Trial"[pt] OR randomized[tiab] OR randomised[tiab] OR placebo[tiab] OR "Clinical Trials as Topic"[mh:noexp] OR randomly[tiab] OR trial[ti]) NOT ("Animals"[mh] NOT "Humans"[mh]))**	**1135026**
#4	Search **((#1 and #2 and #3))**	**620**
#5	Search **(Case Reports[Publication Type] OR Comment[Publication Type] OR Editorial[Publication Type] OR Letter[Publication Type] OR Review[Publication Type] OR case[Title])**	**5987474**
#6	Search **((#4 not #5))**	**348**

CENTRAL database search

Search	Query	Items found
#1	Search **[mh "Carcinoma, Renal Cell"] OR [mh "Kidney Neoplasms"]**	993
#2	Search **((renal or kidney) AND (cancer or carcinoma or adenocarcinoma or tumor or tumour)):ti,ab,kw or (MRCC or RCC):ti,ab**	6559
#3	Search **(tivozanib OR tivopath or Fotivda or AV-951 OR sunitinib or sutent or su11248 or pazopanib OR votrient):ti,ab,kw**	1060
#4	Search **#1 or #2**	6602
#5	Search **#3 and #4**	576
#6	Search **"conference abstract":pt or review:pt or NCT*:au**	256943
#7	Search **#5 not #6 in Trials**	262

The database search results were loaded into EndNote bibliographic software. The records were deduplicated by using the EndNote “Find Duplicates” function, as well as by manual review.

A.2 Study Selection

The literature search resulted in 451 records screened, 34 articles assessed for eligibility, of which 8 articles reporting results from 4 studies were included for narrative synthesis (see Table A2.A to Table A2.D).

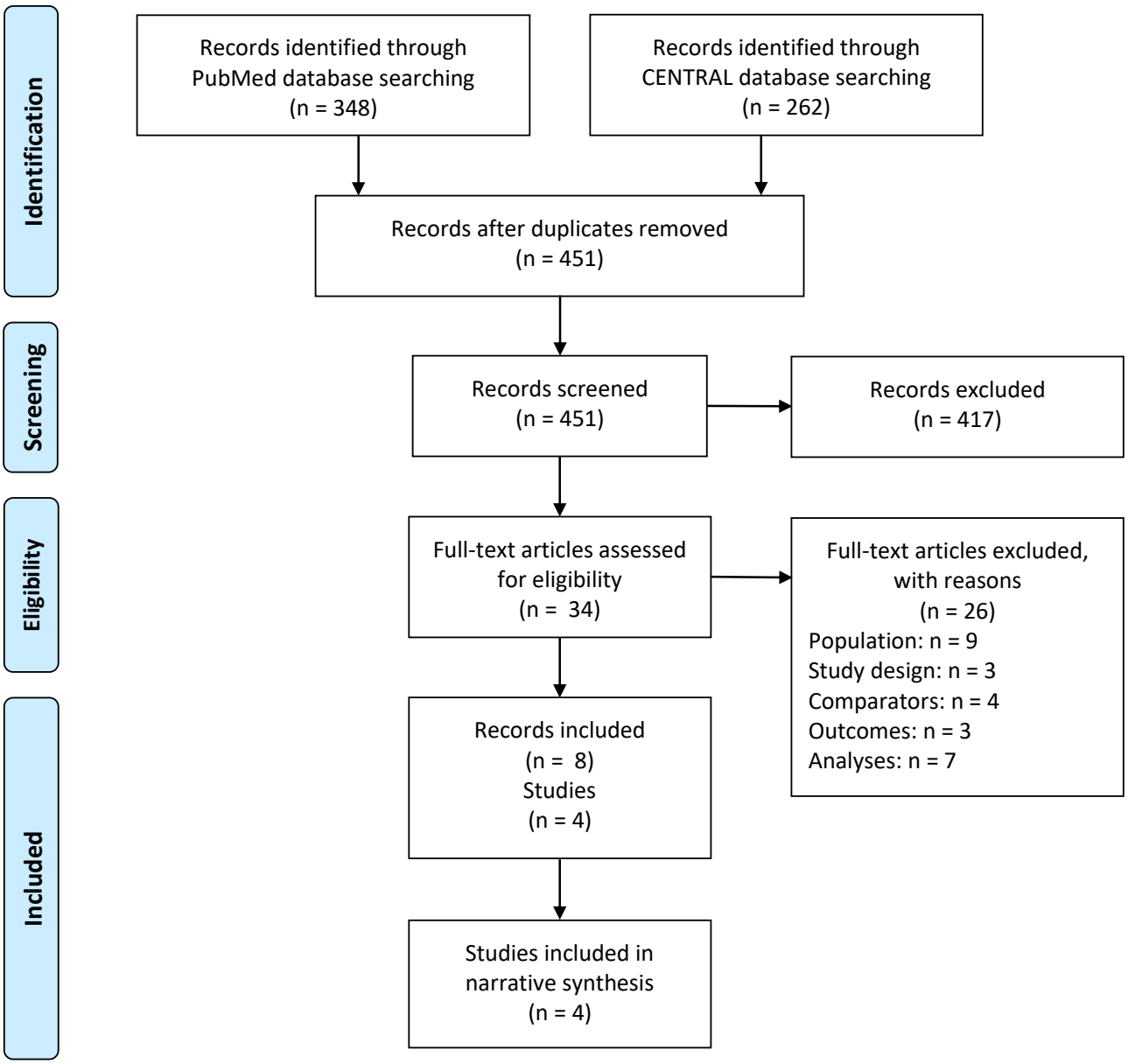
The 4 clinical studies included the three pivotal trials for each of the TKIs and a direct comparison of pazopanib and sunitinib.

In addition, one study compared combination of nivolumab and ipilimumab to sunitinib in first line treatment of clear cell advanced/ metastatic renal cell cancer. The evidence network that may be established from the available studies do not include any common comparator that would allow meta-analysis of data for any of the TKIs or quantitative indirect comparison across TKIs. The pivotal studies and the direct comparison of sunitinib and pazopanib were included in a narrative comparison. The comparison of biologic treatment to sunitinib (NCT02231749. Motzer et al. N Engl J Med. 2018;378(14):1277-90.) was excluded after consultation with the Medicine Council secretariat. This approach was taken because inclusion of the trial would not add new options for meta-analysis of the sunitinib data nor new options for quantitative indirect comparison.

Records excluded after assessment of the full text publications are listed in a table with the reasons for exclusion (Appendix B).

The PRISMA study flow diagram (Figure A.2) shows the number of records identified by the search and the numbers excluded at various selection stages.

FIGURE A.2 PRISMA DIAGRAM



A.3 Main characteristics of included studies

A.4 Study characteristics

TABLE A2.A MAIN STUDY CHARACTERISTICS

Trial name	Sternberg 2010 (VEG105192)
NCT number	NCT00334282
Objective	To evaluate efficacy and safety of pazopanib compared to placebo in patients with locally advanced and/ or metastatic renal cell carcinoma (RCC).
Publications – title, author, journal, year	1. Pazopanib in locally advanced or metastatic renal cell carcinoma: results of a randomized phase III trial. Sternberg CN, Davis ID, Mardiak J, et al. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2010;28(6):1061-1068. 2. A randomised, double-blind phase III study of pazopanib in patients with advanced and/or metastatic renal cell carcinoma: final overall survival results and safety update. Sternberg CN, Hawkins RE, Wagstaff J, et al. *European journal of cancer (Oxford, England : 1990).* 2013;49(6):1287-1296.
Study type and design	Phase 3, randomized placebo-controlled study. Enrolled patients were be stratified and randomized in a 2:1 ratio. An Independent Data Monitoring Committee monitored safety and evaluated interim efficacy data on overall survival. Subsequent anticancer therapy for patients with progressive disease was at the discretion of the patients and their physicians. Patients who progressed were unblinded, and if found to be on placebo, had the option of receiving pazopanib via an open-label study (VEG107769)
Follow-up time	Not stated in the publication of final OS results (Sternberg et al., 2013) According to the protocol, final OS analysis was to be conducted when 297 death had occurred. Clinical cutoff for the final OS analysis was reached on March 15, 2010, when 290 deaths had been recorded. In the pazopanib arm, 190 patients (66%) died. In the placebo arm, 100 patients (69%) died.
Population (inclusion and exclusion criteria)	Inclusion • Signed written informed consent. • Diagnosis of clear cell RCC that is predominantly clear cell histology. • Locally advanced RCC (defined as disease not amenable to curative surgery or radiation therapy) or metastatic RCC (equivalent to Stage IV RCC according to American Joint Committee on Cancer (AJCC) staging. • Must have measurable disease, i.e. presenting with at least one measurable lesion per Response Evaluation Criteria in Solid Tumors (RECIST). A measurable lesion is defined as a lesion that can be accurately measured in at least one dimension with the longest diameter ≥ 20 mm using conventional techniques, or ≥ 10 mm with spiral CT scan. • Patients who have received only one prior systemic treatment for locally advanced or metastatic RCC with documented disease progression or documented treatment discontinuation due to unacceptable toxicity. This first-line systemic treatment must be cytokine based. Or, • Patients who have received no prior systemic therapy for advanced/metastatic RCC can be enrolled if under any of the following circumstances:

	• Patients who live in countries or regions where there is no established standard first-line therapy for advanced/metastatic RCC or where there are barriers to the access of established therapies such as sunitinib, sorafenib, IFNα or IL-2. • Patients who live in countries or regions where IL-2 or INF-α has been approved for the treatment of advanced/metastatic RCC, however, these agents are generally not recognized by the local clinical community as a standard treatment for advanced/metastatic RCC, or where the physician and the patient have determined that the available cytokine therapies are not an acceptable therapeutic option. • Patients who have recurred following prior adjuvant or neo-adjuvant cytokine therapy for RCC are eligible to participate without receiving a first-line systemic treatment for locally advanced or metastatic RCC. These patients should be stratified as the first-line population. • Male or female ≥ 18 years of age. • A woman is eligible to participate in the study if she is of: • Non-childbearing potential (i.e., physiologically incapable of becoming pregnant) • A man with a female partner of childbearing potential is eligible to enter and participate in the study if he is abstinent or uses a barrier method of contraception during the study. • Eastern Cooperative Oncology Group Performance Status (ECOG PS) 0 or 1 • Adequate baseline organ function defined as: • Hematologic function: • Absolute Neutrophil Count (ANC) ≥1 x 10^9/L Hemoglobin ≥ 9 g/dL Platelet ≥75 x 10^9/L • Hepatic function: Total bilirubin ≥ 1.5 x Upper Limit of Normal (ULN) Aspartate Aminotransferase (AST) and Alanine Aminotransferase (ALT) ≥ 2 x ULN • Renal function: Calculated creatinine clearance≥30 mL/min and ≥ Urine protein is 0, trace, or +1 determined by dipstick urinalysis, or < 1.0 gram determined by 24-hour urine protein analysis. Corrected serum calcium level within normal range per local clinical laboratory standard. • At least 4 weeks must have elapsed since the last surgery and 2 weeks must have elapsed since radiotherapy or the last systemic cytokine therapy. • Complete recovery from prior surgery, and/or reduction of all AEs to Grade 1 from prior systemic therapy or radiotherapy. Exclusion • Pregnant or lactating female. • History of another malignancy. • Note: Patients who have had another malignancy and have been disease-free for 5 years, or patients with a history of completely resected non-melanomatous skin carcinoma or successfully treated in situ carcinoma are eligible. • History or presence of central nervous system (CNS) metastasis or leptomeningeal tumors as documented by CT or MRI scan, analysis of cerebrospinal fluid or neurological exam. • Malabsorption syndrome or disease that significantly affects gastrointestinal function, or major resection of the stomach or small bowel that could affect the absorption of pazopanib. • Unable to swallow and retain orally administered medication. • Active peptic ulcer disease, inflammatory bowel disease, ulcerative colitis, or other gastrointestinal conditions with increased risk of perforation; history of

<table>
<tr><td></td><td>abdominal fistula, gastrointestinal perforation, or intra-abdominal abscess within 4 weeks prior to beginning study treatment.
• History of human immunodeficiency virus infection.
• Presence of uncontrolled infection.
• Corrected QT interval (QTc) prolongation defined as QTc interval > 470 msecs.
• History of Class III or IV congestive heart failure according to New York Heart Association (NYHA) classification.
• History of any one of the following cardiac conditions within the past 6 months:
• Cardiac angioplasty or stenting, or
• Myocardial infarction, or
• Unstable angina.
• History of cerebrovascular accident within the past 6 months.
• Poorly controlled hypertension [defined as systolic blood pressure (SBP) of ≥140mmHg, or diastolic blood pressure (DBP) of ≥ 90mmHg].
• History of untreated deep venous thrombosis (DVT) within the past 6 months (e.g. a calf vein thrombosis that is not treated).
• Presence of any non-healing wound, fracture, or ulcer, or presence of symptomatic peripheral vascular disease.
• Evidence of bleeding diathesis or coagulopathy.
• Any serious and/or unstable pre-existing medical, psychiatric, or other conditions that could interfere with patient's safety, obtaining informed consent or compliance to the study.
• Has taken any prohibited medications within 14 days of the first dose of study medication.
• Current or prior use of an investigational anti-cancer drug within 4 weeks of start of study.
• Prior use of an investigational or licensed drug that targets VEGF or VEGF receptors (eg. bevacizumab, sunitinib, sorafenib, etc).</td></tr>
<tr><td>Intervention</td><td>800 mg pazopanib once daily (N:290) or matching placebo (N:145). Patients received continuous treatment until disease progression, death, unacceptable toxicity, or withdrawal of consent for any reason.</td></tr>
<tr><td>Baseline characteristics</td><td>
<table>
<tr><th></th><th>Pazopanib (n=290; 155 treatment-naive)</th><th>Placebo (n=145; 78 treatment-naive)</th></tr>
<tr><td>Age</td><td>Median 59, range 28-85</td><td>Median 60, range 25-81</td></tr>
<tr><td>Gender</td><td>198 male</td><td>109 male</td></tr>
<tr><td>Ethnicity/ location</td><td>International
White: 252
Asian: 36
Black: 1
Other: 1</td><td>International
White: 122
Asian: 23
Black: 0
Other: 0</td></tr>
<tr><td>Performance status</td><td>ECOG:
0: 123
1: 167
MSKCC risk:
Favourable: 113
Intermediate: 159
Poor: 9</td><td>ECOG:
0: 60
1: 85
MSKCC risk:
Favourable: 57
Intermediate: 77
Poor: 5</td></tr>
<tr><td>Disease stage</td><td>All advanced/ metastatic</td><td>All advanced/ metastatic</td></tr>
<tr><td>Histology</td><td>Clear cell: 264
Predominantly clear cell: 25</td><td>Clear cell: 129
Predominantly clear cell: 16</td></tr>
<tr><td>Prior treatments</td><td>Nephrectomy: 258
Prior cytokines: 135</td><td>Nephrectomy: 127
Prior cytokines: 67</td></tr>
</table>
</td></tr>
</table>

