Medicinrådet

Bilag til Medicinrådets anbefaling vedrørende selpercatinib til behandling af RET-forandret kræft i skjoldbruskkirtlen eller ikke-småcellet lungekræft

Vers. 1.0

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Medicinrådet

Medicinrådets sundheds-økonomiske afrapportering

Selpercatinib

RET-forandret kræft i skjoldbruskkirtlen eller ikke-småcellet lungekræft

Version 1.0

Om Medicinrådet

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

Dokumentets formål

Den sundhedsøkonomiske analyse indeholder Medicinrådets vurdering af de inkrementelle omkostninger pr. patient og budgetkonsekvenserne ved anbefaling. Værdien for patienten og omkostningerne for samfundet danner grundlaget for Medicinrådets beslutning om, hvorvidt lægemidlet anbefales som mulig standardbehandling. Dette bliver sammenfattet i Medicinrådets anbefaling vedr. lægemidlet.

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

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Indholdsfortegnelse

1. Begreber og forkortelser

AIP	Apotekernes indkøbspris
AE	*Adverse events*
BSC	*Best supportive care*
DKK	Danske kroner
DRG	Diagnose Relaterede Grupper
HR	Hazard ratio
MTC	Medullær kræft i skjoldbruskkirtlen
NGS	*Next-generation-sequencing*
NMA	Netværks-metaanalyse (*Network meta-analysis*)
NSCLC	Ikke-småcellet lungekræft (*Non-small cell lung cancer*)
OS	*Overall survival*
PFS	*Progression free survival*
PD	Progressive disease
PD-L1	Programmed Cell Death 1 Ligand 1
RECIST	*Response Evaluation Criteria in Solid Tumors*
RET	*Rearranged during transfection*
SAIP	Sygehusapotekernes indkøbspris
SPC	Produktresumé (*summary of product characteristics*)
TC	Kræft i skjoldbruskkirtlen

2. Konklusion

Inkrementelle omkostninger og budgetkonsekvenser ved kræft i skjoldbruskkirtlen (TC) og medullær kræft i skjoldbruskkirtlen (MTC)
I det scenarie, Medicinrådet mener er mest sandsynligt, er de inkrementelle omkostninger for selpercatinib ca. [redacted] DKK pr. patient sammenlignet med vandetanib. Når analysen er udført med apotekernes indkøbspris (AIP), er de inkrementelle omkostninger til sammenligning ca. 1,2 mio. DKK pr. patient.

Når selpercatinib sammenlignes med sorafenib, er de inkrementelle omkostninger ca. [redacted] DKK pr. patient. Hvis analysen udføres med AIP, er de inkrementelle omkostninger ca. 1,4 mio. DKK.

De inkrementelle omkostninger er ved sammenligning med cabozantinib ca. [redacted] DKK pr. patient. Hvis analysen udføres med AIP, er de inkrementelle omkostninger ca. 2,3 mio. DKK.

I Medicinrådets hovedanalyse ændres den relative dosisintensitet for alle komparatorerne til at være 50 %, da det er denne dosisintensitet fagudvalget mener bedst stemmer overens med dansk klinisk praksis og deres erfaring med behandling af patienter med TC og MTC. En reduktion af dosisintensiteten har stor betydning for analysernes resultater, og derfor er der også udført følsomhedsanalyser, der undersøger de inkrementelle omkostninger ved en dosisintensitet på 100 %. Ved sammenligningen med vandetanib falder de inkrementelle omkostninger med ca. [redacted] DKK, når dosisintensiteten ændres til 100 %. For sorafenib stiger de inkrementelle omkostninger i stedet med ca. [redacted] DKK, mens de for cabozantinib falder med ca. [redacted] DKK.

Medicinrådet vurderer, at budgetkonsekvenserne for regionerne ved anbefaling af selpercatinib som mulig standardbehandling vil være ca. [redacted]. DKK i det femte år efter en anbefaling for patienter med TC. Når analysen er udført med AIP, er budgetkonsekvenserne ca. 2,4 mio. DKK i det femte år.

Ved anbefaling af selpercatinib som mulig standardbehandling til patienter med MTC, vil budgetkonsekvenserne være ca. [redacted] DKK i det femte år efter en anbefaling. Når analysen er udført i AIP, er budgetkonsekvenserne ca. 14,4 mio. DKK i det femte år.

Inkrementelle omkostninger og budgetkonsekvenser for ikke-småcellet lungekræft (NSCLC)
I det scenarie, Medicinrådet mener er mest sandsynligt, er de inkrementelle omkostninger for selpercatinib ca. [redacted] DKK og [redacted] DKK pr. patient sammenlignet med hhv. platinbaseret kemoterapi (klinisk spørgsmål 3) og docetaxel (klinisk spørgsmål 4). Når analysen er udført med apotekernes indkøbspris (AIP), er de inkrementelle omkostninger til sammenligning ca. 1,3 og 1,6 mio. DKK pr. patient sammenlignet med hhv. platinbaseret kemoterapi (klinisk spørgsmål 3) og docetaxel (klinisk spørgsmål 4).

De inkrementelle omkostninger er næsten udelukkende drevet af lægemiddelomkostningerne for selpercatinib, men der er dog betydelige usikkerheder forbundet med estimering af det endelige resultat, og konklusioner skal drages med usikkerhederne in mente. Konkret er der usikkerhed ift. det anvendte datagrundlag, ekstrapoleringerne samt de forventede testomkostninger.

Medicinrådet vurderer, at budgetkonsekvenserne for regionerne ved anbefaling af selpercatinib som mulig standardbehandling vil være ca. [redacted] DKK i år 5 sammenlignet med platinbaseret kemoterapi (klinisk spørgsmål 3) og ca. [redacted] sammenlignet med docetaxel (klinisk spørgsmål 4). Når analysen er udført med AIP, er budgetkonsekvenserne ca. 9,2 mio. DKK sammenlignet med platinbaseret kemoterapi (klinisk spørgsmål 3) og 19,3 mio. DKK sammenlignet med docetaxel (klinisk spørgsmål 4) i det femte år.

3. Introduktion

Formålet med analysen er at estimere de gennemsnitlige inkrementelle omkostninger pr. patient og de samlede budgetkonsekvenser for regionerne ved anbefaling af selpercatinib som mulig standardbehandling på danske hospitaler til behandling af RET-forandret kræft i skjoldbruskkirtlen og ikke-små-cellet lungekræft.

Analysen er udarbejdet, fordi Medicinrådet har modtaget en endelig ansøgning fra Eli Lilly. Medicinrådet modtog ansøgningen den 29. april 2021.

3.1 Patientpopulation

Forandringer i genet *rearranged during transfection* (RET) ses i forskellige kræftformer bl.a. i skjoldbruskkirtel og lunger. RET-genet koder for en tyrosinkinasereceptor, som har en vigtig rolle i udviklingen i flere væv [1]. RET-mutationer og RET-fusioner er to forskellige mekanismer for forandringer i og medfølgende overaktivering af RET-proteinet, der kan virke som onkogen driver [1].
RET-mutationer er hyppigst i medullær kræft i skjoldbruskkirtlen, mens RET-fusioner er hyppigst ved papillær kræft i skjoldbruskkirtlen og forskellige former for lungekræft [2]. Samlet set ses RET-forandringer i ca. 0,5-2 % af tumorvæv på tværs af kræftformer [2–4], og i disse tumorer repræsenterer det overaktive RET-protein en genetisk forandring, man kan målrette behandling imod.