	Treatment naïve: 155 Treatment naïve: 78
Primary and secondary endpoints	The primary end point was progression-free survival (PFS), defined as the time interval between the date of random assignment and the date of progression or death. The principal secondary end point was overall survival (OS), defined as the time interval between the date of random assignment and date of death. Other secondary end points included confirmed objective response rate (complete response [CR] plus partial response [PR]), duration of response, and safety. Health-related quality of life (HRQoL) was accessed using EORTC QLQ-C30 and EQ-5D. Disease assessments using computed tomography or magnetic resonance imaging were performed at baseline, every 6 weeks until week 24, and every 8 weeks thereafter until progression. Bone scans were performed at least every 24 weeks in all patients and on confirmation of objective response. Objective responses were confirmed at the next scheduled disease-assessment visit. Patients who discontinued study treatment before disease progression were to continue disease assessments until progression or initiation of an alternate anticancer treatment. All imaging scans were evaluated by an independent imaging-review committee (IRC) blinded to study treatment. Tumor response evaluations by the investigators and the IRC were based on RECIST (Therasse et al, 2000). Follow-up for OS was performed every 3 months after disease progression until death or study withdrawal
Method of analysis	Efficacy end points were analyzed according to the intention-to-treat principle. Safety analyses were performed on the basis of the actual treatment received in patients who were randomized and received at least one dose of investigational product. Kaplan-Meier methods were used to analyze PFS and OS. Comparisons between arms were made using a log-rank test (one sided) stratified by ECOG PS and prior therapy. Hazard ratios were calculated using a stratified Pike estimator utilizing the same factors. The primary analysis of PFS was based on IRC assessments. Progression and censoring dates for the primary analysis were assigned to the visit time point for scheduled visits. Progressions found at unscheduled visits were assigned to the next scheduled visit time point to adjust for any unplanned deviations from the protocol-defined visit schedule, as agreed to with the FDA during the study-design process. Nine predefined sensitivity analyses of PFS were performed to confirm the robustness of the primary result using various assumptions, including alternate definitions of progression and censoring dates, data sources (IRC v investigator), and analysis methods. Duration of response and time to response were summarized descriptively using medians and quartiles. A mixed-model repeated-measures analysis of change from baseline was performed for QoL measures
Subgroup analyses	Comparison of PFS between treatment arms was done using the log-rank test in predefined subgroup analyses based on prior treatment, age, sex, MSKCC risk group, and ECOG PS. Approximate 95% CIs for response rate (RR) differences were calculated.

TABLE A2.B MAIN STUDY CHARACTERISTICS

Trial name	Motzer 2007 (A6181034)
NCT number	NCT00098657 and NCT00083889
Objective	To test whether sunitinib has activity and is safe compared to interferon-alfa as first-line therapy in patients with metastatic renal cell carcinoma
Publications – title, author, journal, year	1. Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. Motzer RJ, Hutson TE, Tomczak P, et al. *New England Journal of Medicine.* 2007;356(2):115-124. 2. Overall survival and updated results for sunitinib compared with interferon alfa in patients with metastatic renal cell carcinoma. Motzer RJ, Hutson TE, Tomczak P, et al. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2009;27(22):3584-3590. 3. Health-related quality of life in patients with metastatic renal cell carcinoma treated with sunitinib vs interferon-alpha in a phase III trial: final results and geographical analysis. Cella D, Michaelson MD, Bushmakin AG, et al. *British journal of cancer.* 2010;102(4):658-664.
Study type and design	International, multicenter, randomized, open label, phase 3 trial. Randomization was stratified according to baseline levels of lactate dehydrogenase (>1.5 vs. ≤1.5 times the upper limit of the normal range), ECOG performance status (0 vs. 1), and previous nephrectomy (yes vs. no). Patients were randomly assigned in a 1:1 ratio to receive either sunitinib or interferon alfa. Random permuted blocks of four were used to attain balance within strata. Response (RECIST criteria) was assessed by independent central reviewer blinded to treatment assignment. The trial was carried out between Aug 2004 and Sep 2008. After a protocol amendment (February 2006), 25 patients (7%) on the IFN-alpha arm crossed over to receive sunitinib. Criteria for final OS analysis (390 deaths) has been reached. Final OS analysis has been published
Follow-up time	Not stated in the publication of final OS analysis Motzer (2009)
Population (inclusion and exclusion criteria)	Inclusion Criteria: • Histologically confirmed renal cell carcinoma of clear cell histology with metastases • Evidence of measurable disease by radiographic technique • Eastern Cooperative Oncology Group [ECOG] performance status of 0 or 1 Exclusion Criteria: • Prior systemic (including adjuvant or neoadjuvant) therapy of any kind for RCC • History of or known brain metastases • Serious acute or chronic illness or recent history of significant cardiac abnormality
Intervention	Sunitinib was administered orally at 50 mg once daily on a 4 weeks on, 2 weeks off dosing schedule IFN-alpha-2a (Roferon-A). IFN was administered by subcutaneous injection thrice weekly on nonconsecutive days at 3 MU per dose the first week, 6 MU the second week,and9 MU thereafter. Intrapatient dose reduction or interruption of

<table>
<tr><td></td><td>either drug was allowed for management of adverse events depending on their type and severity, according to the protocol. Treatment in both groups was continued until disease progression, unacceptable adverse events, or consent withdrawal.</td></tr>
<tr><td>Baseline characteristics</td><td>
<table>
<tr><th></th><th>Sunitinib (n=375)</th><th>Interferon-alpha (n=375)</th></tr>
<tr><td>Age</td><td>Median 62, range 27-87</td><td>Median 59, range 34-85</td></tr>
<tr><td>Gender</td><td>267 male</td><td>269 male</td></tr>
<tr><td>Ethnicity/ location</td><td>Australia, Brazil, Canada, Europe, US</td><td>Australia, Brazil, Canada, Europe, US</td></tr>
<tr><td>Performance status</td><td>ECOG:
0: 231
1: 144
MSKCC risk:
Favourable (0): 143
Intermediate (1-2): 209
Poor (3+): 23</td><td>ECOG:
0: 229
1: 146
MSKCC risk:
Favourable (0): 121
Intermediate (1-2): 212
Poor (3+): 25</td></tr>
<tr><td>Disease stage</td><td>All metastatic</td><td>All metastatic</td></tr>
<tr><td>Histology</td><td>All clear cell</td><td>All clear cell</td></tr>
<tr><td>Prior treatments</td><td>Nephrectomy: 340
Radiotherapy: 53</td><td>Nephrectomy: 335
Radiotherapy: 54</td></tr>
</table>
</td></tr>
<tr><td>Primary and secondary endpoints</td><td>The primary end point of the study was progression-free survival, defined as the time from randomization to the first documentation of objective disease progression (RECIST criteria) or to death from any cause. Secondary end points included the objective response rate, overall survival, patient-reported outcomes (FKSI-DRS and FACT-G), and safety</td></tr>
<tr><td>Method of analysis</td><td>The primary end point was analyzed according to ITT. A blinded central review of radiologic images was used to assess the primary end point and the objective response rate. Safety analyses were performed on the basis of the treatment actually received. Time-to-event analyses were performed with the use of the Kaplan–Meier method.. ORR was compared by the Pearson chi-square method. For the analyses of health-related quality-of life data, repeated-measures mixed effects models were used to test overall differences between the two treatment groups. All reported P values are two-sided and were not adjusted for multiple testing</td></tr>
<tr><td>Subgroup analyses</td><td>Potential influences of the baseline characteristics of the patients — such as age, sex, and known risk factors on progression-free survival was explored with the use of a stratified log-rank test and a Cox regression model</td></tr>
</table>

TABLE A2.C MAIN STUDY CHARACTERISTICS

Trial name	COMPARZ
NCT number	Pooled data from NCT00720941 and NCT01147822
Objective	*Briefly state the overall objective of the study*
Publications – title, author, journal, year	1. Pazopanib versus sunitinib in metastatic renal-cell carcinoma. Motzer RJ, Hutson TE, Cella D, et al. *The New England journal of medicine.* 2013;369(8):722-731. 2. Overall survival in renal-cell carcinoma with pazopanib versus sunitinib. Motzer RJ, Hutson TE, McCann L, Deen K, Choueiri TK. *The New England journal of medicine.* 2014;370(18):1769-1770.
Study type and design	The study was a randomized, open-label, phase 3, non-inferiority trial of pazopanib versus sunitinib. Randomization was stratified according to Karnofsky performance status score (70 or 80 vs. 90 or 100), level of lactate dehydrogenase (>1.5 vs. ≤1.5 times the upper limit of the normal range), and nephrectomy (yes vs. no). Patients were randomly assigned to one of the two study drugs in a 1:1 ratio in permuted blocks of four. An independent review committee blinded to treatment assignments assessed progression and tumor response according to RECIST 1.0.
Follow-up time	Not stated in the correct OS analysis (Motzer et al. 2014). The final analysis of overall survival in the intention-to-treat population was to be performed when 650 patients had died or 2 years after the last patient was enrolled.
Population (inclusion and exclusion criteria)	Reported here from NCT00720941 (data was pooled with NCT01147822 – a study with same design and inclusion criteria – conducted in China, Taiwan, and South Korea) Inclusion Criteria: • Diagnosis of renal cell carcinoma with clear-cell component histology. • Received no prior systemic therapy (interleukin-2, interferon-alpha, chemotherapy, bevacizumab, mTOR inhibitor, sunitinib, sorafenib or other VEGF TKI) for advanced or metastatic RCC • Locally advanced or metastatic renal cell carcinoma • Measurable disease by CT or MRI • Karnofsky performance scale status of >=70 • Age >=18 years • A female is eligible to enter and participate in this study if she is of: non-childbearing or agrees to use adequate contraception. • Adequate organ system function • Total serum calcium concentration <12.0mg/dL • Left ventricular ejection fraction >= lower limit of institutional normal. Exclusion Criteria: • Pregnant or lactating female (unless agrees to refrain from nursing throughout the treatment period and for 14 days following the last dose of study) • History of another malignancy (unless have been disease-free for 3 years) • History or clinical evidence of central nervous system (CNS) metastases (unless have previously-treated CNS metastases and meet all 3 of the following criteria

	are: are asymptomatic, have had no evidence of active CNS metastases for >=6 months prior to enrolment, and have no requirement for steroids or enzyme-inducing anticonvulsants) • Clinically significant gastrointestinal abnormalities. • Presence of uncontrolled infection. • Prolongation of corrected QT interval (QTc) > 480 milliseconds • History of any one or more of the following cardiovascular conditions within the past 12 months: cardiac angioplasty or stenting, myocardial infarction, unstable angina, coronary artery by-pass graft surgery, symptomatic peripheral vascular disease, Class III or IV congestive heart failure, as defined by the New York Heart Association • History of cerebrovascular accident including transient ischemic attack within the past 12 months • History of pulmonary embolism or untreated deep venous thrombosis (DVT) within the past 6 months (unless had recent DVT and have been treated with therapeutic anti-coagulating agents for at least 6 weeks) • Poorly controlled hypertension (defined as systolic blood pressure of >=150mmHg or diastolic blood pressure of >=90mmHg). Initiation or adjustment of antihypertensive medication(s) is permitted prior to study entry • Prior major surgery or trauma within 28 days prior to first dose of study drug and/or presence of any non-healing wound, fracture, or ulcer. • Evidence of active bleeding or bleeding susceptibility • Spitting/coughing up blood within 6 weeks of first dose of study drug • Known endobronchial lesions and/or lesions infiltrating major pulmonary vessels • Any serious and/or unstable pre-existing medical, psychiatric, or other conditions that could interfere with patient's safety, obtaining informed consent or compliance to the study. • Use any prohibited medications within 14 days of the first dose of study medication. • Use of an investigational agent, including an investigational anti-cancer agent, within 28 days or 5 half-lives, whichever is longer, prior to the first dose of study drug. • Prior use of an investigational or licensed drug that targets VEGF or VEGF receptors (eg. bevacizumab, sunitinib, sorafenib, etc), or are mTOR inhibitors (eg. temsirolimus, everolimus, etc). • Is now undergoing and/or has undergone in the 14 days immediately prior to first dose of study drug, any cancer therapy (surgery, tumor embolization, chemotherapy, radiation therapy, immunotherapy, biological therapy, or hormonal therapy) • Any ongoing toxicity from prior anti-cancer therapy that is >Grade 1 and/or that is progressing in severity. • Known immediate or delayed hypersensitivity reaction or idiosyncrasy to drugs chemically related to pazopanib or sunitinib.
Intervention	Pazopanib was administered orally at a once-daily dose of 800 mg, with continuous dosing. Sunitinib was administered orally in 6-week cycles at a once-daily dose of 50 mg for 4 weeks, followed by 2 weeks without treatment. Dose reductions for pazopanib (to 600 mg and then to 400 mg) and sunitinib (to 37.5 mg and then to 25

<table>
<tr><td></td><td>mg) were determined according to the severity of adverse events. Patients were treated until progression of disease, the occurrence of unacceptable toxic effects, or withdrawal of consent.</td></tr>
<tr><td>Baseline characteristics</td><td>
<table>
<tr><th>COMPARZ (N=1110)</th><th>Pazopanib (n=557)</th><th>Sunitinib (n=553)</th></tr>
<tr><td>Age</td><td>Median 61, range 18-88</td><td>Median 62, range 23-86</td></tr>
<tr><td>Gender</td><td>398 male</td><td>415 male</td></tr>
<tr><td>Ethnicity/ location</td><td>Europe: 153
N America: 195
Asia: 188
Australia: 21</td><td>Europe: 157
N America: 187
Asia: 179
Australia: 30</td></tr>
<tr><td>Performance status</td><td>KPS: 70-80: 141
90-100: 416
MSKCC risk:
Favourable: 151
Intermediate: 322
Poor: 67</td><td>KPS: 70-80: 130
90-100: 423
MSKCC risk:
Favourable: 152
Intermediate: 328
Poor: 52</td></tr>
<tr><td>Disease stage</td><td>Advanced or metastatic</td><td>Advanced or metastatic</td></tr>
<tr><td>Histology</td><td>All clear cell</td><td>All clear cell</td></tr>
<tr><td>Prior treatments</td><td>Nephrectomy: 459
Radiotherapy: 46</td><td>Nephrectomy: 465
Radiotherapy: 42</td></tr>
</table>
</td></tr>
<tr><td>Primary and secondary endpoints</td><td>The primary end point was progression-free survival, Secondary end points included the objective response rate, overall survival, safety, health related quality of life (FACIT-F; KSI-19; SQLQ), and medical resource utilization. The primary end point and tumor response was assessed using CT or MRI imaging and reevaluated by an independent, blinded review committee according to RECIST 1.0.</td></tr>
<tr><td>Method of analysis</td><td>Efficacy data were analyzed in the ITT population for non-inferiority of pazopanib vs sunitnib using Cox proportional hazards model adjusted for stratification factors with a noninferiority margin of 1.25 on HR. Stratification factors included Karnofsky performance status score (70 or 80 vs. 90 or 100), level of lactate dehydrogenase (>1.5 vs. ≤1.5 times the upper limit of the normal range), and nephrectomy (yes vs. No). OS was compared with the use of a stratified log-rank test. Objective response rates were compared with the use of Fisher’s exact test. The relative risks of adverse events and the associated 95% confidence intervals (unadjusted for multiple comparisons) were estimated in the safety population (patients who received ≥1 dose of the study drug).

Changes in mean scores over time were analyzed for 11 of 14 health-related quality-of-life domains with the use of repeated-measures ANCOVA, with baseline score as the covariate.</td></tr>
<tr><td>Subgroup analyses</td><td>Cox analysis was used to analyze progression-free survival in patient subgroups defined according to baseline characteristics. No formal testing of the hypothesis was planned for any of the subgroup analyses</td></tr>
</table>

TABLE A2.A MAIN STUDY CHARACTERISTICS

Trial name	TIVO-1
NCT number	NCT01030783
Objective	To compare the PFS, OS, ORR, DR, safety and tolerability, and kidney specific symptoms/health outcome measurements of tivozanib and sorafenib.
Publications – title, author, journal, year	1. Tivozanib versus sorafenib as initial targeted therapy for patients with metastatic renal cell carcinoma: results from a phase III trial. Motzer RJ, Nosov D, Eisen T, et al. *Journal of Clinical Oncology.* 2013;31(30):3791-3799.
Study type and design	An open-label, randomized, controlled, multi-national, multi-center, parallel-arm trial comparing tivozanib to sorafenib in subjects with advanced RCC. Subjects were randomized (1:1) to treatment with tivozanib or sorafenib and stratified by geographic region (North America/Western Europe, Central/Eastern Europe, or rest of the world); number of prior treatments (0 or 1); and number of metastatic sites/organs involved (1 or ≥ 2). Tumor response was evaluated according to RECIST version 1.0 based on CT or MR imaging and assessed by an independent radiology review (blinded to treatment assignment). Patients randomly assigned to sorafenib who had progressive disease per investigator assessment were given the option to cross over to receive tivozanib.
Follow-up time	Not stated. A total of 219 deaths (42% of patients) had occurred at the protocol-specified final OS analysis in the ITT population (data cutoff was August 27, 2012)
Population (inclusion and exclusion criteria)	Inclusion Criteria: • ≥ 18-years of age. • Subjects with recurrent or metastatic RCC. • Subjects must have undergone prior nephrectomy (complete or partial) for excision of the primary tumor. • Histologically or cytologically confirmed RCC with a clear cell component (subjects with pure papillary cell tumor or other non-clear cell histologies, including collecting duct, medullary, chromophobe, mixed tumor containing predominantly sarcomatoid cells, and unclassified RCC are excluded). • Measurable disease per the RECIST criteria Version 1.0. • Treatment naïve subjects or subjects who have received no more than one prior systemic treatment (immunotherapy, including interferon-alfa or interleukin-2 based therapy, chemotherapy, hormonal therapy or an investigational agent) for metastatic RCC. Postoperative or adjuvant systemic therapy will not be counted as a prior therapy unless recurrence is detected within 6 months of completion of treatment, in which case it will be counted as a prior therapy for metastatic disease. • ECOG performance status of 0 or 1, and life expectancy ≥ 3 months. • If female and of childbearing potential, documentation of negative pregnancy test prior to enrollment. • Ability to give written informed consent and comply with protocol requirements.

	Exclusion Criteria: • Any prior VEGF-directed therapy including VEGF antibody (eg, bevacizumab), VEGF receptor tyrosine kinase inhibitor (eg, sunitinib, sorafenib, axitinib, pazopanib, etc.), VEGF trap (eg, aflibercept), or any other agent or investigational agent targeting the VEGF pathway. • Any prior therapy with an agent targeting the mTOR pathway (eg, temsirolimus, everolimus, etc) • Primary CNS malignancies or CNS metastases; subjects with previously treated brain metastasis will be allowed if the brain metastasis have been stable without steroid treatment for at least 3 months following prior treatment (radiotherapy or surgery). • Any hematologic abnormalities (as noted in the protocol). • Any serum chemistry abnormalities (as noted in the protocol). • Significant cardiovascular disease. • Non-healing wound, bone fracture, or skin ulcer. • Active peptic ulcer disease, inflammatory bowel disease, ulcerative colitis, or other gastrointestinal condition with increased risk of perforation; history of abdominal fistula, gastrointestinal perforation, or intra-abdominal abscess within 4 weeks prior to administration of first dose of study drug. • Serious/active infection or infection requiring parenteral antibiotics. • Inadequate recovery from any prior surgical procedure or major surgical procedure within 4 weeks prior to administration of first dose of study drug. • Significant thromboembolic or vascular disorders within 6 months prior to administration of first dose of study drug. • Significant bleeding disorders within 6 months prior to administration of first dose of study drug. • Currently active second primary malignancy, including hematologic malignancies (leukemia, lymphoma, multiple myeloma, etc.), other than non-melanoma skin cancers, non-metastatic prostate cancer, in situ cervical cancer and ductal or lobular carcinoma in situ of the breast. Subjects are not considered to have a currently active malignancy if they have completed anti-cancer therapy and have been disease free for >2 years. • Pregnant or lactating females. • History of genetic or acquired immune suppression disease such as HIV; subjects on immune suppressive therapy for organ transplant. • Life-threatening illness or organ system dysfunction compromising safety evaluation. • Requirement for hemodialysis or peritoneal dialysis. • Inability to swallow pills, malabsorption syndrome or gastrointestinal disease that severely affects the absorption of tivozanib or sorafenib, major resection of the stomach or small bowel, or gastric bypass procedure. • Psychiatric disorder or altered mental status precluding informed consent or necessary testing. • Sexually active pre-menopausal female subjects (and female partners of male subjects) must use adequate contraceptive measures, while on study and for 50 days after the last dose of study drug. Sexually active male subjects must use adequate contraceptive measures, while on study for at least 90 days after the last dose of drug

<table>
<tr><td>Intervention</td><td>Tivozanib was administered orally at 1.5 mg once per day every day for 3 weeks followed by 1 week off (one cycle is 3 weeks on, 1 week off). Sorafenib was administered orally at a dose of 400 mg (two 200-mg tablets) twice per day continuously (one cycle is 4 weeks on). Patients continued to receive the study drug until disease progression, unacceptable toxicity, death, or for some other reason for discontinuing the study drug. Hypertension for tivozanib16 or skin toxicity for sorafenib17 was managed according to specific guidelines. For other AEs, tivozanib dose reduction to 1.0 mg per day and sorafenib dose reductions to 400mgonce daily and then to 400 mg every other day were allowed for patients with grade 3 or above drug-related AEs.</td></tr>
<tr><td>Baseline characteristics</td><td>
<table>
<tr><th></th><th>Tivozanib (n=260)</th><th>Sorafenib (n=257)</th></tr>
<tr><td>Age</td><td>Median 59, range 23-83</td><td>Median 59, range 23-85</td></tr>
<tr><td>Gender</td><td>185 male</td><td>189 male</td></tr>
<tr><td>Ethnicity/ location</td><td>International
White: 249
Asian: 10
Black: 1</td><td>International
white: 249
Asian: 8
Black: 0</td></tr>
<tr><td>Performance status</td><td>ECOG:
0: 116
1: 144
MSKCC risk:
Favourable: 70
Intermediate: 173
Poor: 17</td><td>ECOG:
0: 139
1: 118
MSKCC risk:
Favourable: 87
Intermediate: 160
Poor: 10</td></tr>
<tr><td>Disease stage</td><td>All recurrent/ metastatic</td><td>All recurrent/ metastatic</td></tr>
<tr><td>Histology</td><td>All clear cell</td><td>All clear cell</td></tr>
<tr><td>Prior treatments</td><td>No systemic therapy: 181
Prior metastatic therapy: 49
Prior adjuvant therapy: 23</td><td>No systemic therapy: 181
Prior metastatic therapy: 55
Prior adjuvant therapy: 22</td></tr>
</table>
</td></tr>
<tr><td>Primary and secondary endpoints</td><td>The primary end point was PFS, defined as the time interval between the

date of random assignment and the date of disease progression or death. Secondary end points included OS, objective response rate (ORR; complete response plus partial response), safety and tolerability, kidney-specific symptoms, and health-related quality of life (FACT-G; FKSI-DRS; EQ-5D). Tumor response was evaluated according to RECIST version 1.0 based on blinded, independent radiology review.</td></tr>
<tr><td>Method of analysis</td><td>Efficacy end points were analyzed in the ITT population, and safety analyses were performed in all randomly assigned patients receiving at least one dose of study drug. PFS between treatment arms was compared using a stratified log-rank test; stratification factors were the number of prior treatments (0 or 1) and the number of metastatic sites/organs involved (1 or ≥ 2). The distribution of the PFS was estimated by using the Kaplan-Meier method. The hazard ratio (HR) and its 95% CI were determined by using the Cox proportional hazards model.ORR was compared between treatment arms by using the Cochran-Mantel-Haenszel statistics, stratified as for the primary PFS analysis. Repeated measures mixed-effects (RMME) models were fitted to test for HRQoL differences between treatment arms. All P values were two-tailed.</td></tr>
<tr><td>Subgroup analyses</td><td>PFS was also compared between treatment arms in predefined subgroup analyses onthe basis of baseline characteristics, including ECOG PS,prior treatment for metastatic disease, and Memorial Sloan-Kettering Cancer Center risk group</td></tr>
</table>

	The subgroup analysis is provided in appendix C and consists of the following population. PFS, OS, and response outcomes were performed as for the overall population.

Characteristic	Tivozanib	Sorafenib
N (% of randomised)	181 (70)	181 (70)
Median age (range)	59 (23–83)	59 (23–85)
Male, n (%)	134 (74)	135 (75)
ECOG performance status, n (%)		
0	85 (47)	94 (52)
1	96 (53)	87 (48)
Region		
North America/Western Europe	19 (11)	15 (8)
Central/Eastern Europe	154 (85)	155 (86)
Rest of world	8 (4)	11 (6)
Number of metastatic organs, n (%)		
1	53 (29)	65 (36)
≥2	128 (71)	116 (64)
MSKCC prognostic group, n (%)		
Favourable	48 (27)	60 (33)
Intermediate	121 (67)	112 (62)
Poor	12 (7)	9 (5)
ECOG: Eastern Cooperative Oncology Group, MSKCC: Memorial Sloan-Kettering Cancer Center		

Results per study

Tables A3a-d are presented in a separate document (*Table A3. Data extraction tables.pdf*)

Results per PICO (clinical question)

Table A4 (*Results referring to clinical question 1*) is not applicable for this submission as no indirect comparison was attempted. This is due to lack of studies with a common comparator in the evidence network for the intervention and the two comparators.

Table A3 Data-extraction tables

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In the following tables the data from the included clinical trials have been extracted. The latest update on OS has been extracted. Note that when an outcome is only reported for the population of first and second-line use, these data are reported but the table entries are marked in *italics*

Table A3a

Trial name:	Sternberg 2010									
NCT number:	***NCT00334282***									
				Estimated absolute difference in effect			**Estimated relative difference in effect**			**Description of methods used for estimation**
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Hazard/Odds / Risk ratio**	**95% CI**	***P* value**	
OS (median months) [1]	Pazopanib	155	22.9 (17.6–25.4)	-0.6*	n.a.	n.a.	1.01	0.72–1.42	0.224	Log-rank test (one-sided) stratified by ECOG PS and prior systemic treatment. Data extracted are from the treatment naïve strata
	Placebo	78	23.5 (12.0–34.3)							
PFS (median months) [2]	Pazopanib	155	11.1 (n.a.)	8.3*	n.a.	n.a.	0.40	0.27-0.60	<0.0001	Comparisons between arms were made using a log-rank test (one sided) stratified by ECOG PS and prior therapy. Hazard ratios were calculated using a stratified Pike estimator utilizing the same factors. IRC assessments. Tx naïve subgroup
	Placebo	78	2.8 (n.a.)							
QoL (EORTC-C30 global score) [2]	*Pazopanib*	*96*	*n.a.*	*0.67*	*-6.48 to 5.14*	*0.82*	*n.a.*	*n.a.*	*n.a.*	*Mixed-model repeated measurements. Result extracted for week 48*
	Placebo	*24*	*n.a.*							
QoL (EQ-5D) [2]	*Pazopanib*	*98*	*n.a.*	*0.03*	*-0.03 to 0.10*	*0.33*	*n.a.*	*n.a.*	*n.a.*	*Mixed-model repeated measurements. Result extracted for week 48*
	Placebo	*24*	*n.a.*							
*Incidence of GRADE 3-4 AE * [2]*	*Pazopanib*	*290*	*21%*	*n.a.*	*n.a.*	*n.a.*	*n.a.*	*n.a.*	*n.a.*	*Common TEAE grade 3 or 4. Own calculation (# events by N)*
	Placebo	*145*	*7%*							

Table A3a

Trial name:	Sternberg 2010									
NCT number:	***NCT00334282***									
				Estimated absolute difference in effect			**Estimated relative difference in effect**			**Description of methods used for estimation**
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Hazard/Odds / Risk ratio**	**95% CI**	***P* value**	
ORR (% patients) [2]	Pazopanib	155	32% (24.3% - 38.9%)	28%*	n.a.	n.a.	RR: 8.0*	2.63-24.3*	n.a.	Events assessed by independent review committee. Tx-naïve. CI for Rate ratio (RR) calculated using normal approximation to log-RR
	Placebo	78	4% (0.0 - 8.1%)							
DOR (median) [2]	*Pazopanib*	*155*	*13.5 (12.0-15.7)*	*n.a.*	*n.a.*	*n.a.*	*n.a.*	*n.a.*	*n.a.*	*Events assessed by independent review committee*
	Placebo	*n.a.*	*n.a.*							
Rows in *italics* do not refer to the treatment-naïve population* Own calculation; n.a.: not available										
1	Sternberg CN, Hawkins RE, Wagstaff J, Salman P, Mardiak J, Barrios CH, et al. A randomised, double-blind phase III study of pazopanib in patients with advanced and/or metastatic renal cell carcinoma: final overall survival results and safety update. European journal of cancer (Oxford, England : 1990). 2013;49(6):1287-96.									
2	Sternberg CN, Davis ID, Mardiak J, Szczylik C, Lee E, Wagstaff J, et al. Pazopanib in locally advanced or metastatic renal cell carcinoma: results of a randomized phase III trial. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2010;28(6):1061-8.									