Fagudvalget forventer, at omkring henholdsvis 1-2 patienter (differentieret) og 7-9 patienter (medullært) om året vil udvikle RET-forandret lokalt avanceret eller metastatisk kræft i skjoldbruskkirtlen, mens fagudvalget forventer, at 20-30 patienter årligt vil udvikle uhelbredelig RET-forandret NSCLC, og langt størstedelen af disse vil have ikke-planocellulær-NSCLC.

Yderligere information om sygdomsområdet kan findes i Medicinrådets vurderingsrapport.

3.1.1 Komparator

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

Klinisk spørgsmål 1:

Hvilken værdi har selpercatinib sammenlignet med sorafenib eller vandetanib for voksne med avanceret RET-forandret jodrefraktær kræft i skjoldbruskkirtlen, der tidligere er progredieret efter behandling med en multikinasehæmmer?

Klinisk spørgsmål 2:

Hvilken værdi har selpercatinib sammenlignet med cabozantinib for voksne og børn ≥ 12 år med avanceret RET-forandret medullær kræft i skjoldbruskkirtlen, der tidligere er progredieret efter behandling med en multikinasehæmmer?

Klinisk spørgsmål 3:

Hvilken værdi har selpercatinib sammenlignet med platinbaseret kemoterapi for voksne med avanceret RET-forandret NSCLC, der er progredieret efter behandling med check point-inhibitor immunterapi?

Klinisk spørgsmål 4:

Hvilken værdi har selpercatinib sammenlignet med docetaxel eller pemetrexed for voksne med avanceret RET-forandret NSCLC, der er progredieret efter behandling med check point-inhibitor immunterapi og platinbaseret kemoterapi?

4. Vurdering af den sundhedsøkonomiske analyse (kræft i skjoldbruskkirtlen)

I sin ansøgning har ansøger indsendt to sundhedsøkonomiske analyser; en samlet for kræft i skjoldbruskkirtlen (TC og MTC) og en for NSCLC. De består hver af en omkostningsanalyse og en budgetkonsekvensanalyse. I omkostningsanalysen for TC og MTC estimeres de inkrementelle omkostninger pr. patient for selpercatinib sammenlignet med sorafenib og vandetanib for patienter med TC og sammenlignet med cabozantinib for patienter med MTC.

I omkostningsanalysen for NSCLC sammenlignes selpercatinib med platinbaseret kemoterapi, docetaxel og pemetrexed.

Medicinrådet vurderer nedenfor den sundhedsøkonomiske analyse, som ansøger har indsendt. Først præsenteres og vurderes analysen for TC og MTC, og efterfølgende præsenteres og vurderes analysen for NSCLC.

4.1 Antagelser og forudsætninger for modellen (TC og MTC)

For selpercatinib anvender ansøger PFS og OS-data fra LIBRETTO-001 [5]. LIBRETTO-001 er et igangværende ikke-kontrolleret fase I/II-studie, der undersøger effekten og sikkerheden af selpercatinib i patienter med RET-forandret kræft i skjoldbruskkirtlen, RET-forandret medullær kræft i skjoldbruskkirtlen eller RET-forandret NSCLC.

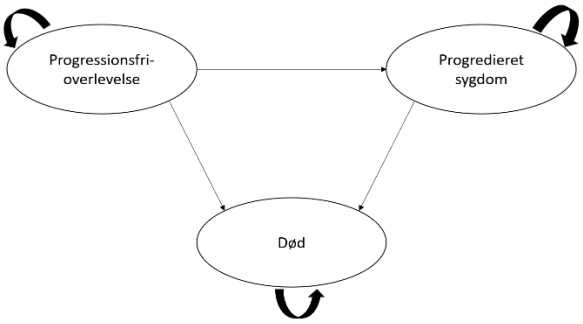
Sammenligningen i TC-populationen med sorafenib er lavet på baggrund af data fra DECISION-studiet [6]. Der er udført en naiv sammenligning, hvor der ikke er justeret for forskelle mellem patientkarakteristika i de to studier, da der ikke var data på patientniveau for komparator, og LIBRETTO-001-studiet kun inkluderer 19 patienter ved det anvendte data cut-off (december 2019).

Sammenligningen i MTC-populationen med cabozantinib er lavet på baggrund af data fra EXAM-studiet[7]. Grundet forskelle i patientkarakteristika mellem behandlingslinjerne, alder og performance, har ansøger ikke lavet en justeret indirekte sammenligning af behandlingerne på baggrund af de omtalte studier. I mangel på en fælles kontrolarm vælger ansøger at udføre en ikke-forankret, justeret indirekte sammenligning. Denne sammenligning laves, så resultaterne fra LIBRETTO-001 studiet afspejler karakteristika for patienterne i EXAM-studiet.

4.1.1 Modelbeskrivelse

Ansøger har indsendt en *partitioned survival* model til at estimere omkostningerne forbundet med behandlingen med selpercatinib.

Modellen indeholder sygdomsstadier, som patienterne skifter mellem i takt med sygdomsprogression. De tre stadier er: progressionsfri overlevelse, progredieret sygdom og stadiet død. Se Figur 1 for de forskellige sygdomsstadier, og hvordan patienten kan bevæge sig mellem dem.



Figur 1. Beskrivelse af modelstrukturen i omkostningsanalysen

Alle patienter starter i sygdomsstadiet progressionsfri overlevelse, hvorfra deres bevægelse gennem modellen bestemmes ud fra ekstrapoleret time-to-event-data. Tiden i behandling med selpercatinib bestemmes ud fra PFS-data fra LIBRETTO-001-studiet både for TC og MTC.

Patienter, der befinder sig i sygdomsstadiet progressionsfri overlevelse, responderer enten på behandlingen eller har stabil sygdom, der ikke er progredierende. Dette stadie er forbundet med omkostninger til behandling, administration, monitorering og bivirkninger. Patienter går til stadiet progredieret sygdom, når de opfylder *Response Evaluation Criteria in Solid Tumors* (RECIST)-kriterier for sygdoms progression.

Modellen har en cykluslængde på én uge.

Ansøger modellerer tiden i de forskellige stadier ved at anvende ekstrapolerede Kaplan-Meier (KM)-data for PFS og OS. Dette er nødvendigt, da opfølgningen i studierne er kortere end den anvendte tidshorisont i modellen.

Til at estimere den gennemsnitlig PFS for TC har ansøger anvendt en stratificeret Weibull til at ekstrapolere PFS-data for både selpercatinib og sorafenib, se Figur 2. For OS har ansøger valgt at ekstrapolere data med en *piecewise* eksponentiel funktion for både selpercatinib og sorafenib, se Figur 3. Ansøger antager, at effekten af vandetanib vil være den samme som af sorafenib. På baggrund af studiedata og ekstrapoleringerne har ansøger estimeret den gennemsnitlige tid, patienten befinder sig i modellens stadier.

Til at estimere gennemsnitlig PFS for MTC har ansøger anvendt en log-logistisk funktion til at ekstrapolere PFS for både selpercatinib og cabozantinib se Figur 4.

For OS har ansøger valgt at ekstrapolere data med en stratificeret log-logistisk funktion for selpercatinib. For cabozantinib har ansøger anvendt hazard ratioer (HR) for RET-mutation-subgruppen i EXAM-studiet mod *best supportive care* (BSC), se Tabel 1 . En stratificeret Weibull er blevet brugt til at estimere HR, da ansøger argumenterer, at dette vil forhindre OS-kurverne for BSC og cabozantinib i at krydse hinanden. Ekstrapolerede data kan ses i Figur 5.

Tabel 1. Estimerede hazard ratio mellem *best supportive care* og cabozantinib

	PFS	OS
Cabozantinib	0,23	0,79

Medicinrådets vurdering af ansøgers modelantagelser

Ansøger har i mangel på en fælles kontrolarm valgt at udføre en ikke-forankret, justeret indirekte sammenligning. Fagudvalget vurderer, at den justerede analyse indeholder mange usikkerheder (se vurderingsrapporten for uddybende kommentarer), men de vurderer dog, at den justerede analyse er det bedste udgangspunkt tilgængeligt for en sammenligning.