Table A3b

Trial name:	Motzer 2007									
NCT number:	***NCT00098657 and NCT00083889***									
				Estimated absolute difference in effect			**Estimated relative difference in effect**			**Description of methods used for estimation**
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Hazard/Odds / Risk ratio**	**95% CI**	***P* value**	
OS (median months)[1]	Sunitinib	375	26.4(23.0-32.9)	4.6*	n.a.	n.a.	HR: 0.821	0.673-1.001	0.051	Time-to-event analyses were performed with the use of the Kaplan–Meier method in ITT population. Unstratified log-rank test was applied to compare treatment arms.
	IFN-α	375	21.8 (17.9-26.9)							
PFS (median months)[2]	Sunitinib	375	11 (10-12)	6*	n.a.	n.a.	HR:0.42	0.32-0.54	<0.001	Events assessed by blinded central review. RECIST criteria applied. KM method used to estimate time to event
	IFN-α	375	5 (4-6)							

Table A3b

Trial name:	Motzer 2007									
NCT number:	***NCT00098657 and NCT00083889***									
				Estimated absolute difference in effect			**Estimated relative difference in effect**			**Description of methods used for estimation**
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Hazard/Odds / Risk ratio**	**95% CI**	***P* value**	
QoL (FKSI-DRS total score) [3]	Sunitinib	n.a.	29.90	2.56	n.a.	<0.0001	n.a.	n.a.	n.a.	Analysis conducted in ITT population (subgroup with base-line assessment and at least one post-randomisation assessment). Predicted means were calculated for each end-point and for each treatment, as estimated using the repeatedmeasures mixed-effects model, controlling for time, treatment, country, treatment-by-time, and treatment-by-country interactions, and baseline score. Means within treatment group and differences in means between treatment groups were estimated across the entire span of the post-baseline period and all available observations.
	IFN-α	n.a.	27.53							
QoL (FACT-G) [3]	Sunitinib	n.a.	80.49	6.62	n.a.	<0.0001	n.a.	n.a.	n.a.	
	IFN-α	n.a.	73.88							
QoL (EQ-5D) [3]	Sunitinib	n.a.	0.75	0.05	n.a.	0.0078	n.a.	n.a.	n.a.	
	IFN-α	n.a.	0.69							

Table A3b

Trial name:	Motzer 2007									
NCT number:	***NCT00098657 and NCT00083889***									
				Estimated absolute difference in effect			**Estimated relative difference in effect**			**Description of methods used for estimation**
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Hazard/Odds / Risk ratio**	**95% CI**	***P* value**	
Incidence of GRADE 3-4 AE * [2]	Sunitinib	375	50%* (n.a.)	0.24	n.a.	n.a.	RR: 1.92*	1.57-2.35*	n.a.	Treatment related AE of interest or occuring in >10% of Sunitinib treated patients. Own calculation sum of tabulated %. Risk ratio calculated. Normal approximation applied to log RR when calculating CI
	IFN-α	360	26%* (n.a.)							
ORR (% patients) [2]	Sunitinib	375	31% (26%-36%)	0.25	n.a.	<0.001	RR: 5.17*	3.37-7.93*	n.a.	Events assessed by blinded central review. RECIST criteria applied. Pearson chi-square test. Rate ratio calculated. Normal approximation applied to log RR when calculating CI
	IFN-α	375	6% (4%-9%)							
DOR (median)	n.a.									
* Own calculation; n.a.: not available										

1	Motzer RJ, Hutson TE, Tomczak P, Michaelson MD, Bukowski RM, Oudard S, et al. Overall survival and updated results for sunitinib compared with interferon alfa in patients with metastatic renal cell carcinoma. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2009;27(22):3584-
2	Motzer RJ, Hutson TE, Tomczak P, Michaelson D, Bukowski RM, Rixe O, et al. Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. New England Journal of Medicine. 2007;356(2):115-24.
3	Cella D, Michaelson MD, Bushmakin AG, et al. Health-related quality of life in patients with metastatic renal cell carcinoma treated with sunitinib vs interferon-alpha in a phase III trial: final results and geographical analysis. British journal of cancer. 2010;102(4):658-664.

Table A3c

Trial name:	COMPARZ									
NCT number:	***NCT00720941*** *(N:927) pooled with NCT01147822 (N:183)*									
				Estimated absolute difference in effect			**Estimated relative difference in effect**			**Description of methods used for estimation**
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Hazard/Odds/ Risk ratio**	**95% CI**	***P* value**	
OS (median months) [1]	Pazopanib	557	28.3 (26.0–35.5)	-0.8*	n.a.	n.a.	HR: 0.92	0.79-1.06	0.24	KM analysis in ITT population. Test of treatment effect using stratified log-rank test. Stratification factors were Karnofsky performancestatus score (70 or 80 vs. 90 or 100), level of lactate dehydrogenase (>1.5 vs. ≤1.5 times the upper limit of the normal range), and nephrectomy (yes vs. no).
	Sunitinib	553	29.1 (25.4–33.1)							
PFS (median months) [2]	Pazopanib	557	8.4 (8.3–10.9)	-1.1*	n.a.	n.a.	HR: 1.05	0.90-1.22	n.a	Cox proportional hazards model adjusted for stratification factors (Karnofsky performancestatus score (70 or 80 vs. 90 or 100), level of lactate dehydrogenase (>1.5 vs. ≤1.5 times the upper limit of the normal range), and nephrectomy (yes vs. no)). ITT population
	Sunitinib	553	9.5 (8.3–11.1)							
QoL (FKSI-19 total score) [2, suppl]	Pazopanib	377	n.a.	1.41	SD: 9.79 SMD: 0.14	0.02	n.a.	n.a.	n.a.	Changes in mean scores over time were with the use of repeated-measures ANCOVA using baseline score as the covariate. SMD in article referred to as 'effect size' defined as 'the difference in the mean change divided by the pooled standard deviation'
	Sunitinib	408	n.a							

Table A3c

Trial name:	COMPARZ									
NCT number:	***NCT00720941*** *(N:927) pooled with NCT01147822 (N:183)*									
				Estimated absolute difference in effect			**Estimated relative difference in effect**			**Description of methods used for estimation**
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Hazard/Odds/ Risk ratio**	**95% CI**	***P* value**	
QoL (FACIT-F) [2, suppl]	Pazopanib	377	n.a.	2.32	SD: 9.64 SMD: 0.24	<0.001	n.a.	n.a.	n.a.	Changes in mean scores over time were with the use of repeated-measures ANCOVA using baseline score as the covariate. SMD in article referred to as 'effect size' defined as 'the difference in the mean change divided by the pooled standard deviation'
	Sunitinib	403	n.a.							
GRADE 3-4 AE [2, suppl] *	Pazopanib	554	74%* (n.a.)	0.00*	n.a.	n.a.	RR: 1.0*	0.93-1.07*	n.a.	Treatment-Emergent Adverse Events reported in >10% of Patients in Either Arm. Own calculation (sum of pct pt with any grade 3 event + any grade 4 event). Risk ratio calculated. Normal approximation applied to log RR when calculating CI
	Sunitinib	548	74%* (n.a.)							
ORR (% patients) [2, suppl]	Pazopanib	557	31% (26.9-34.5)	0.06	0.7-11.2	0.03	RR: 1.24*	1.03-1.50*	n.a	Objective response rates were compared with the use of Fisher's exact test. Independent review committee assessed. Rate ratio calcuation. Normal approximation applied to log RR when calculating CI
	Sunitinib	553	25% (21.2-28.4)							
DOR (median)	n.a..									Outcome not reported
* Own calculation; n.a.: not available										
1	Motzer RJ, Hutson TE, McCann L, Deen K, Choueiri TK. Overall survival in renal-cell carcinoma with pazopanib versus sunitinib. The New England journal of medicine. 2014;370(18):1769-1770.									
2	Motzer RJ, Hutson TE, Cella D, Reeves J, Hawkins R, Guo J, et al. Pazopanib versus sunitinib in metastatic renal-cell carcinoma. The New England journal of medicine. 2013;369(8):722-31.									

Table A3d

Trial name:	TIVO-1									
NCT number:	**NCT01030783**									
				Estimated absolute difference in effect			**Estimated relative difference in effect**			**Description of methods used for estimation**
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Hazard/Odds / Risk ratio**	**95% CI**	***P* value**	
OS (median months) [4]	Tivozanib	181	27.1 (not reported)	-2.4*	n.a.	n.a.	1.14	0.860- 1.532	n.s.	Subgroup KM analysis of treatment-naïve patients in TIVO-1 (ITT). HR and 95% CI were determined using Cox proportional hazard model. No adjustment for cross-over
	Sorafenib	181	29.5 (not reported)							
PFS (median months) [2,4]	Tivozanib	181	12.7 (9.1-15.0)	3.6*	n.a.	n.a.	0.756	0.580-0.985	0.037	The hazard ratio (HR) and its 95% CI were determined by using the Cox proportional hazards model. Tx naïve population
	Sorafenib	181	9.1 (7.3-10.8)							
QoL (FKSI-DRS total score) [1]	*Tivozanib*	*256*	*Baseline: 29.16 (SD:4.77)*	*-0.94 (SMD*: -0.2)*	*SE: 0.33*	*0.805*	*n.a.*	*n.a.*	*n.a.*	*The least-square means for each treatment arm were estimated by using data from the first 12 months of assessments by repeated-measures mixed-effects models controlling for treatment and base-line characterics. Tx-naïve and previosly treated patients. Extracted data is baseline score (index) and change from baseline.*
	Sorafenib	*248*	*Baseline 29.35 (SD:5.10)*	*-0.93 (SMD*: -0.18)*	*SE: 0.34*					
QoL (EQ-5D) [1]	*Tivozanib*	*256*	*Baseline 0.73 (SD: 0.25)*	*-0.05 (SMD* : -0.20)*	*SE:0.02*	*0.391*	*n.a.*	*n.a.*	*n.a.*	
	Sorafenib	*250*	*Baseline 0.73 (SD: 0.26)*	*-0.06 (SMD*: -0.23)*	*SE:0.02*					

Table A3d

Trial name:	TIVO-1									
NCT number:	**NCT01030783**									
				Estimated absolute difference in effect			**Estimated relative difference in effect**			**Description of methods used for estimation**
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Hazard/Odds / Risk ratio**	**95% CI**	***P* value**	
Incidence of GRADE ≥3 AE [2,4]	Tivozanib	181	62%* (n.a.)	-0.08*	n.a.	n.a.	RR: 0.89*	0.76-1.03*	n.a.	Safety population.Tx-naïve. Any event grade ≥3. Risk ratio calculated. Normal approximation applied to log RR when calculating CI
	Sorafenib	181	70% (n.a.)							
ORR (% patients) [2,4]	Tivozanib	181	34.2% (27%-42%)	0.09	n.a.	0.038	OR: 1.62 RR: 1.41*	1.03-2.56 1.01-1.95*	n.a.	Blinded, independent event review using RECIST criteria. ORR tested using Cochran-Mantel-Haenszel test. Tx naïve. For comparison rate ratio was calculated. Normal approximation applied to log RR when calculating CI
	Sorafenib	181	24.3% (18%-31%)							
DOR (median) [3]	*Tivozanib*	*256*	*15.0 (n.a.)*	*n.a.*	*n.a.*	*n.a.*	*HR: 0.823*	*0.488- 1.388*	*n.a.*	*Blinded, independent event review using RECIST criteria. ITT population. Full population (Tx naïve and previously treated)*
	Sorafenib	*248*	*12.9 (n.a.)*							

Rows in *italics* do not refer to the treatment-naïve population. * Own calculation

1	Motzer RJ, Nosov D, Eisen T, Bondarenko I, Lesovoy V, Lipatov O, et al. Tivozanib versus sorafenib as initial targeted therapy for patients with metastatic renal cell carcinoma: results from a phase III trial. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2013;31(30):3791-9.
2	Sternberg CN, Eisen T, Tomczak P, Strahs AL, Esteves B, Berkenblit A, et al. Tivozanib in patients treatment-naive for metastatic renal cell carcinoma: A subset analysis of the phase III TIVO-1 study. Journal of Clinical Oncology. 2013;31(15).
3	European Medicines Agency. CHMP assessment report Fotivda (EMA/CHMP/15251/2017). 2017.
4	Appendix C

Appendix B Excluded records with reasons

Application to the Danish Medicine Council. January 2019. Fotivda in advanced RCC

TABLE B.1 EXCLUDED RECORDS

Reference (title, author, journal)	Reason for exclusion
Quality-adjusted time without symptoms or toxicity analysis of pazopanib versus sunitinib in patients with renal cell carcinoma. Beaumont et al. Cancer. 2016;122(7):1108-15.	Outcomes exclusion criterion: No data reported on relevant outcome.
Sunitinib does not accelerate tumor growth in patients with metastatic renal cell carcinoma. Blagoev et al. Cell Rep. 2013;3(2):277-81.	Analyses exclusion criterion: Analysis not relevant.
Comparison of Immediate vs Deferred Cytoreductive Nephrectomy in Patients with Synchronous Metastatic Renal Cell Carcinoma Receiving Sunitinib: The SURTIME Randomized Clinical Trial. Bex et al. JAMA Oncol. Epub 2018 Dec 14.	Outcomes exclusion criterion: No data reported on relevant outcome.
Patient-reported outcomes in a phase III, randomized study of sunitinib versus interferon-{alpha} as first-line systemic therapy for patients with metastatic renal cell carcinoma in a European population. Castellano et al. Ann Oncol. 2009;20(11):1803-12.	Analyses exclusion criterion: Analysis not relevant.
Quality of life in patients with metastatic renal cell carcinoma treated with sunitinib or interferon alfa: results from a phase III randomized trial. Cella et al. J Clin Oncol. 2008;26(22):3763-9.	Analyses exclusion criterion: Analysis not relevant.
Health-related quality of life in patients with advanced renal cell carcinoma receiving pazopanib or placebo in a randomised phase III trial. Cella et al. Eur J Cancer. 2012;48(3):311-23.	Analyses exclusion criterion: Analysis not relevant.
Important Group Differences on the Functional Assessment of Cancer Therapy-Kidney Symptom Index Disease-Related Symptoms in Patients with Metastatic Renal Cell Carcinoma. Cella et al. Value Health. 2018;21(12):1413-8.	Outcomes exclusion criterion: No data reported on relevant outcome.
SWITCH: A Randomised, Sequential, Open-label Study to Evaluate the Effic0acy and Safety of Sorafenib-sunitinib Versus Sunitinib-sorafenib in the Treatment of Metastatic Renal Cell Cancer. Eichelberg et al. Eur Urol. 2015;68(5):837-47.	Study design exclusion criterion: Other study design.
Safety of pazopanib and sunitinib in treatment-naive patients with metastatic renal cell carcinoma: Asian versus non-Asian subgroup analysis of the COMPARZ trial. Guo et al. J Hematol Oncol. 2018;11(1):69. Epub 2018 May 24.	Analyses exclusion criterion: Analysis not relevant.
Adjuvant Treatment for High-Risk Clear Cell Renal Cancer: Updated Results of a High-Risk Subset of the ASSURE Randomized Trial. Haas et al. JAMA Oncol. 2017;3(9):1249-52.	Population exclusion criterion: No data reported on relevant population.
Adjuvant sunitinib or sorafenib for high-risk, non-metastatic renal-cell carcinoma (ECOG-ACRIN E2805): a	Population exclusion criterion: No data reported on relevant population.