Medicinrådets fagudvalg er enige i, at det er forventeligt, at vandetanib har samme effekt som sorafenib.

Ansøger benytter en stratificeret log-logistisk fordeling til selpercatinibarmen ved ekstrapolering af OS-data for MTC-populationen, mens der bruges en stratificeret

Weibull-fordeling til cabozantinib og placebo/BSC-armene. Generelt er det anbefalet at benytte den samme type parametriske fordeling til alle armene i en sammenligning.

Derfor vælger Medicinrådet at ændre valgte fordelinger til at ekstrapolere OS-data for MTC-populationen. Baseret på AIC/BIC vælger Medicinrådet at anvende en eksponentialfunktion til at ekstrapolere data i hovedanalysen. Andre parametriske funktioner undersøges i følsomhedsanalyser.

Medicinrådet ændrer valgte kurver til ekstrapolering af OS-data for MTC, men accepterer ansøgers øvrige estimater for behandlingsvarighed. Estimaterne er præsenteret i Tabel 2.

Tabel 2. Gennemsnitlig tid i behandling, tid til progression og samlet overlevelse

Behandling	Behandlingsvarighed [år]	PFS [år]	OS [år]
Selpercatinib (TC)	[redacted]	[redacted]	[redacted]
Vandetanib (TC)	1,2	1,2	6,3
Sorafenib (TC)	1,2	1,2	6,3
Selpercatinib (MTC)	2,9	2,9	11,1
Cabozantinib (MTC)	1,4	1,4	5,5

*Tid i behandling (ToT), progressionsfri overlevelse (PFS), samlet overlevelse (OS).

Medicinrådet accepterer ansøgers tilgang vedr. modelantagelser, men ændrer ansøgers valgte funktion til ekstrapolering af OS-data for MTC-populationen.

4.1.2 Analyseperspektiv

I overensstemmelse med Medicinrådets metoder har ansøger valgt et begrænset samfundsperspektiv til sin analyse. Analysen har en tidshorisont på 25 år, hvilket, ansøger argumenterer, er svarende til livstid i den pågældende population.

Omkostninger, der ligger efter det første år, er diskonteret med en rate på 3,5 % pr. år.

Medicinrådets vurdering af ansøgers analyseperspektiv
Medicinrådet accepterer ansøgers valgte tidshorisont på 25 år, hvor den gennemsnitlige behandlingslængde ligger inden for. Det betyder ikke, at patienterne modtager behandling med selpercatinib i hele tidshorisonten, men at analysen opfanger alle direkte og afledte økonomiske forskelle mellem selpercatinib og komparatorerne set over en tidshorisont på 25 år.

Medicinrådet accepterer ansøgers valg vedr. analyseperspektiv.

4.2 Omkostninger

I det følgende præsenteres ansøgers antagelser for omkostningerne i den sundhedsøkonomiske analyse af selpercatinib sammenlignet med sorafenib, vandetanib og cabozantinib. Ansøger har inkluderet lægemiddelomkostninger, hospitalsomkostninger og patientomkostninger. Da behandlingsmulighederne for MTC og TC er begrænsede, har ansøger ikke inkluderet nogle omkostninger til efterfølgende behandling. Medicinrådets fagudvalg mener dog, at nogle patienter vil blive tilbudt cabozantinib efter selpercatinib. Fagudvalget mener dog også, at mange af disse patienter vil indgå i protokoller, og derfor vil der ikke være hospitalsomkostninger forbundet med behandlingen af dem alle.

4.2.1 Lægemiddelomkostninger

Ansøger har, jf. *Metodevejledning for omkostningsanalyser af nye lægemidler og indikationer i hospitalssektoren,* estimeret lægemiddelomkostninger på baggrund af apotekernes indkøbspris (AIP). Priserne er hentet fra Medicinpriser.dk. Dosis for selpercatinib baserer ansøger på dosis fra LIBRETTO-001. Her er der data for, hvor mange patienter, der har modtaget hvert dosisniveau. I tilfælde hvor der ikke var tilgængeligt data for komparators relative dosisintensitet, har ansøger anvendt dosisintensiteten for selpercatinib fra LIBRETTO-001. [5]

Ansøger har inkluderet omkostninger til lægemiddelspild. Lægemidlerne administreres alle oralt, og ansøger antager, at lægemidlerne udleveres til fire uger ad gangen, hvilket betyder, at lægemidler udleveret til en patient, der efterfølgende ophører behandlingen, vil være spildt.

Medicinrådets vurdering af ansøgers antagelser vedr. lægemiddelomkostninger
Medicinrådet har udskiftet AIP med sygehusapotekernes indkøbspris (SAIP), se Tabel 3.

Tabel 3. Anvendte lægemiddelpriser, SAIP (juni 2021)

Lægemiddel	Styrke	Mg/dosis	Pris [DKK]	Kilde
Selpercatinib	40 mg	60 stk.	[redacted]	Amgros
	80 mg	60 stk.	[redacted]	Amgros
Cabozantinib	20 mg + 80 mg	84 stk. + 28. stk.	[redacted]	Amgros
Vandetanib	100 mg	30 stk.	[redacted]	Amgros
	300 mg	30 stk.	[redacted]	Amgros
Sorafenib	200 mg	112 stk.	[redacted]	Amgros

*Prisen er betinget af en anbefaling på et af de kliniske spørgsmål

Fagudvalget er blevet konsulteret for at validere de antagelser, ansøger har lavet vedr. lægemiddeldoser. Fagudvalget mener, at dosisintensiteten for cabozantinib, vandetanib og sorafenib er overestimeret i forhold til dansk klinisk praksis. Fagudvalget mener, på

baggrund af deres kliniske erfaring med behandling af patienter med de specifikke lægemidler, at en mere realistisk dosisintensitet for lægemidlerne vil være omkring 50 %. Fagudvalget finder, at ansøgers antagelse om dosisintensitet på [redacted] for selpercatinib er realistisk. På baggrund af fagudvalgets vurdering ændres dosisintensiteten for cabozantinib, vandetanib og sorafenib til 50 %. Denne ændring vurderes at have stor betydning for analysens resultat, da lægemidlerne udgør en stor del af de samlede omkostninger i analysen.

Medicinrådet ændrer dosisintensiteten for cabozantinib, vandetanib og sorafenib til 50 %.

4.2.2 Hospitalsomkostninger

Administrationsomkostninger

Ansøger har estimeret administrationsomkostninger ved at anvende DRG-takster. For selpercatinib og alle komparatorerne antages der at være én engangsomkostning på 1.543 DKK til administration gennem hele modellens tidshorisont.

Medicinrådets vurdering af ansøgers antagelser vedr. administrationsomkostninger
Medicinrådet accepterer ansøgers tilgang til estimering af administrationsomkostninger. Anvendte enhedsomkostninger kan ses i Tabel 4.

Tabel 4. Omkostninger til lægemiddeladministration

	Enhedsomkostning [DKK]	Frekvens	Kode	Kilde
Administration af orale lægemidler	1.543	Engangsomkostning	10MA01	DRG-2021

Medicinrådet accepterer ansøgers tilgang vedr. administrationsomkostninger.

Monitoreringsomkostning

Omkostninger til sygdoms- og behandlingsmonitorering estimeres som helbredsstadieomkostninger, det vil sige, at ansøger estimerer, hvilke ydelser der er forbundet med at være i progressionsfri overlevelsesstadiet, og hvilke der er ved at være i stadiet progredieret. Ansøger anvender DRG-takster til at estimere omkostningerne ved de forskellige monitoreringsundersøgelser.

For selpercatinib er ressourcerne for det første halve år estimeret separat i begge helbredsstadier, ved at ekskludere omkostninger til EKG. Omkostningerne ekskluderes, da der i monitoreringsomkostningerne er inkluderet omkostninger for syv EKG, og ved at ekskludere omkostninger i helbredsstadierne forhindres dobbelttælling.

Medicinrådets vurdering af ansøgers antagelser vedr. monitoreringsomkostninger
I Tabel 5 er frekvensen af undersøgelser ved monitorering af patienterne i stadiet progressionsfri overlevelse og stadiet progredieret sygdom vist.

Tabel 5. Årlige ressourcer forbundet med helbredsstadierne progressionsfri overlevelse og progredieret sygdom

	Progressionsfri	Progredieret sygdom
Ambulant besøg	[redacted]	[redacted]
EKG	[redacted]	[redacted]
Blodprøver	[redacted]	[redacted]
CT-scanning	[redacted]	[redacted]

Medicinrådet accepterer ansøgers tilgang vedr. monitoreringsomkostninger.

Bivirkningsomkostninger

Ansøger har inkluderet omkostninger forbundet med bivirkninger i modellens første cyklus og benytter frekvenser for bivirkninger af grad 3-4 med en forekomst på mindst 2 % som mål for bivirkningerne. For selpercatinib har ansøger benyttet de rapporterede bivirkningsrater fra LIBRETTO-001 [5]. For cabozantinib anvendes bivirkningsfrekvenser fra EXAM-studiet, for sorafenib anvendes bivirkningsfrekvenser fra DECISION-studiet, og for vandetanib anvendes bivirkningsfrekvenser fra ZETA-studiet[6–8]. Ressourcerne brugt i forbindelse med de forskellige bivirkninger har ansøger baseret på DRG 2021.

Medicinrådets vurdering af ansøgers antagelser vedr. bivirkningsomkostninger

Fagudvalget vurderer, at bivirkningerne, forlænget QT, øget ALT, øget AST, hypertension og udslæt ikke vil udgøre en omkostning, og derfor vælger Medicinrådet at ekskludere disse omkostninger. Medicinrådet vurderer, at de øvrige omkostninger kan være rimelige. Bivirkningsfrekvenser og anvendte takster kan ses i Tabel 6.

Ansøger har anvendt ZETA-studiet til at estimere omkostninger for vandetanib. I Zeta-studiet blev vandetanib anvendt til patienter med MTC og ikke TC, men bivirkningsprofilen forventes at være lignende, og derfor medvirker ZETA-studiet til større datamængde.

Tabel 6. Rapporterede bivirkningsfrekvenser ved behandling med selpercatinib og cabozantinib, sorafenib og vandetanib samt enhedsomkostninger for bivirkningerne

	Selpercatinib [%]	Cabozantinib [%]	Sorafenib [%]	Vandetanib [%]	DRG-kode	Takst
Diarré	[redacted]	21,50	5,80	10,82	06MA11	5.130
Hånd-fod-syndrom	[redacted]	12,62	19,32	0,00	09MA98	1.735
Hypertension	[redacted]	8,885	9,18	8,66	-	0
EKG QT-forlænget	[redacted]	0,00	0,00	7,79	-	0

	Selpercatinib [%]	Cabozantinib [%]	Sorafenib [%]	Vandetanib [%]	DRG-kode	Takst
Nedsat vægt	[redacted]	9,81	5,80	0,00	10MA98	1.518
Abdominale-smerter	[redacted]	3,27	-	-	06MA11	5.130
Blødning	[redacted]	3,27	-	-	05MA08	1.837
Dysfagi	[redacted]	4,21	-	-	06MA11	5.130
Træthed	[redacted]	9,81	4,83	5,63	23MA03	3.987
Nedsat appetit	[redacted]	7,01	1,93	3,90	10MA98	1.518
Asteni	[redacted]	6,54	0,00	2,60	09MA98	1.735
Slimhinde-betændelse	[redacted]	3,27	-	-	23MA03	3.987
Opkast	[redacted]	2,34	-	-	06MA11	5.130
Dyspnø (åndenød)	[redacted]	2,34	4,35	0,43	04MA98	1.732
Hovedpine	[redacted]	0,47	0,00	0,00	23MA03	3.987
Rygsmerter	[redacted]	4,21	-	-	23MA03	3.987
Øget alanin amino-transferase	[redacted]	5,14	2,90	0,00	-	0
Øget aspartat amino-transferase	[redacted]	1,87	0,97	0,00	-	0
Hyponatriæmi	[redacted]	0,93	0,00	0,00	10MA98	1.518
Lymfopeni	[redacted]	7,48	0,00	0,00	16MA98	2.777
Pneumoni	[redacted]	0,00	0,00	0,00	04MA14	25.695
Hypocalcæmi	[redacted]	10,75	8,70	0,00	10MA98	1.518
Dehydrering	[redacted]	0,00	0,00	0,00	10MA98	1.518
Øget vægt	[redacted]	0,00	-	-	10MA98	1.518
Udslæt	[redacted]	-	4,83	3,46	-	0

Medicinrådet accepterer ansøgers tilgang vedr. bivirkningsomkostninger, men ekskluderer omkostninger til forlænget QT, øget ALT, øget AST, hypertension og udslæt.

Testomkostninger

Ansøger har ikke inkluderet omkostninger til diagnostiske test til at identificere patienter med RET-forandring i analysen. Omkostningerne ved diagnostiske test er dog undersøgt i en følsomhedsanalyse.

Medicinrådets vurdering af ansøgers antagelser vedr. testomkostninger

Fagudvalget vurderer, at der ikke vil være yderligere omkostninger til diagnostiske test ved en anbefaling af selpercatinib til TC og MTC, da den diagnostiske test allerede som standard anvendes til disse patienter.

Medicinrådet accepterer ansøgers tilgang vedr. testomkostninger.

4.2.3 Patientomkostninger

Patientomkostninger er estimeret på baggrund af administrationsbesøg, monitoreringsbesøg og besøg ved behandling af bivirkninger på hospitalet og inkluderer patientens effektive tid på hospitalet, ventetid og transporttid.

Ansøger anvender en enhedsomkostning for patienttid på 179 DKK pr. time og transportomkostninger på 100 DKK pr. besøg, jf. *Medicinrådets værdisætning af enhedsomkostninger.*

Medicinrådets vurdering af ansøgers antagelser vedr. patientomkostninger

Medicinrådet accepterer ansøgers tilgang vedr. patientomkostninger.

4.3 Følsomhedsanalyser

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

Ansøger har udarbejdet en række følsomhedsanalyser, hvor effekten af variation i forskellige parametre undersøges. Følgende følsomhedsanalyser er udført:

Tabel 7. Følsomhedsanalyser og beskrivelse

Følsomhedsanalyse	Beskrivelse
Variation af diskonteringsrenten	Diskonteringsrenten sættes til hhv. 0 og 6 %.
Variation af behandlingseffekten af cabozantinib	Omkostningerne sættes til øvre og nedre konfidensinterval, som er konstrueret med antagelsen om en standardfejl på 10 % af punktestimatet.