Reference (title, author, journal)	Reason for exclusion
double-blind, placebo-controlled, randomised, phase 3 trial. Haas et al. Lancet. 2016;387(10032):2008-16.	
Circulating proteins as potential biomarkers of sunitinib and interferon-alpha efficacy in treatment-naive patients with metastatic renal cell carcinoma. Harmon et al. Cancer Chemother Pharmacol. 2014;73(1):151-61.	Analyses exclusion criterion: Analysis not relevant.
Tumor Microvessel Density as a Prognostic Marker in High-Risk Renal Cell Carcinoma Patients Treated on ECOG-ACRIN E2805. Jilaveanu et al. Clin Cancer Res. 2018;24(1):217-23.	Population exclusion criterion: No data reported on relevant population.
A serum metabolomic fingerprint of bevacizumab and temsirolimus combination as first-line treatment of metastatic renal cell carcinoma. Jobard et al. Br J Cancer. 2015;113(8):1148-57.	Study design exclusion criterion: Other study design.
Sunitinib Alone or after Nephrectomy in Metastatic Renal-Cell Carcinoma. Mejean et al. N Engl J Med. 2018;379(5):417-27.	Comparators exclusion criterion: No data reported on relevant comparator.
Randomized Phase III Trial of Adjuvant Pazopanib Versus Placebo After Nephrectomy in Patients With Localized or Locally Advanced Renal Cell Carcinoma. Motzer et al. J Clin Oncol. 2017;35(35):3916-23.	Population exclusion criterion: No data reported on relevant population.
Adjuvant Sunitinib for High-risk Renal Cell Carcinoma After Nephrectomy: Subgroup Analyses and Updated Overall Survival Results. Motzer et al. Eur Urol. 2018;73(1):62-8.	Population exclusion criterion: No data reported on relevant population.
Nivolumab plus Ipilimumab versus Sunitinib in Advanced Renal-Cell Carcinoma. Motzer et al. N Engl J Med. 2018;378(14):1277-90.	Other (see text in Appendix A section A.2).
Adjuvant Sunitinib in High-Risk Renal-Cell Carcinoma after Nephrectomy. Ravaud et al. N Engl J Med. 2016;375(23):2246-54.	Population exclusion criterion: No data reported on relevant population.
SWITCH II: Phase III randomized, sequential, open-label study to evaluate the efficacy and safety of sorafenib-pazopanib versus pazopanib-sorafenib in the treatment of advanced or metastatic renal cell carcinoma (AUO AN 33/11). Retz et al. Eur J Cancer. 2018;107:37-45.	Study design exclusion criterion: Other study design.
IMA901, a multipeptide cancer vaccine, plus sunitinib versus sunitinib alone, as first-line therapy for advanced or metastatic renal cell carcinoma (IMPRINT): a multicentre, open-label, randomised, controlled, phase 3 trial. Rini et al. Lancet Oncol. 2016;17(11):1599-1611.	Comparators exclusion criterion: No data reported on relevant comparator.
Angiotensin system inhibitors and survival in patients with metastatic renal cell carcinoma treated with VEGF-targeted therapy: A pooled secondary analysis of clinical trials. Sorich et al. Int J Cancer. 2016;138(9):2293-9.	Comparators exclusion criterion: No data reported on relevant comparator.
Adjuvant sunitinib in patients with high-risk renal cell carcinoma: safety, therapy management, and patient-reported outcomes in the S-TRAC trial. Staehler et al. Ann Oncol. 2018;29(10):2098-104.	Population exclusion criterion: No data reported on relevant population.
Pazopanib Exposure Relationship with Clinical Efficacy and Safety in the Adjuvant Treatment of Advanced Renal Cell Carcinoma. Sternberg et al. Clin Cancer Res. 2018;24(13):3005-13.	Comparators exclusion criterion: No data reported on relevant comparator.

Reference (title, author, journal)	Reason for exclusion
Carbonic anhydrase 9 expression increases with vascular endothelial growth factor-targeted therapy and is predictive of outcome in metastatic clear cell renal cancer. Stewart et al. Eur Urol. 2014;66(5):956-63.	Population exclusion criterion: No data reported on relevant population.
Fatigue among patients with renal cell carcinoma receiving adjuvant sunitinib or sorafenib: patient-reported outcomes of ECOG-ACRIN E2805 trial. Zhao et al. Support Care Cancer. 2018;26(6):1889-95.	Population exclusion criterion: No data reported on relevant population.

Appendix C. Results from the treatment-naïve population from TIVO-1

Application to the Danish Medicine Council. January 2019. Fotivda in advanced RCC

- In TIVO-1 most patients, 70%, received no prior systemic treatment for metastatic disease[1].
- Outcomes were slightly better in the treatment-naïve population compared with the overall population.
- Tivozanib significantly prolonged PFS compared with sorafenib. Median PFS, based on IRR, was 12.7 months for tivozanib versus 9.1 months for sorafenib (HR 0.756; 95% CI 0.580 to 0.985, p=0.037)[2].
- Median OS was estimated at 27.1 months for tivozanib versus 29.5 months for sorafenib (HR 1.14; 95% CI 0.8599 to 1.532, p=ns).

The VEGFR-TKIs pazopanib and sunitinib have replaced cytokines and are now generally recognised as first-line treatment options for advanced and metastatic disease. Given that tivozanib is a comparator to pazopanib and sunitinib we have provided efficacy data for the subgroup of patients in TIVO-1 who were treatment-naïve.

Outcomes data is presented on the treatment-naïve population of TIVO-1 where available. Data is derived from the CSR[3], a poster presented at ASCO in 2013[2] and from individual patient level data for this submission.

Baseline demographics

Most baseline characteristics for the treatment-naïve subpopulation were balanced across the two groups and were comparable with those of the total trial population. However, some characteristics indicate the sorafenib group might have slightly better prognosis than the tivozanib group.

- More people in the sorafenib group than the tivozanib group had an ECOG performance score of 0 in the total trial population (score of 0: 54% sorafenib versus 45% tivozanib), though the difference was less marked in the treatment-naïve subpopulation (52% sorafenib versus 47% tivozanib).
- More people in the sorafenib group had a favourable MSKCC prognostic status, both in the total population and treatment-naïve subpopulation (sorafenib 34% versus tivozanib 27% and 33% versus 27% for total and treatment naïve, respectively).
- More people in the tivozanib group than the sorafenib group had involvement of two or more metastatic organs in the total population (71% tivozanib versus 66% sorafenib), and this difference was slightly more pronounced in the treatment-naïve subpopulation (71% tivozanib versus 64% sorafenib).

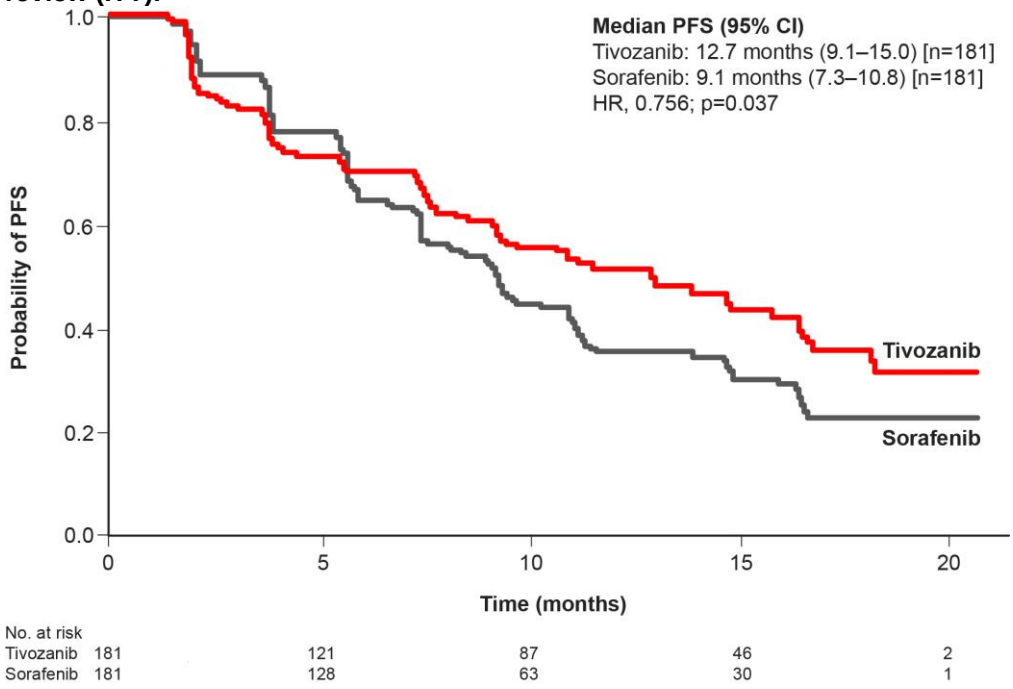
Table 1: Baseline characteristics of the treatment-naïve sub-population[2].

Characteristic	Tivozanib	Sorafenib
N (% of randomised)	181 (70)	181 (70)
Median age (range)	59 (23–83)	59 (23–85)
Male, n (%)	134 (74)	135 (75)
ECOG performance status, n (%)		
0	85 (47)	94 (52)
1	96 (53)	87 (48)
Region		
North America/Western Europe	19 (11)	15 (8)
Central/Eastern Europe	154 (85)	155 (86)
Rest of world	8 (4)	11 (6)
Number of metastatic organs, n (%)		
1	53 (29)	65 (36)
≥2	128 (71)	116 (64)
MSKCC prognostic group, n (%)		
Favourable	48 (27)	60 (33)
Intermediate	121 (67)	112 (62)
Poor	12 (7)	9 (5)
ECOG: Eastern Cooperative Oncology Group, MSKCC: Memorial Sloan-Kettering Cancer Center		

Efficacy

Tivozanib significantly prolonged PFS compared with sorafenib. Median PFS, based on IRR, was 12.7 months for tivozanib versus 9.1 months for sorafenib (HR 0.756; 95% CI 0.580 to 0.985, p=0.037)[2].

Figure 1: KM plot of PFS in the treatment-naïve population as determined by independent radiology review (ITT).

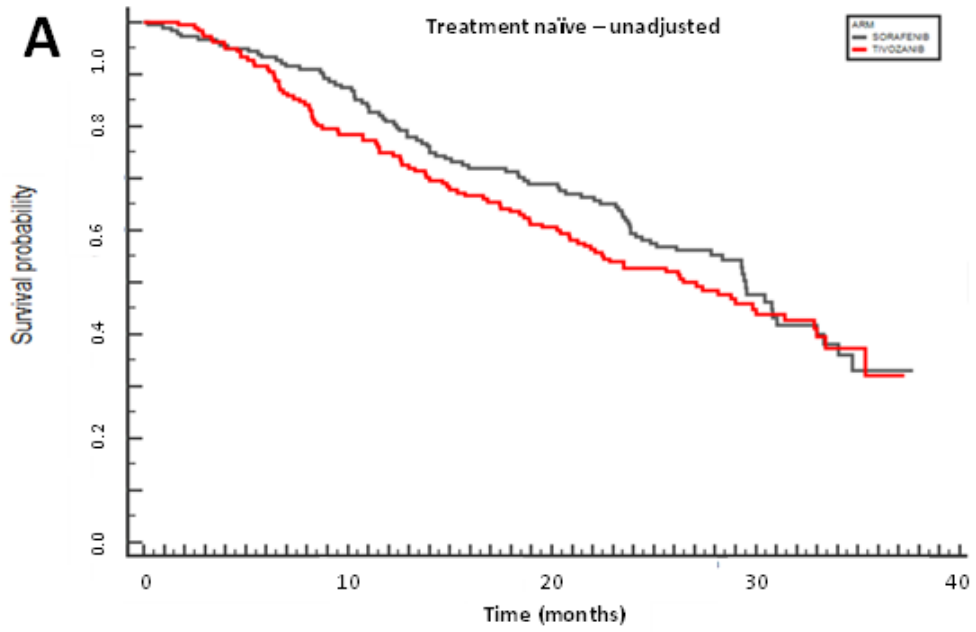


Results of relevant secondary analyses of the primary outcome and analyses of relevant secondary outcomes

Overall survival

OS for the treatment-naïve population is not available in published literature or in the CSR, therefore a post-hoc KM curve was produced from individual patient data. Median OS was estimated at 27.1 months for tivozanib versus 29.5 months for sorafenib (HR 1.14; 95% CI 0.8599 to 1.532, p=ns).

Figure 2: KM plot of OS, treatment-naïve population only.



Response

ORR was significantly higher with tivozanib compared with sorafenib: 34.2% versus 24.3%, (OR 1.62, 95% CI 1.03 to 2.56, p=0.038), see Table 2.

Table 2: Response in TIVO-1 (ITT population, independent radiology review)[2].

	Tivozanib (n=181)		Sorafenib (n=181)	
	n	**%**	**n**	**%**
CR	3	1.6	2	1.1
PR	59	32.6	42	23.2
SD	89	49.2	114	63.0
PD	27	14.9	15	8.3
Not evaluable	3	1.6	8	4.4
ORR	62	34.2	44	24.3
CR: Complete response, PR: Partial response, SD: Stable disease, PD: Progressive disease, ORR: Objective response rate				

Adverse events in TIVO-1: treatment-naïve population

- AE in the treatment-naïve population were similar to those seen in the overall population.
- Discontinuations due to AE were identical and relatively low in both arms: 8% for both. However, significantly fewer patients had treatment interruptions due to AE (20% versus 36%, p<0.001) and dose reductions due to AE(26% versus 41%, p<0.001) in the tivozanib arm compared with the sorafenib arm[2].
- Common treatment-emergent AE were seen at similar rates as in the overall TIVO-1 population[2].

Data on AE in the treatment-naïve population was presented in an abstract and poster at ASCO 2013[2, 4].