Følsomhedsanalyse	Beskrivelse
Variation af omkostningerne for helbredsstadiet progredieret sygdom	Omkostningerne sættes til øvre og nedre konfidensinterval, som er konstrueret med antagelsen om en standardfejl på 10 % af punktestimatet.
Variation af omkostningerne for helbredsstadiet progressionsfri overlevelse	Omkostningerne sættes til øvre og nedre konfidensinterval, som er konstrueret med antagelsen om en standardfejl på 10 % af punktestimatet.
Variation af lægemiddelafhængige monitoreringsomkostninger for selpercatinib	Omkostningerne sættes til øvre og nedre konfidensinterval, som er konstrueret med antagelsen om en standardfejl på 10 % af punktestimatet.
Variation af omkostninger til EKG for selpercatinib	Omkostningerne sættes til øvre og nedre konfidensinterval, som er konstrueret med antagelsen om en standardfejl på 10 % af punktestimatet.

Medicinrådets vurdering af ansøgers valg af følsomhedsanalyser

Da Medicinrådet har fortaget flere ændringer i de antagelser, der ligger til grund for ansøgers hovedanalyse og følsomhedsanalyser, vil disse ikke blive præsenteret.

Medicinrådet vælger i stedet at lave egne følsomhedsanalyser, som kan ses i Tabel 8

Tabel 8. Medicinrådets følsomhedsanalyser og beskrivelse

Følsomhedsanalyse	Beskrivelse
Gompertz-funktion i MTC-analysen	Gompertz-funktionen anvendes til at ekstrapolere OS-data i MTC-populationen.
Weibull-funktionen i MTC-analysen	Weibull-funktionen anvendes til at ekstrapolere OS-data i MTC-populationen.
Gamma-funktionen i MTC-analysen	Gamma-funktionen anvendes til at ekstrapolere OS-data i MTC-populationen.
Log-logistisk-funktionen i MTC-analysen	Log-logistisk-funktionen anvendes til at ekstrapolere OS-data i MTC-populationen.
Relativ dosisintensitet på 100 %	Den relative dosisintensitet sættes til at være 100 % for alle lægemidler i analyserne.

Medicinrådet vælger ikke at præsentere ansøgers følsomhedsanalyser, men udfører egne følsomhedsanalyser.

4.4 Opsummering af basisantagelser

I Tabel 9 opsummeres basisantagelserne i henholdsvis ansøgers og Medicinrådets hovedanalyse.

Tabel 9. Basisantagelser for ansøgers og Medicinrådets hovedanalyse

Basisantagelser	Ansøger	Medicinrådet
Tidshorisont	25 år	25 år
Diskonteringsrate	3,5 %	3,5 %
Inkluderede omkostninger	Lægemiddelomkostninger Hospitalsomkostninger Bivirkningsomkostninger Patient- og transportomkostninger Terminale omkostninger	Lægemiddelomkostninger Hospitalsomkostninger Bivirkningsomkostninger Patient- og transportomkostninger
Relativ dosisintensitet		
Selpercatinib	[redacted]	[redacted]
Vandetanib	94,9 %	50,0 %
Sorafenib	81,4 %	50,0 %
Cabozantinib	[redacted]	50,0 %
Behandlingslinje	2. linje	2. linje
MTC Parametriske funktioner for PFS		
Intervention:	Log-logistisk	Log-logistisk
Komparator:	Log-logistisk	Log-logistisk
MTC Parametriske funktioner for OS		
Intervention:	Stratificeret log-logistisk	Eksponentiel
Komparator:	Stratificeret Weibull	Eksponentiel
TC Parametriske funktioner for PFS		
Intervention:	Stratificeret Weibull	Stratificeret Weibull
Komparator:	Stratificeret Weibull	Stratificeret Weibull

Basisantagelser	Ansøger	Medicinrådet
TC		
Parametriske funktioner for OS		
Intervention:	Piecewise exponential	Piecewise exponential
Komparator:	Piecewise xkponential	Piecewise exponential
Inkludering af spild	Ja	Ja

5. Resultater

5.1 Resultatet af Medicinrådets hovedanalyse

Medicinrådets hovedanalyse bygger på samme antagelser som ansøgers hovedanalyse med undtagelse af de væsentligste ændringer, der fremgår af Tabel 9.

Den gennemsnitlige inkrementelle omkostning pr. patient med TC bliver ca. [redacted] DKK ved sammenligning med vandetanib i Medicinrådets hovedanalyse.

Er analysen udført med AIP, bliver den inkrementelle omkostning pr. patient 1,2 mio. DKK.

Resultaterne fra Medicinrådets hovedanalyse er præsenteret i Tabel 10.

Tabel 10. Resultatet af Medicinrådets hovedanalyse ved sammenligning med vandetenib, DKK, diskonterede tal

	Selpercatinib	Vandetanib	Inkrementelle omkostninger
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Hospitalsomkostninger	125.143	135.320	-10.177
Patientomkostninger	5.321	4.435	886
Totale omkostninger	[redacted]	[redacted]	[redacted]

Den gennemsnitlige inkrementelle omkostning pr. patient med TC bliver ca. [redacted] DKK ved sammenligning med sorafenib i Medicinrådets hovedanalyse.

Er analysen udført med AIP, bliver den inkrementelle omkostning pr. patient 1,4 mio. DKK.

Resultaterne fra Medicinrådets hovedanalyse er præsenteret i Tabel 11.

Tabel 11. Resultatet af Medicinrådets hovedanalyse ved sammenligning med sorafenib, DKK, diskonterede tal

	Selpercatinib	Sorafenib	Inkrementelle omkostninger
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Hospitalsomkostninger	125.143	135.526	-10.383
Patientomkostninger	6.639	7.401	-762
Totale omkostninger	[redacted]	[redacted]	[redacted]

Den gennemsnitlige inkrementelle omkostning pr. patient med MTC bliver ca. [redacted] DKK ved sammenligning med cabozantinib i Medicinrådets hovedanalyse.

Er analysen udført med AIP, bliver den inkrementelle omkostning pr. patient 2,3 mio. DKK.

Resultaterne fra Medicinrådets hovedanalyse er præsenteret i Tabel 12.

Tabel 12. Resultatet af Medicinrådets hovedanalyse ved sammenligning med cabozantinib, DKK, diskonterede tal

	Selpercatinib	Cabozantinib	Inkrementelle omkostninger
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Hospitalsomkostninger	293.706	92.342	201.364
Patientomkostninger	15.312	5.321	9.991
Totale omkostninger	[redacted]	[redacted]	[redacted]

5.1.1 Resultatet af Medicinrådets følsomhedsanalyser

Ved samme antagelser som i Medicinrådets hovedanalyse for meromkostninger har Medicinrådet udført en følsomhedsanalyse på parametrene listet i Tabel 13.

Tabel 13. Resultatet af Medicinrådets følsomhedsanalyse sammenlignet med hovedanalysen, DKK

Scenarie	Inkrementelle omkostninger
Resultatet af hovedanalyse (TC, vandetanib)	[redacted]
Relativ dosisintensitet 100 %	[redacted]
Resultatet af hovedanalysen (TC, sorafenib)	[redacted]

Scenarie	Inkrementelle omkostninger
Relativ dosisintensitet 100 %	[redacted]
Resultatet af hovedanalysen (MTC)	[redacted]
Gompertz-funktion i MTC-analysen	[redacted]
Weibull-funktionen i MTC-analysen	[redacted]
Spline-knot-1-funktionen i MTC-analysen	[redacted]
Relativ dosisintensitet 100 %	[redacted]

6. Budgetkonsekvenser

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

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

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

6.1 Estimat af patientantal og markedsandel

Ansøger har antaget, at der vil være ca. 2 patienter med TC om året, der ved anbefaling vil være kandidater til behandling med selpercatinib, mens der vil være ca. 8 patienter med MTC, der vil være kandidater til behandling med selpercatinib. Ansøger forventer, at ved en anbefaling af selpercatinib, vil [redacted] af patienterne med TC modtage behandlingen, mens [redacted] vil modtage vandetanib, [redacted] sorafenib og [redacted] BSC.

Ansøger forventer, at ved en anbefaling af selpercatinib vil 80 % af patienterne med MTC modtage behandlingen, mens 10 % vil modtage cabozantinib, og 30 % vil modtage BSC.

Medicinrådets vurdering af ansøgers budgetkonsekvensanalyse
Fagudvalget er blevet konsulteret i forhold til patientantal, hvis selpercatinib anbefales som mulig standardbehandling, og hvis ikke selpercatinib anbefales. Fagudvalget estimerer, at 2 nye patienter pr. år med TC forventes at være kandidater til behandling med selpercatinib til den pågældende indikation, mens 8 nye patienter med MTC forventes at være kandidater til den pågældende indikation. Fagudvalget vurderer, at en højere andel af patienterne, 90 %, vil modtage behandling med selpercatinib ved anbefaling, både af patienterne med TC og MTC, se Tabel 14 og Tabel 15.

Tabel 14. Medicinrådets estimat af markedsoptag for patienter med TC

	År 1	År 2	År 3	År 4	År 5
			Anbefales		
Selpercatinib	90 %	90 %	90 %	90 %	90 %
Sorafenib	0 %	0 %	0 %	0 %	0 %
Vandetanib	0 %	0 %	0 %	0 %	0 %
Ingen aktiv behandling	10 %	10 %	10 %	10 %	10 %
			Anbefales ikke		
Selpercatinib	0 %	0 %	0 %	0 %	0 %
Sorafenib	10 %	10 %	10 %	10 %	10 %
Vandetanib	70 %	70 %	70 %	70 %	70 %
Ingen aktiv behandling	20 %	20 %	20 %	20 %	20 %

Tabel 15. Medicinrådets estimat af markedsoptag for patienter med MTC

	År 1	År 2	År 3	År 4	År 5
			Anbefales		
Selpercatinib	90 %	90 %	90 %	90 %	90 %
Cabozantinib	0 %	0 %	0 %	0 %	0 %
Ingen aktiv behandling	10 %	10 %	10 %	10 %	10 %
			Anbefales ikke		
Selpercatinib	0 %	0 %	0 %	0 %	0 %
Cabozantinib	70 %	70 %	70 %	70 %	70 %
Ingen aktiv behandling	30 %	30 %	30 %	30 %	30 %

Medicinrådet har udført sin egen budgetkonsekvensanalyse, hvor markedsoptaget er ændret.

6.2 Medicinrådets budgetkonsekvensanalyse

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

- Ændret markedsoptag ved anbefaling af selpercatinib til 90 % for både TC og MTC

Medicinrådet estimerer, at anvendelse af selpercatinib vil resultere i budgetkonsekvenser på ca. [redacted] DKK i det femte år efter en anbefaling for patienter med TC, mens anvendelsen vil resultere i budgetkonsekvenser på ca. [redacted] DKK i det femte år efter en anbefaling for patienter med MTC. Resultaterne er præsenteret i Tabel 16 og Tabel 17.

Er analysen udført med AIP, bliver budgetkonsekvenserne ca. 2,4 mio. DKK for TC og 14,4 mio. DKK for MTC i år 5.

Tabel 16. Medicinrådets analyse af totale budgetkonsekvenser for TC, mio. DKK, ikke-diskonterede tal

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

Tabel 17. Medicinrådets analyse af totale budgetkonsekvenser for MTC, mio. DKK, ikke-diskonterede tal

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

7. Diskussion

Behandling med selpercatinib er forbundet med inkrementelle omkostninger på ca. [redacted] DKK sammenlignet med behandling med vandetanib. Ved sammenligning med sorafenib er behandlingen forbundet med omkostninger på ca. [redacted] DKK, mens de inkrementelle omkostninger ved sammenligning med cabozantinib er ca. [redacted] DKK.

De inkrementelle omkostninger er i høj grad drevet af prisen for selpercatinib i alle sammenligningerne, dog medfører den længere aktive behandling med selpercatinib, sammenlignet med komparatorerne, også øgede hospitalsomkostninger, især ved sammenligning med cabozantinib.

Ansøger har ikke inkluderet omkostninger til efterfølgende behandling i deres analyse, da de mener, at patienterne er i så sent et sygdomsstadie, at efterfølgende behandling ikke er realistisk. Fagudvalget mener dog, at nogle patienter med MTC, efter behandling med selpercatinib, vil være kandidater til cabozantinib. Dette er ikke inkluderet i analysen, da fagudvalget samtidig mener, at en del af patienterne vil indgå i protokoller, hvorved der ikke vil ske en regional betaling af behandlingen. Omkostningen inkluderes derfor ikke, da det vurderes at tilføje yderligere usikkerhed til analysen. Det ville dog potentielt medføre øgede omkostninger for selpercatinibarmen, hvis efterfølgende behandling blev inkluderet.

I Medicinrådets hovedanalyse ændres den relative dosisintensitet for alle komparatorerne til at være 50 %, da det er denne dosisintensitet, fagudvalget mener, bedst stemmer overens med dansk klinisk praksis og deres erfaring med behandling af patienter med TC og MTC. En reduktion af dosisintensiteten har stor betydning for analysernes resultater, og derfor er der også udført følsomhedsanalyser, der undersøger de inkrementelle omkostninger ved en dosisintensitet på 100 %. Ved sammenligningen med vandetanib falder de inkrementelle omkostninger med ca. [redacted] DKK, når dosisintensiteten ændres til 100 %. For sorafenib stiger de inkrementelle omkostninger i stedet med ca. [redacted] DKK, mens de for cabozantinib falder med ca. [redacted] DKK.

8. Vurdering af den sundhedsøkonomiske analyse (NSCLC)

8.1 Antagelser og forudsætninger for model (NSCLC)

Sammenligningen mellem selpercatinib og platinbaseret kemoterapi er lavet på baggrund af en naiv sammenligning, hvor data fra LIBRETTO-001-studiet er anvendt for selpercatinib, mens ansøger har anvendt en række studier til at udføre en netværksmetaanalyse (NMA) for platinbaseret kemoterapi, hvor effekten sættes i forhold til docetaxel.

LIBRETTO-001 er beskrevet ovenfor (se afsnit 4.1).

Sammenligningen mellem selpercatinib og docetaxel er også lavet på baggrund af en naiv sammenligning, hvor data fra LIBRETTO-001-studiet [9] er anvendt for selpercatinib, mens data fra placeboarmen i REVEL-studiet [10] er anvendt for docetaxel.

8.1.1 Modelbeskrivelse

Ansøger har indsendt en *partitioned survival model* til at estimere omkostningerne forbundet med behandlingen med selpercatinib.

Modellen indeholder tre sygdomsstadier, som patienterne skifter mellem i takt med sygdomsprogression. De tre stadier er: progressionsfri overlevelse, post-progression og stadiet død. Se Figur 1 for de forskellige sygdomsstadier, og hvordan patienten kan bevæge sig mellem dem.

Alle patienter starter i sygdomsstadiet progressionsfri overlevelse, hvorfra deres bevægelse gennem modellen bestemmes ud fra ekstrapoleret time-to-event data. For patienter i behandling med selpercatinib er tiden i stadiet progressionsfri overlevelse bestemt ud fra PFS-data fra LIBRETTO-001 for både klinisk spørgsmål 3 og 4, da ansøger antager, at effekten af selpercatinib er uafhængig af PD-L1-ekspression. For patienter i behandling med docetaxel er PFS bestemt ud fra PFS-data fra REVEL-studiet (klinisk spørgsmål 4), men da RET-fusion ikke er opgjort i REVEL-studiet, justeres kurven med effekten af RET-fusion fra Flatiron databasen. For patienter i behandling med platinbaseret kemoterapi (klinisk spørgsmål 3) har ansøger udført en NMA og udledt en hazard ratio mellem docetaxel og platinbaseret kemoterapi. Denne hazard ratio anvender ansøger til at generere PFS-data for platinbaseret kemoterapi. De estimerede hazard ratioer udledt af NMA'en er præsenteret i Tabel 18.