Discontinuations due to AE were the same in both arms: 8% (n=15) and were slightly higher than in the overall TIVO-1 population. Significantly fewer patients had treatment interruptions and dose reductions due to AE in the tivozanib arm compared with the sorafenib arm, rates were almost identical to those seen in the overall TIVO-1 population[2]. (p values calculated, not noted in the poster).

- Treatment interruptions: 20% (n=36) versus 36% (n=65), p<0.001.
- Dose reductions: 14% (n=26) versus 41% (n=75), p<0.001.

Almost all patients experienced at least one treatment emergent AE (88% in the tivozanib arm and 97% in the sorafenib arm). AE of grade 3 or above were reported by 62% in the tivozanib arm and 70% in the sorafenib arm. These rates were similar to those seen in the overall TIVO-1 population.

Common treatment-emergent AE were seen at similar rates as in the overall TIVO-1 population and are shown in Table 3 and Table 4.

Table 3: Common treatment-emergent AE in treatment-naïve patients: all grades[2].

	All grades					
	Tivozanib (n=259)		**Sorafenib (n=257)**		**RR**	**95% CI**
Variable	**No.**	**%**	**No.**	**%**		
AE						
Hypertension	73	40	63	45	1.16	0.89-1.51
Diarrhoea	**40**	**22**	**60**	**33**	**0.67**	**0.47-0.94**
Dysphonia	**33**	**18**	**10**	**6**	**3.30**	**1.68-6.49**
Fatigue	36	20	27	15	1.33	0.85-2.10
Weight decreased	34	19	33	18	1.03	0.67-1.59
Asthenia	26	14	32	18	0.81	0.51-1.31
HFS	**21**	**12**	**95**	**52**	**0.22**	**0.14-0.34**
Back pain	27	15	15	8	1.80	0.99-3.27
Nausea	19	10	13	7	1.46	0.74-2.87
Stomatitis	18	10	21	12	0.86	0.47-1.55
Dyspnoea	21	12	15	8	1.40	0.75-2.63
Decreased appetite	20	11	17	9	1.18	0.64-2.17
Alopecia	**4**	**2**	**41**	**23**	**0.17**	**0.06-0.49**
AE: Adverse event, HFS: Hand-foot syndrome						

Table 4: Common treatment-emergent AE in treatment-naïve patients: grades 3 and above[2].

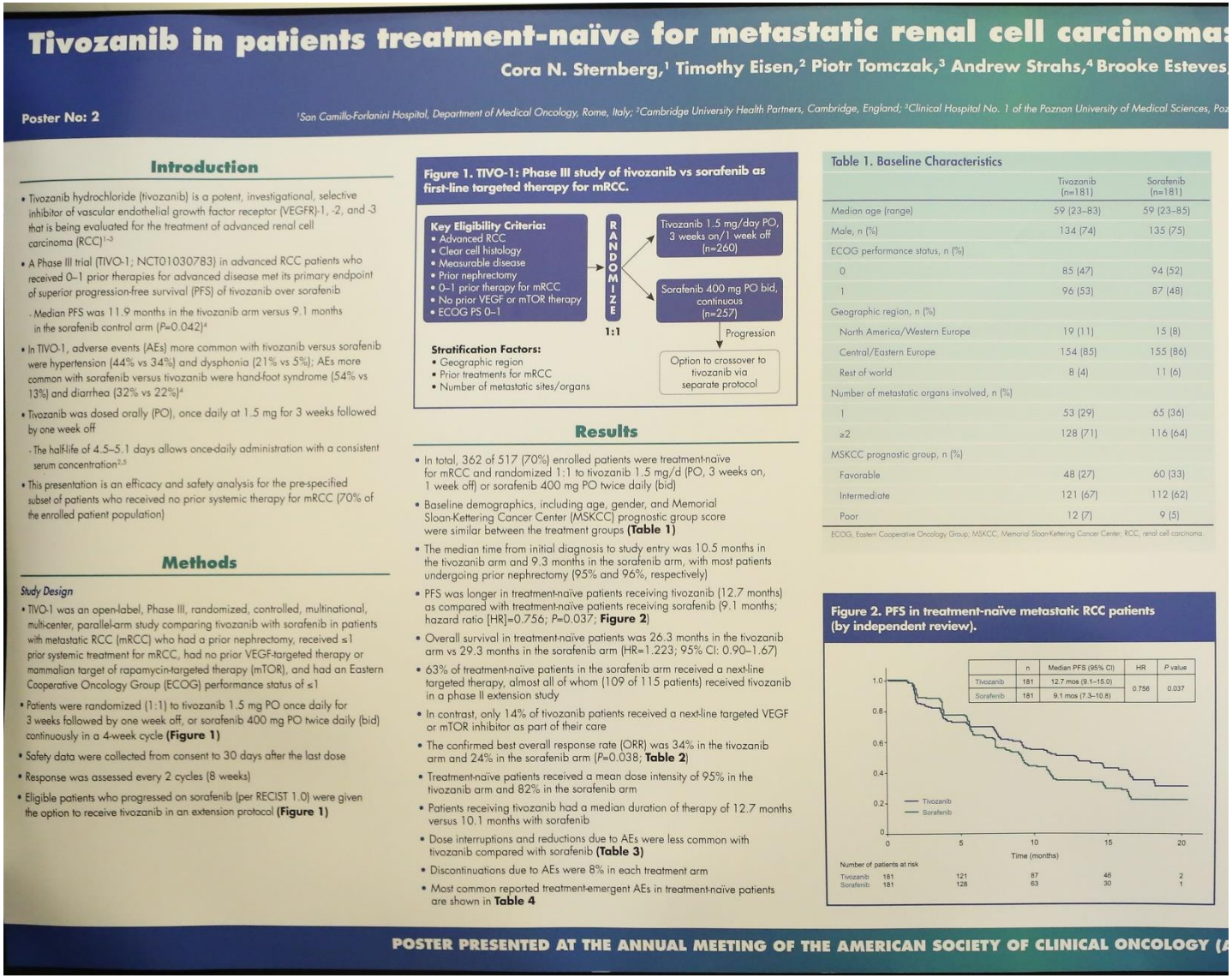
	Grades 3 and above					
	Tivozanib (n=259)		Sorafenib (n=257)		RR	95% CI
Variable	**No.**	**%**	**No.**	**%**		
AE						
Hypertension	46	25	33	18	1.39	0.94-2.07
Diarrhoea	4	2	12	7	0.33	0.11-1.01
Dysphonia	0	0	0	0		
Fatigue	11	6	6	3	1.83	0.69-4.85
Weight decreased	6	3	4	2	1.50	0.43-5.23
Asthenia	5	3	6	3	0.83	0.26-2.68
HFS	**3**	**2**	**29**	**16**	**0.10**	**0.03-0.33**
Back pain	4	2	4	2		
Nausea	1	1	1	1		
Stomatitis	1	1	2	1	0.50	0.05-5.47
Dyspnoea	21	12	15	8	1.40	0.75-2.63
Decreased appetite	20	11	17	9	1.18	0.64-2.17
AE: Adverse event, HFS: Hand-foot syndrome						

References

1. Motzer RJ, Nosov D, Eisen T, Bondarenko I, Lesovoy V, Lipatov O, et al. Tivozanib versus sorafenib as initial targeted therapy for patients with metastatic renal cell carcinoma: results from a phase III trial. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2013;31(30):3791-9.
2. Sternberg CN, Eisen T, Tomczak P, Strahs AL, Esteves B, Berkenblit A, et al., editors. Tivozanib in patients treatment-naive for metastatic renal cell carcinoma: A subset analysis of the phase III TIVO-1 study (poster). American Society of Clinical Oncology; 2013; Chicago, US.
3. AVEO Pharmaceuticals I. Clinical study report protocol AV-951-09-301. A phase 3, randomized, controlled, multi center, open-label study to compare tivozanib (AV 951) to sorafenib in subjects with advanced renal cell carcinoma.; 2016.
4. Sternberg CN, Eisen T, Tomczak P, Strahs AL, Esteves B, Berkenblit A, et al. Tivozanib in patients treatment-naive for metastatic renal cell carcinoma: A subset analysis of the phase III TIVO-1 study. Journal of Clinical Oncology. 2013;31(15).

Appendix D. Sternberg et al ASCO tx naive results ASCO poster

Application to the Danish Medicine Council. January 2019. Fotivda in advanced RCC



Tivozanib in patients treatment-naïve for metastatic renal cell carcinoma

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Poster No: 2

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Introduction

- Tivozanib hydrochloride (tivozanib) is a potent, investigational, selective inhibitor of vascular endothelial growth factor receptor (VEGFR)-1, -2, and -3 that is being evaluated for the treatment of advanced renal cell carcinoma (RCC)[1-3]
- A Phase III trial (TIVO-1; NCT01030783) in advanced RCC patients who received 0–1 prior therapies for advanced disease met its primary endpoint of superior progression-free survival (PFS) of tivozanib over sorafenib
  - Median PFS was 11.9 months in the tivozanib arm versus 9.1 months in the sorafenib control arm (*P*=0.042)[4]
- In TIVO-1, adverse events (AEs) more common with tivozanib versus sorafenib were hypertension (44% vs 34%) and dysphonia (21% vs 5%); AEs more common with sorafenib versus tivozanib were hand-foot syndrome (54% vs 13%) and diarrhea (32% vs 22%)[4]
- Tivozanib was dosed orally (PO), once daily at 1.5 mg for 3 weeks followed by one week off
  - The half-life of 4.5–5.1 days allows once-daily administration with a consistent serum concentration[2,5]
- This presentation is an efficacy and safety analysis for the pre-specified subset of patients who received no prior systemic therapy for mRCC (70% of the enrolled patient population)

Methods

Study Design

- TIVO-1 was an open-label, Phase III, randomized, controlled, multinational, multi-center, parallel-arm study comparing tivozanib with sorafenib in patients with metastatic RCC (mRCC) who had a prior nephrectomy, received ≤1 prior systemic treatment for mRCC, had no prior VEGF-targeted therapy or mammalian target of rapamycin-targeted therapy (mTOR), and had an Eastern Cooperative Oncology Group (ECOG) performance status of ≤1
- Patients were randomized (1:1) to tivozanib 1.5 mg PO once daily for 3 weeks followed by one week off, or sorafenib 400 mg PO twice daily (bid) continuously in a 4-week cycle **(Figure 1)**
- Safety data were collected from consent to 30 days after the last dose
- Response was assessed every 2 cycles (8 weeks)
- Eligible patients who progressed on sorafenib (per RECIST 1.0) were given the option to receive tivozanib in an extension protocol **(Figure 1)**

Figure 1. TIVO-1: Phase III study of tivozanib vs sorafenib as first-line targeted therapy for mRCC.

Results

- In total, 362 of 517 (70%) enrolled patients were treatment-naïve for mRCC and randomized 1:1 to tivozanib 1.5 mg/d (PO, 3 weeks on, 1 week off) or sorafenib 400 mg PO twice daily (bid)
- Baseline demographics, including age, gender, and Memorial Sloan-Kettering Cancer Center (MSKCC) prognostic group score were similar between the treatment groups **(Table 1)**
- The median time from initial diagnosis to study entry was 10.5 months in the tivozanib arm and 9.3 months in the sorafenib arm, with most patients undergoing prior nephrectomy (95% and 96%, respectively)
- PFS was longer in treatment-naïve patients receiving tivozanib (12.7 months) as compared with treatment-naïve patients receiving sorafenib (9.1 months; hazard ratio [HR]=0.756; *P*=0.037; **Figure 2**)
- Overall survival in treatment-naïve patients was 26.3 months in the tivozanib arm vs 29.3 months in the sorafenib arm (HR=1.223; 95% CI: 0.90–1.67)
- 63% of treatment-naïve patients in the sorafenib arm received a next-line targeted therapy, almost all of whom (109 of 115 patients) received tivozanib in a phase II extension study
- In contrast, only 14% of tivozanib patients received a next-line targeted VEGF or mTOR inhibitor as part of their care
- The confirmed best overall response rate (ORR) was 34% in the tivozanib arm and 24% in the sorafenib arm (*P*=0.038; **Table 2**)
- Treatment-naïve patients received a mean dose intensity of 95% in the tivozanib arm and 82% in the sorafenib arm
- Patients receiving tivozanib had a median duration of therapy of 12.7 months versus 10.1 months with sorafenib
- Dose interruptions and reductions due to AEs were less common with tivozanib compared with sorafenib **(Table 3)**
- Discontinuations due to AEs were 8% in each treatment arm
- Most common reported treatment-emergent AEs in treatment-naïve patients are shown in **Table 4**

Table 1. Baseline Characteristics

	Tivozanib (n=181)	Sorafenib (n=181)
Median age (range)	59 (23–83)	59 (23–85)
Male, n (%)	134 (74)	135 (75)
ECOG performance status, n (%)		
0	85 (47)	94 (52)
1	96 (53)	87 (48)
Geographic region, n (%)		
North America/Western Europe	19 (11)	15 (8)
Central/Eastern Europe	154 (85)	155 (86)
Rest of world	8 (4)	11 (6)
Number of metastatic organs involved, n (%)		
1	53 (29)	65 (36)
≥2	128 (71)	116 (64)
MSKCC prognostic group, n (%)		
Favorable	48 (27)	60 (33)
Intermediate	121 (67)	112 (62)
Poor	12 (7)	9 (5)

ECOG, Eastern Cooperative Oncology Group; MSKCC, Memorial Sloan-Kettering Cancer Center; RCC, renal cell carcinoma.

Figure 2. PFS in treatment-naïve metastatic RCC patients (by independent review).

POSTER PRESENTED AT THE ANNUAL MEETING OF THE AMERICAN SOCIETY OF CLINICAL ONCOLOGY (A

: a subset analysis of the Phase III TIVO-1 study

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znan, Poland; [4]AVEO Oncology, Cambridge, MA, USA; [5]Memorial Sloan-Kettering Cancer Center, New York, NY, USA

Table 2. Summary of Best Overall Responses in Treatment-naïve Patients (by independent review)

	Tivozanib (n=181)	Sorafenib (n=181)
Best ORR (confirmed), n (%)		
Complete response (CR)	3 (2)	2 (1)
Partial response (PR)	59 (33)	42 (23)
Stable disease	89 (49)	114 (63)
Progressive disease	27 (15)	15 (8)
Not evaluable	3 (2)	8 (4)
Confirmed ORR (CR + PR), n (%)	**62 (34)**	**44 (24)**
95% CI	(27–42)	(18–31)
P-value	0.038	

CI, confidence interval; ORR, overall response rate.