Tabel 18. Estimerede hazard ratio mellem platinbaseret kemoterapi og docetaxel

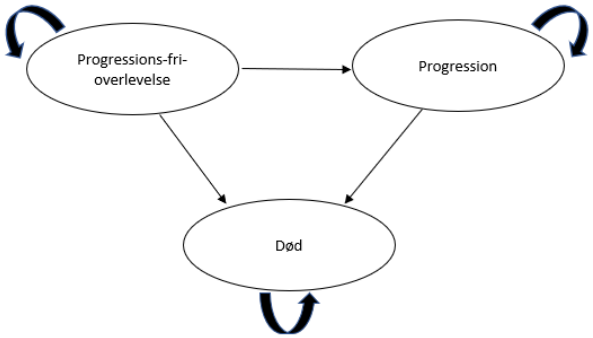
Behandling	PFS	OS
Platinbaseret kemoterapi	[redacted]	[redacted]

Fra progressionsfri overlevelse kan patienten bevæge sig videre til stadiet post-progression og til stadiet død.

Patienter, der er progredieret, men ikke døde, vil befinde sig i post-progression. Tiden, patienterne befinder sig i dette stadie, estimeres ud fra PFS- og OS-data som den andel af patienter, der hverken er i progressionsfri eller død stadierne. Fra post-progression kan patienten udelukkende bevæge sig til det absorberende stadie død.

Andelen af patienter i stadiet død bliver estimeret ud fra OS-data, som er genereret på samme måde som for PFS, som beskrevet ovenfor.

Modellen har en cykluslængde på én uge.



Figur 2: Beskrivelse af modelstrukturen i omkostningsanalysen.

Ansøger modellerer tiden i de forskellige stadier ved at anvende ekstrapolerede Kaplan-Meier (KM)-data for PFS og OS. Dette er nødvendigt, da opfølgningen i studierne er kortere end den anvendte tidshorisont.

Ansøger har anvendt en stratificeret Gompertz-fordeling til at ekstrapolere PFS for både selpercatinib og docetaxel. PFS-kurven for platinbaseret kemoterapi er genereret ved at anvende den estimerede hazard ratio fra NMA'en og den ekstrapolerede kurve for docetaxel og vil derfor også følge en Gompertz-fordeling. De ekstrapolerede PFS-kurver er præsenteret i Figur 7. For OS har ansøger valgt at ekstrapolere data med en ikke-parametrisk spline-fordeling med én *knot* for både selpercatinib og for docetaxel. OS-kurven for platinbaseret kemoterapi er ligeledes genereret ved at anvende den estimerede hazard ratio fra NMA'en og den ekstrapolerede kurve for docetaxel og vil derfor også følge en ikke-parametrisk spline-fordeling med én *knot*. De ekstrapolerede OS-kurver er præsenteret i Figur 8. Disse parametriske funktioner er valgt, da de jf. AIC- og BIC-værdierne har det bedste statistiske fit, og da ansøger argumenterer for, at de er klinisk plausible.

[redacted]

[redacted]

[redacted]

[redacted]

Ansøger antager, at patienter får behandling indtil progression, og dermed at behandlingslængden er lig med PFS. På baggrund af studiedata og ekstrapoleringerne har ansøger estimeret den gennemsnitlige tid, patienten befinder sig i modellens stadier.

Medicinrådets vurdering af ansøgers modelantagelser
Medicinrådet vurderer, at der er betydelig usikkerhed ved de anvendte studier i ansøgers analyse, da disse ikke er baseret på en direkte eller indirekte sammenligning, men blot en naiv sammenligning af studier, hvoraf RET-fusion status er ukendt for patienter, der indgår i studierne anvendt for komparator. Medicinrådet accepterer dog ansøgers tilgang, da kvantitative estimater er nødvendige i sundhedsøkonomiske analyser, og da det tilgængelig data ikke tillader en anderledes tilgang. Medicinrådet understreger dog, at dette er behæftet med meget usikkerhed.

Fagudvalget vurderer, at de ekstrapolerede kurver er forbundet med stor usikkerhed, men vurderer dog, at de ekstrapolerede kurver kan være rimelige, omend halen på kurverne virker optimistiske. Medicinrådet accepterer ansøgers estimerede og ekstrapolerede kurver trods usikkerhederne, men vælger på grund af usikkerhederne at foretage følsomhedsanalyser, hvor kurverne ekstrapoleres med andre parametriske fordelinger for at illustrere effekt af den valgte ekstrapolering på det endelige resultat. Den gennemsnitlige tid i de respektive stadier i hovedanalysen er præsenteret i Tabel 19.

Tabel 19. Gennemsnitlig tid i behandling og i stadierne PFS, OS og PD

Behandling	Behandlingsvarighed [måneder]	PFS [måneder]	PD [måneder]	OS [måneder]
Selpercatinib	[redacted]	[redacted]	[redacted]	[redacted]
Docetaxel	[redacted]	[redacted]	[redacted]	[redacted]

Behandling	Behandlingsvarighed [måneder]	PFS [måneder]	PD [måneder]	OS [måneder]
Platinbaseret kemoterapi	[redacted]	[redacted]	[redacted]	[redacted]

*Progredieret sygdom (PD), progressionsfri overlevelse (PFS), samlet overlevelse (OS).

Medicinrådet accepterer ansøgers tilgang vedr. modelantagelser, men vælger at udføre følsomhedsanalyser af den valgte parametriske fordeling til ekstrapolering af både PFS og OS.

8.1.2 Analyseperspektiv

I overensstemmelse med metoderne har ansøger valgt et begrænset samfundsperspektiv til sin analyse. Analysen har en tidshorisont på 25 år.

Omkostninger, der ligger efter det første år, er diskonteret med en rate på 3,5 % pr. år.

Medicinrådets vurdering af ansøgers analyseperspektiv
Medicinrådet vurderer, at den anvendte tidshorisont er rimelig, da den gennemsnitlige behandlingslængde ligger inden for denne tidshorisont. Det betyder ikke, at patienterne modtager behandling med selpercatinib i hele tidshorisonten, men at analysen opfanger alle direkte og afledte økonomiske forskelle mellem selpercatinib og komparatorerne set over en tidshorisont på 25 år.

Medicinrådet accepterer ansøgers valg vedr. analyseperspektiv.

8.2 Omkostninger

I det følgende er ansøgers antagelser for omkostningerne i den sundhedsøkonomiske analyse af selpercatinib sammenlignet med komparatorerne præsenteret. Ansøger har inkluderet lægemiddelomkostninger, hospitalsomkostninger, bivirkningsomkostninger, testomkostninger og patientomkostninger.

Omkostningerne er cyklusbestemt, hvilket betyder, at omkostningerne påregnes for hver cyklus, patienten befinder sig i stadiet.

8.2.1 Lægemiddelomkostninger

Ansøger har jf. *Metodevejledning for omkostningsanalyser af nye lægemidler og indikationer i hospitalssektoren* estimeret lægemiddelomkostninger på baggrund af apotekets indkøbspris (AIP). Doser anvendt i ansøgers analyse er hentet i de respektive produkters produktresuméer (SPC'er).