Table 3. Dose Interruptions, Reductions, and Discontinuations in Treatment-naïve Patients

	Tivozanib (n=181)	Sorafenib (n=181)
Dose interruptions due to AE, n (%)	**36 (20)**	**65 (36)**
Dose reductions due to AE, n (%)	**26 (14)**	**75 (41)**
Discontinuations, n (%)	**130 (72)**	**154 (85)**
AE	15 (8)	15 (8)
Death	11 (6)	6 (3)
Lack of efficacy	3 (2)	2 (1)
Other[a]	10 (6)	12 (7)
Progressive disease	90 (50)	119 (66)

[a]Other discontinuations includes non compliance, patient withdrawal, treatment interruption >2 weeks, and other reasons.
AE, adverse event.

Discussion and Conclusions

- In this subset analysis of treatment-naïve patients with mRCC, tivozanib demonstrated significantly improved PFS and ORR based on:
  - Median PFS: 12.7 months with tivozanib versus 9.1 months with sorafenib (HR=0.756; *P*=0.037)
  - ORR: 34% with tivozanib versus 24% with sorafenib (*P*=0.038)
- Rates of dose reductions and dose interruptions due to AEs for tivozanib were lower (14% and 20%, respectively) compared to sorafenib (41% and 36%, respectively)
- Discontinuations due to AEs were identical in each treatment arm (8%)
- The AE profile of tivozanib was differentiated from that of sorafenib, and consistent with the previous reports of tivozanib in the intent-to-treat population of TIVO-1[2-4]

Table 4. Common Treatment-emergent AEs in Treatment-naïve Patients

	Tivozanib (n=181)		Sorafenib (n=181)	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Any AE	**160 (88)**	**113 (62)**	**175 (97)**	**126 (70)**
Hypertension	73 (40)	46 (25)	63 (35)	33 (18)
Diarrhea	40 (22)	4 (2)	60 (33)	12 (7)
Fatigue	36 (20)	11 (6)	27 (15)	6 (3)
Weight loss	34 (19)	6 (3)	33 (18)	4 (2)
Dysphonia	33 (18)	0	10 (6)	0
Asthenia	26 (14)	5 (3)	32 (18)	6 (3)
Back pain	27 (15)	4 (2)	15 (8)	4 (2)
Dyspnea	21 (12)	4 (2)	15 (8)	2 (1)
Decreased appetite	20 (11)	1 (1)	17 (9)	2 (1)
Hand-foot syndrome	21 (12)	3 (2)	95 (52)	29 (16)
Nausea	19 (10)	1 (1)	13 (7)	1 (1)
Stomatitis	18 (10)	1 (1)	21 (12)	2 (1)
Alopecia	4 (2)	0	41 (23)	0
Increased lipase	8 (4)	7 (4)	14 (8)	14 (8)

AE, adverse event.

AE ≥5% more common with tivozanib AE ≥5% more common with sorafenib

References

1. Nakamura K, Taguchi E, Miura T *et al.* KRN951, a highly potent inhibitor of vascular endothelial growth factor receptor tyrosine kinases, has antitumor activities and affects functional vascular properties. *Cancer Res* 2006;66:9134–9142.
2. Eskens FA, de Jonge MJ, Bhargava P *et al.* Biologic and clinical activity of tivozanib (AV-951, KRN-951), a selective inhibitor of VEGF receptor-1, -2, and -3 tyrosine kinases, in a 4-week-on, 2-week-off schedule in patients with advanced solid tumors. *Clin Cancer Res* 2011;17:7156–7163.
3. Nosov DA, Esteves B, Lipatov ON *et al.* Antitumor activity and safety of tivozanib (AV-951) in a phase II randomized discontinuation trial in patients with renal cell carcinoma. *J Clin Oncol* 2012;30:1678–1685.
4. Motzer RJ, Eisen T, Bondarenko IN *et al.* Tivozanib versus sorafenib as initial targeted therapy for patients with advanced renal cell carcinoma: Results from a phase III randomized, open label, multicenter trial. *J Clin Oncol* 2012;30(suppl: Abstract 4501.
5. Catreou M, King T, Mousmanian L *et al.* The effect of food on the pharmacokinetics of tivozanib. In: *Proceedings of the 103rd Annual Meeting of the American Association for Cancer Research*; Mar 31–Apr 4, 2012, Chicago, Illinois. Philadelphia (PA): American Association for Cancer Research; 2012. Abstract 752.

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Protokol for vurdering af den kliniske merværdi af tivozanib til behandling af nyrecellekarcinom

Handelsnavn	Fotivda
Generisk navn	Tivozanib
Firma	EUSA Pharma UK Ltd.
ATC-kode	L01XE34
Virkningsmekanisme	Vaskulær endotelial vækstfaktorreceptor (1, 2 og 3) inhibitor
Administration/dosis	1340 µg én gang dagligt i 21 dage (efterfulgt af en pause på 7 dage). Behandlingsskemaet fortsættes til sygdomsprogression eller uacceptabel toxicitet.
Forventet EMA Indikation	1. linjebehandling af avanceret renalcellekarcinom til voksne patienter i god, intermediær eller dårlig prognosegruppe i henhold til IMCD's kriterier og som 2. linjebehandling til patienter, som er VEGFR og mTOR inhibitornaive som følge af sygdomsprogression efter én tidligere behandling med cytokinterapi.
Godkendelsesdato Offentliggørelsesdato Dokumentnummer Versionsnummer (Fagudvalgets sammensætning og sekretariatets arbejdsgruppe se bilag 1)	12. april 2018 12. april 2018 17663 1.0

Indhold

Forkortelser

ARR:	Absolut risiko reduktion
CI:	Konfidensinterval
DOR:	Responsvarighed
EMA:	*European Medicines Agency*
EORTC-QLQ C-30:	*European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire-Core 30*
EPAR:	*European Public Assessment Report*
EQ- 5D:	*EuroQol-5 Dimension*
GRADE:	System til vurdering af evidens (*Grading of Recommendations Assessment, Development and Evaluation*)
HR:	Hazard Ratio
HRQoL:	*Health related quality of life*
IMDC:	*International Metastatic Renal Cell Carcinoma Database Consortium* (redskab til prognosegruppeallokering)
mRCC:	Lokalavanceret inoperabelt eller metastatisk nyrekræft
MSKCC:	*Memorial Sloan Kettering Cancer Center (*redskab til prognosegruppeallokering)
mTOR:	Proliferative signalhæmmere
NCCN-FKSI-19:	*National comprehensive cancer network/Functional assessment of Cancer therapy (FACT)-Kidney Symptom Index*
OR:	Odds Ratio
ORR:	Objektiv responsrate
OS:	Samlet overlevelse (*overall survival*)
PICO:	Fokuserede forskningsspørgsmål *(Population, Intervention, Comparator, Outcome)*
RADS:	Rådet for anvendelse af dyr sygehusmedicin
RR:	Relativ Risiko
SAE:	Alvorlig uønsket hændelse (s*erious adverse event*)
SAR:	Alvorlig bivirkning (s*erious adverse reaction*)
PFS:	Progressionsfri overlevelse (*Progression free survival*)
TKI:	Tyrosin kinase inhibitorer
VEGF:	Vaskulær endotelial vækstfaktor
VEGFR:	Vaskulær endotelial vækstfaktor receptor

1 Formål

Protokollen har til formål at definere de kliniske spørgsmål, der ønskes belyst i vurderingen af tivozanib med henblik på anbefaling som mulig standardbehandling til patienter med lokalavanceret inoperabelt eller metastaserende nyrecellekarcinom (mRCC). I protokollen defineres population, komparator og effektmål, der skal præsenteres i den endelige ansøgning samt metoder, der ønskes anvendt til den komparative analyse. Arbejdet med protokollen er igangsat på baggrund af den foreløbige ansøgning vedrørende tivozanib modtaget den 9. januar 2018.

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

Ved indsendelse af den endelige ansøgning skal Medicinrådets ansøgningsskema, som findes på Medicinrådets hjemmeside, anvendes.

2 Baggrund

Renalcellekarcinom (RCC) er den mest almindelige form for nyrekræft og udgør ca. 85 % af alle tilfælde af nyrekræft - og ca. 2 % af alle kræftformer i Danmark [1].

RCC opstår fra nyreepitelet, og tumorvævet har et højt indhold af blodkar. Den høje forekomst af blodkar i tumorvævet skyldes en øget produktion af vaskulær endotelial vækstfaktor (VEGF) [2]. RCC opdeles i forskellige histologiske subtyper. De fire mest almindelige subtyper er: clearcelle, papillært, kromofobt- og samlerørsrenalcellekarcinomer. Af disse er clearcellekarcinom den mest almindelige og udgør ca. 70-85 % af tilfældene af RCC [3].

Prævalens og incidens

Der diagnosticeres cirka 900 nye tilfælde årligt i Danmark [4]. Sygdommen debuterer hyppigst i 60-70 års alderen og sjældent hos personer under 40 år. Fordelingen mellem mænd og kvinder er ca. 2:1 [4]. Omkring halvdelen af tumorerne opdages ofte ved udredning af anden sygdom, og ca. 20 % af patienterne har fjernmetastaser på diagnosetidspunktet. Cirka 20 % af de patienter, der opereres med kurativt sigte, udvikler senere lokalrecidiv eller metastaser [4]. Fagudvalget vurderer derfor, at der årligt er ca. 300 nye patienter med mRCC, som vil være egnede til behandling.

Prognosen af RCC er væsentligt forbedret de sidste 15 år, og 5-års overlevelsen var i 2016 ca. 60 % mod ca. 43 % tidligere [4]. Forbedringen skyldes hovedsageligt flere tilfældigt fundne lokaliserede RCC-tilfælde, forbedrede kirurgiske teknikker og løbende introduktion af nye targetterede lægemidler siden 2006, herunder tyrosin kinasehæmmere (TKI) og proliferative signalhæmmere (mTOR) [5].

2.1 Nuværende behandling

Patienter i god almen tilstand (< 5 % af det samlede antal patienter) tilbydes i udgangspunktet kurativ behandling med kirurgi [5]. Er kirurgisk behandling ikke en mulighed, tilbydes patienten medicinsk behandling.

Opstart af medicinsk behandling sker ved hjælp af det prognostiske stratificeringsredskab International Metastatic RCC Database Consortium (IMDC) [6]. IMDC anvendes som standard i Danmark og opdeler, på baggrund af seks risikofaktorer, patienterne i tre prognosegrupper; god, intermediær og dårlig.

Risikofaktorerne for prognosestratificering er som følger:

- Karnofsky performance status < 80
- Mindre end et år fra diagnose til opstart af onkologisk behandling
- Hæmoglobin < laveste normalgrænse
- Hyperkalcæmi (korrigeret kalcium koncentration > øverste normalgrænse)
- Neutrofil antal > øverste normalgrænse
- Blodplade antal > øverste normalgrænse.

Patienterne allokeres til prognosegrupperne på baggrund af forekomst af ovennævnte risikofaktorer.

- 0 risikofaktorer: **god prognosegruppe**
- 1-2 risikofaktorer: **intermediær prognosegruppe**
- ≥ 3 risikofaktorer: **dårlig prognosegruppe.**

Den nuværende behandling i Danmark er, i henhold til RADS-behandlingsvejledning fra 2016, som følger [5]:

I *1. linjebehandling* af patienter med mRCC (god/intermediær og dårlig prognosegruppe) er pazopanib førstevalg, mens sunitinib bør overvejes som andetvalg til alle tre prognosegrupper. Derudover bør temsirolimus overvejes som andetvalg til patienter i dårlig prognosegruppe. Pazopanib anbefales som førstevalg fremfor sunitinib, da pazopanib vurderes at have en tendens til mere favorabel bivirkningsprofil samt en mere favorabel HRQoL-profil.

Fagudvalget vurderer, trods indplacering af pazopanib som førstevalg i RADS behandlingsvejledning, at det er relevant at angive både pazopanib og sunitinib som komparatorer, da dette giver mulighed for at vurdere den kliniske merværdi af tivozanib på baggrund af et stærkere datagrundlag.

I *2. linjebehandling* af patienter med mRCC (god/intermediær og dårlig prognosegruppe) er nivolumab førstevalg for alle prognosegrupper, mens cabozantinib bør overvejes som andetvalg til alle tre prognosegrupper. Derudover bør axitinib overvejes som andetvalg til patienter i dårlig prognosegruppe.

2.2 Tivozanib

Tivozanib er en tyrosin kinasehæmmer, som blokerer tre vaskulære endotelial vækstfaktorreceptorer (VEGFR-1, VEGFR-2 og VEGFR-3). VEGF øger celledeling og spiller en central rolle i dannelsen af nye blodkar i tumorvævet og blodkarrenes gennemtrængelighed. Tivozanib virker ved at blokere den VEGF-inducerede VEGFR-aktivering og dermed hæmme tumorvækst [7].

Tivozanib er indiceret til 1. linjebehandling af voksne patienter med mRCC og til voksne patienter, som er VEGRF og mTOR pathway-hæmmernaive som følge af sygdomsprogression efter tidligere behandling af

mRCC med cytokiner [7]. Danske patienter behandles ikke længere med cytokinterapi i 1. linje. Fagudvalget vurderer derfor, at det i dansk behandlingsregi ikke er relevant at vurdere den kliniske merværdi af 2. linjebehandling med targetterede lægemidler efter én cytokinbehandling (jf. afsnit 2.1). Behandling med tivozanib vil derfor kun blive vurderet i henhold til indikationen for 1. linjebehandling.

Tivozanib er formuleret som oral kapselbehandling i styrkerne 1340 mikrogram og 890 mikrogram. Anbefalet dosis er 1340 mikrogram én gang om dagen i 21 dage efterfulgt af en pause på 7 dage. Ved behov for dosisreduktion kan tivozanib reduceres til 890 mikrogram én gang om dagen i henhold til det normale behandlingsskema med dosering i 21 dage og en pause på 7 dage [7]. Behandlingsskemaet forsættes til sygdomsprogression eller uacceptabel toxicitet.

3 Kliniske spørgsmål

Nedenfor beskrives det kliniske spørgsmål, som danner grundlag for Medicinrådets vurdering af den kliniske merværdi af tivozanib som 1. linjebehandling til mRCC. Fagudvalget for nyrekræft definerer klinisk betydende forskelle for et lægemiddel som 10 % forbedring i effekt og livskvalitet og 10 % reduktion i alvorlige bivirkninger i forhold til komparator.

Jf. afsnit 2.2 vurderer fagudvalget, at behandling med et targetteret lægemiddel efter cytokinbehandling ikke længere udgør relevant behandling i Danmark. Der opsættes på den baggrund derfor kun ét klinisk spørgsmål.

3.1 *Hvad er den kliniske merværdi af tivozanib til voksne patienter med mRCC, der ikke har modtaget tidligere behandling?*

Population
Data ønskes, i henhold til EMA-indikationen, opgjort samlet for:

- Voksne patienter i god, intermediær eller dårlig prognosegruppe, i henhold til IMDC kriterier, med lokalavanceret inoperabelt eller metastaserende nyrekræft (mRCC), der ikke har modtaget tidligere behandling.

Herudover ønsker fagudvalget at orientere sig i resultaterne opgjort separat for begge prognosegrupper (god, intermediær og dårlig), dette vil ikke vægte i den samlede vurdering af klinisk merværdi.

Intervention
Tivozanib (Som beskrevet i afsnit 2.2)

Komparator
Pazopanib (Som beskrevet i afsnit 2.1)
Sunitinib

Effektmål (Se tabel 1)

3.2 Valg af effektmål

Tabel 1 summerer de valgte effektmål, deres vigtighed, mindste klinisk relevante forskel og kategori. Fagudvalget vurderer følgende tre effektmål som kritiske: samlet overlevelse (OS), progressionsfri

overlevelse (PFS) samt livskvalitet; og følgende tre effektmål som vigtige: alvorlige bivirkninger, objektiv responsrate (ORR) og responsvarighed.

For alle effektmål ønskes både absolutte og relative værdier jævnfør ansøgningsskemaet. For de relative værdier vurderes den kliniske 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.

Da der er stor variation i forventet overlevelse for de tre prognosegrupper (god, intermediær og dårlig) udtrykt ved en variation på 6-34 måneder afhængigt af prognosegruppe [8], ønsker fagudvalget at orientere sig i data opgjort for patienter i hver enkelt prognosegruppe. Vurderingen af klinisk merværdi baseres på den samlede population.

Effektmål	**Vigtighed**	**Kategori**	**Måleenhed**	**Mindste klinisk relevante forskelle (absolutte værdier)**
Samlet Overlevelse (OS)	Kritisk	Overlevelse	Median OS i måneder	3 måneder
			OS-rate	10 % absolut forbedring sammenlignet med komparator
Progressions-fri overlevelse (PFS)	Kritisk	Alvorlige symptomer og bivirkninger	Median PFS i måneder	3 måneder
			PFS-rate	10 % absolut forbedring sammenlignet med komparator
Livskvalitet (fx EORTC-QLQ-30)	Kritisk	Livskvalitet	Gennemsnitlig ændring over tid fx i EORTC-QLQ-30	10 point eller 10 % absolut forbedring sammenlignet med komparator
Alvorlige bivirkninger (SAE eller bivirkninger af grad 3-4)	Vigtig	Alvorlige symptomer og bivirkninger	Andel af patienter (%)	10 % absolut forbedring sammenlignet med komparator
Objektiv responsrate (ORR)	Vigtig	Alvorlige symptomer og bivirkninger	Andel af patienter der opnår ORR (%)	10 % absolut forbedring sammenlignet med komparator
Responsvarighed (Duration of response, DOR)	Vigtig	Alvorlige symptomer og bivirkninger	Median DOR i måneder	2 måneder

Tabel 1: Oversigt over valgte effektmål. For hver 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 ikke-alvorlige symptomer og bivirkninger).

Tidshorisont

Den samlede kliniske merværdi af tivozanib baseres, med udgangspunkt i den indsendte foreløbige ansøgning, på en beregning af effekt ved 12 måneder og 24 måneder. Såfremt der ikke eksisterer data med denne tidshorisont, ønskes en så lang opfølgningstid som muligt for hvert effektmål for både intervention og komparator.

Kritiske effektmål

Overlevelse

Forbedret samlet overlevelse med mindst mulig toksicitet er det optimale mål for kræftbehandling. For OS anvendes to mål til at vurdere den absolutte effekt: median OS og OS-rate. Disse to mål vil supplere hinanden. Median OS giver svar på, hvor lang tid der går, inden halvdelen af populationen er døde. OS-raten giver et estimat af hvor mange, som er i live ved 12 måneder og 24 måneder. Fagudvalget har derfor vurderet overlevelse som et kritisk effektmål. Fagudvalget vurderer, at en absolut 10 % forbedring i OS-rate og 3 måneders forbedring i median overlevelse sammenlignet med komparator er klinisk relevant for den samlede population.

Progressionsfri overlevelse

Progressionsfri overlevelse (PFS) anvendes til vurdering af sygdomsprogression. PFS er en ofte anvendt surrogatmarkør for overlevelse i onkologiske studier. I modsætning til OS påvirkes PFS ikke af akkumulerede effekter af efterfølgende behandlinger, da patienterne følges over kortere tid. Fagudvalget vurderer derfor, at PFS er et kritisk effektmål. Med eksisterende behandling vurderer fagudvalget, at kun få patienter vil have en median PFS på > 12 måneder. Fagudvalget vurderer, at en absolut 10 % forbedring i PFS rate sammenlignet med komparator vil være klinisk relevant. Herudover vurderer fagudvalget at, den mindste klinisk relevante forskel for median PFS er 3 måneder.

Livskvalitet

Livskvalitet kan for mRCC-patienter måles med flere forskellige instrumenter. I dette tilfælde vil vurdering af livskvalitet blive baseret på følgende instrumenter: European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire-Core 30 (EORTC-QLQ C-30) [9], EQ- 5D (EuroQol- 5 Dimension) eller NCCN functional assessment of cancer therapy-kidney symptom index (FKSI-19) eller tilsvarende sygdomsspecifik målemetode af livskvalitet [10]. EORTC-QLQ C-30 består af fem funktionsskalaer, tre symptomskalaer og en "global" livskvalitetsskala. Der anvendes en scoringsskala fra 0-100. Den mindste klinisk relevante forskel baserer sig på Osoba et al. [11], hvor en lille ændring er defineret som ca. 5-10 point. En moderat ændring er ca. 10-20 point, og en stor ændring er > 20 point.

EQ-5D er et standardiseret generisk måleinstrument, der beskriver og evaluerer helbredsrelateret livskvalitet og funktionsevne. Fagudvalget finder det vigtigt, at resultater for livskvalitet og de øvrige effektmål trækker i samme retning, således at den samlede effekt af behandlingen ikke påvirker patientens livskvalitet negativt. Fagudvalget vurderer, at den mindste klinisk relevante forskel på en 100-pointskala er en ændring på 10 point eller en absolut forbedring på 10 % sammenlignet med komparator.

Livskvalitet vurderes på en generisk livskvalitetsskala (fx EORTC-QLQ C-30), men såfremt der findes data på et specifikt instrument for nyrekræft, ønsker fagudvalget også data fra dette. Disse data vil indgå i den samlede vurdering, og der er ikke defineret en mindste klinisk relevant forskel.

Vigtige effektmål

Alvorlige bivirkninger (bivirkninger af grad 3-4)

Forekomst af både alvorlige bivirkninger grad III-IV er et udtryk for alvorlig men ikke fatal toksicitet af lægemidlet defineret ved European Organisation for Research and Treatment of Cancer – Common Terminology Criteria for Adverse Events [12]. Fagudvalget anser grad 3-4 bivirkninger som et vigtigt effektmål og vurderer, at den mindste klinisk relevante forskel er en absolut reduktion i alvorlige bivirkninger på 10 % sammenlignet med komparator. Der ønskes også en udspecificering af alle SAE og frekvens heraf i hhv. komparator og interventionsgruppe. Data for SAEs vil blive anvendt som proxy for bivirkninger, hvis der ikke findes data for sidstnævnte.

Objektiv responsrate

Objektiv responsrate (ORR) anvendes til belysning af behandlingsrespons og indikerer potensen af lægemidlet [13]. Fagudvalget vurderer, at ORR skal indgå som et vigtigt men ikke kritisk effektmål. Fagudvalget vurderer, at en absolut forskel i responsrate sammenlignet med komparator på 10 % ARR er klinisk relevant. ORR underinddeles i følgende kategorier:

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

Objektiv respons opnås for en patient, hvis vedkommende er klassificeret som CR eller PR, og ORR defineres som CR + PR delt med det samlede patientantal.

Responsvarighed

Responsvarighed (DOR) er defineret som tiden fra opnåelse af respons til progression [13]. Fagudvalget vurderer, at DOR er et vigtigt effektmål. Fagudvalget vurderer, at den mindste klinisk relevante forskel er 2 måneder. .

Mindre vigtige effektmål

Behandlingsstop pga. bivirkninger

De negative effekter i introduktion af en ny behandling indgår i forekomsten af alvorlige bivirkninger, hvorfor fagudvalget vurderer behandlingsstop pga. øvrige bivirkninger som et mindre vigtigt effektmål i vurdering af klinisk merværdi. Fagudvalget vurderer, at det fortrinsvis vil være bivirkninger ved begyndelsen af behandlingen, som er relevante, og finder generelt, at det samlede antal alvorlige bivirkninger vil være et bedre udtryk for ulemperne ved behandlingen. Som følge heraf ekstraheres der ikke data for dette effektmål.

Ikke-alvorlige bivirkninger (Grad I-II)

Fagudvalget finder, at forekomsten af ikke-alvorlige bivirkninger er mindre vigtigt ift. vurdering af den kliniske merværdi.

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 både det aktuelle lægemiddel og dets komparator(er), 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 (fx Medical Subject Headings, MeSH) og fritekst søgning skal anvendes.

<table>
<tr>
<td>Lægemiddel

• tivozanib, Fotivda

Udover termer for det generiske navn, handelsnavn og alternative stavemåder og evt MeSH/supplementary concepts kombineres med OR. AND kan bruges hvor flere termer skal forekomme samtidigt for at beskrive lægemidlet korrekt, f.eks. ved co-formuleringer.</td>
<td rowspan="4">Blokkene til venstre og højre kombineres med AND</td>
<td rowspan="4">Indikation

• renal cell carcinoma

Termer for indikationerne, alternative stavemåder og eventuelle MeSH termer kombineres med OR. AND kan bruges hvor flere termer skal forekomme samtidigt for at beskrive indikationen korrekt.</td>
</tr>
<tr>
<td>Ovenstående og nedenstående blokke kombineres med OR.</td>
</tr>
<tr>
<td>Komparator

• pazopanib, Votrient
• sunitinib, Sutent

Udover termer for det generiske navn, handelsnavn og alternative stavemåder og evt. MeSH/supplementary concepts kombineres med OR. AND kan bruges hvor flere termer skal forekomme samtidigt for at beskrive lægemidlet korrekt, f.eks. ved co-formuleringer.</td>
</tr>
</table>

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 abstract-niveau lever op til inklusions- og eksklusionskriterierne, skal der anvendes et forsigtighedsprincip til fordel for artiklen, hvorved fuldtekstartiklen vurderes.

Vurderingen af klinisk merværdi baseres på data fra publicerede fuldtekstartikler og data fra EMA's EPAR – Public assessment report. Data skal derudover stemme overens med protokollens beskrivelser. Upublicerede data kan fremsendes og vil indgå i vurderingen, såfremt Medicinrådet finder, at de er nødvendige. 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.

Alt 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 ift. præspecificeret population og effektmål, begrundes dette.

Hvis data for et effektmål ikke er tilgængelig for alle deltagere i et studie, vil der ikke blive gjort 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 vil derefter blive beregnet 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*0.5 = 15 %-point).

Hvis der er mere end et sammenlignende studie, 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, vil eventuelle metaanalyser blive baseret på standardized mean difference (SMD). Den estimerede SMD vil blive omregnet 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 per 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 Referencer

1. Engholm G, Ferlay J, Christensen N, Hansen HL, Hertzum-Larsen R, Johannesen TB, Kejs AMT, Khan S, Ólafsdóttir E, Petersen T, Schmidt LKH VA and SH. Kræftstatistik: Nøgletal og figurer Danmark – Nyre NORDCAN: Cancer Incidence, Mortality, Prevalence and Survival in the Nordic Countries. 2017. Tilgængelig fra: https://www.ancr.nu/

2. Lægehåndbogen. Nyrekræft. 2017. Tilgængelig fra: https://www.sundhed.dk/sundhedsfaglig/laegehaandbogen/nyrer-og-urinveje/tilstande-og-sygdomme/nyresygdomme/nyrekraeft/

3. Kliniske retningslinjer. Nyrecancer. Dansk Renal Cancer Gruppe (DaRenCa) og Dansk Urologisk Cancer Gruppe (DUCG). 2013.

4. Dansk Renal Cancer Gruppe (DaRenCa). Årsrapport 2016.

5. Rådet for Anvendelse af Dyr Sygehusmedicin (RADS). RADS Baggrundsnotat for behandling af metastaserende nyrekræft. 2017. Tilgængelig fra: http://www.regioner.dk/media/4297/bgn-mrcc-268708.pdf

6. Heng DYC, Xie W, Regan MM, Harshman LC, Bjarnason GA, Vaishampayan UN, et al. External validation and comparison with other models of the International Metastatic Renal-Cell Carcinoma Database Consortium prognostic model: A population-based study. Lancet Oncol. 2013; 14: 141-48.

7. European Medicines Agency EMA. Produktresumé. Tivozanib (Fotivda) 2017. Tilgængelig fra: http://www.ema.europa.eu/docs/da_DK/document_library/EPAR_-_Product_Information/human/004131/WC500239033.pdf

8. Soerensen A V., Donskov F, Hermann GG, Jensen N V., Petersen A, Spliid H, et al. Improved overall survival after implementation of targeted therapy for patients with metastatic renal cell carcinoma: Results from the Danish Renal Cancer Group (DARENCA) study-2. Eur J Cancer. 2014; 50:553–62.

9. Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst [internet]. 1993;85:365–76.

10. Brooks R, Rabin R de CF. The Measurement and Valuation of Health Status Using EQ-5D: A European Perspective - Evidence from the EuroQol BIOMED Research Programme. 2003.

11. Osoba D, Rodrigues G, Myles J, Zee B, Pater J. Interpreting the significance of changes in health-related quality-of-life scores. J Clin Oncol. 1998;16:139–44.

12. National Cancer Institute Cancer Therapy Evaluation Program. Common Terminology Criteria for Adverse Events v4.0 (CTCAE). 2009.

13. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009; 45:228–47.

7 Bilag 1: Sammensætning af fagudvalg og kontaktinformation til Medicinrådet

Medicinrådets fagudvalg vedrørende Nyrekræft

Formand	*Indstillet af*
Frede Donskov, formand Overlæge, dr.med.	LVS, DSKO og Region Midtjylland
Medlemmer	*Udpeget af*
Andreas Carus Overlæge	Region Nordjylland
Niels Viggo Jensen Overlæge	Region Syddanmark
Mads Nordahl Svendsen Ledende overlæge	Region Sjælland
Kan ikke udpege en kandidat, der opfylder Medicinrådets habilitetskrav	Region Hovedstaden
Lars Lund Professor, overlæge, dr.med.	Dansk Renal Cancer Gruppe
Ljubjana Vukelic Andersen Overlæge	DSKF
2 Patienter	Danske Patienter

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