Selpercatinib:
Selpercatinib 160 mg to gange dagligt

Platinbaseret kemoterapi:
Pemetrexed 500 mg/M^2 hver 3. uge
Carboplatin 5mg/ml/min hver 3. uge i maksimalt 6 cyklusser

Docetaxel:
Docetaxel 75 mg/M^2 hver 3. uge

Pemetrexed:
Pemetrexed 500 mg/M^2 hver 3. uge

Ansøger antager en dosisintensitet på [redacted] for selpercatinib. Dette er baseret på data fra LIBRETTO-001-studiet [9]. For de øvrige komparatorer anvender ansøger den samme dosisintensitet, da ansøger ikke har data vedr. dosisintensitet for disse. Ansøger har dog ikke redegjort for, hvorfor dette er rimeligt.

Medicinrådets vurdering af ansøgers antagelser vedr. lægemiddelomkostninger
Medicinrådet har udskiftet AIP med sygehusapotekets indkøbspris (SAIP), se Tabel 20.

Tabel 20. Anvendte lægemiddelpriser, SAIP, (september 2021)

Lægemiddel	Styrke	Pakningsstørrelse	Pris [DKK]	Kilde
Selpercatinib	80 mg	60 stk.	[redacted]	Amgros
	40 mg	60 stk.	[redacted]	Amgros
Docetaxel	20 mg/ml	4 ml	[redacted]	Amgros
	20 mg/ml	8 ml	[redacted]	Amgros
Pemetrexed	500 mg	1 htgl.	[redacted]	Amgros
	100 mg	1 htgl.	[redacted]	Amgros
Carboplatin	10 mg/ml	15 ml	[redacted]	Amgros
	10 mg/ml	45 ml	[redacted]	Amgros

*Prisen er betinget af en anbefaling på et af de kliniske spørgsmål

Medicinrådet accepterer ansøgers valg vedr. lægemiddelomkostninger.

8.2.2 Hospitalsomkostninger

Administrationsomkostninger
Ansøger har inkluderet administrationsomkostninger for både selpercatinib og komparator i form af DRG-takster. Ansøger antager, at der for selpercatinib vil være et oplæringsbesøg på hospitalet, hvorefter patienter selv kan administrere selpercatinib. Ansøger takserer dette oplæringsbesøg med en takst på 1.732 DKK (DRG 2021 04MA98). For de øvrige lægemidler, som administreres IV, antager ansøger, at det er nødvendigt

med et hospitalsbesøg ved hver administration. Ansøger takserer disse besøg med en takst på 17.556 DKK (DRG 2021 27MP21).

Medicinrådets vurdering af ansøgers antagelser vedr. administrationsomkostninger
Medicinrådet vurderer, at ansøgers tilgang til estimering af administrationsomkostninger er rimelige. Anvendte enhedsomkostninger kan ses i Tabel 21.

Tabel 21. Omkostninger til lægemiddeladministration

	Enhedsomkostning [DKK]	Frekvens	Kode	Kilde
Administration af selpercatinib	1.732	Engangsomkostning	04MA98	[DRG-2021]
Administration af docetaxel	17.556	Ved hver administration (hver. 3 uge)	27MP21	[DRG-2021]
Administration af platinbaseret kemoterapi	17.556	Ved hver administration (hver. 3 uge)	27MP21	[DRG-2021]
Administration af pemetrexed	17.556	Ved hver administration (hver. 3 uge)	27MP21	[DRG-2021]

Medicinrådet accepterer ansøgers tilgang vedr. administrationsomkostninger.

Monitoreringsomkostninger

Ansøger har inkluderet omkostninger til monitorering og antager, at patienter bliver monitoreret hver 3. måned af en onkolog og får foretaget en CT-scanning med 100 dages mellemrum. Ansøger antager, at denne monitorering er uafhængig af, hvorvidt en patient modtager behandling med selpercatinib eller en af komparatorerne.

Medicinrådets vurdering af ansøgers antagelser vedr. monitoreringsomkostninger
Fagudvalget vurderer, at monitorering af patienter ikke er afhængig af behandling, men vurderer, at monitorering sker hver måned, og at patienterne også i forbindelse med monitorering modtager CT- og MR-scanning hver 3. måned. Derfor vælger Medicinrådet at justere monitoreringsfrekvensen og at inkludere omkostninger til CT og MR-scanninger, se Tabel 22.

Ansøger har ikke inkluderet terminale omkostninger i modellen.

Tabel 22. Monitoreringsomkostninger

	Enhedsomkostning [DKK]	Frekvens	Kode	Kilde
Monitorering hos onkolog	1.732	Hver måned	04MA98	[DRG-2021]

	Enhedsomkostning [DKK]	Frekvens	Kode	Kilde
CT-scanning	2.433	Hver 3. måned	36PR07	[DRG-2021]
MR-scanning	2.319	Hver 3. måned	30PR03	[DRG-2021]

Medicinrådet accepterer ansøgers tilgang vedr. monitoreringsomkostninger, men vælger at justere frekvensen for monitoreringsbesøg samt at inkludere omkostninger til CT- og MR-scanning.

Bivirkningsomkostninger

Ansøger har inkluderet omkostninger forbundet med bivirkninger ved behandlingsstart og begrunder det med, at bivirkninger forekommer oftere ved behandlingsstart for selpercatinib og komparatorerne. Ansøgers model benytter frekvenser for uønskede hændelser (AE) af grad 3-4 som mål for bivirkningerne. For selpercatinib har ansøger benyttet de rapporterede bivirkningsrater fra LIBRETTO-001-studiet [9], mens ansøger for platinbaseret kemoterapi og pemetrexed har anvendt GOIRC-02-studiet og REVEL-studiet [10] for docetaxel. Ressourcerne brugt i forbindelse med de forskellige bivirkninger har ansøger baseret på DRG 2021.

Medicinrådets vurdering af ansøgers antagelser vedr. bivirkningsomkostninger

Fadudvalget vurderer, at bivirkningerne, forlænget QT, øget ALT, øget AST og hypertension ikke vil udgøre en omkostning, og derfor vælger Medicinrådet at ekskludere disse omkostninger, men vurderer, at de øvrige omkostninger kan være rimelige. Medicinrådet fremhæver, at bivirkningsomkostninger er vanskelige at estimere, og at det bidrager med usikkerhed til modellen, men bivirkningsomkostninger påvirker de inkrementelle omkostninger i begrænset omfang, og derfor udføres der ikke følsomhedsanalyser af bivirkningsomkostninger trods usikkerheden. Bivirkningsfrekvenser og anvendte takster kan ses i Tabel 23.

Tabel 23. Rapporterede bivirkningsfrekvenser ved behandling med selpercatinib og komparatorerne samt enhedsomkostninger for bivirkningerne

	Selpercatinib [%]	Platinbaseret kemoterapi [%]	Docetaxel	Pemetrexed	DRG-kode	Takst
Diarré	[redacted]	0,9 %	3,1 %	1,7 %	06MA11	5.130
Hypertension	[redacted]	0,0 %	2,1 %	0,0 %	05MA98	0
EKG QT-forlænget	[redacted]	0,0 %	0,0 %	0,0 %	05MA07	0

	Selpercatinib [%]	Platinbaseret kemoterapi [%]	Docetaxel	Pemetrexed	DRG-kode	Takst
Blødning	[redacted]	0,0 %	2,3 %	0,0 %	05MA08	1.837
Træthed	[redacted]	5,4 %	10,5 %	6,8 %	23MA03	3.987
Dyspnø (åndenød)	[redacted]	0,0 %	8,3 %	0,0 %	04MA98	1.732
Øget alanin amino-transferase	[redacted]	0,0 %	0,0 %	0,0 %	23MA98	0
Øget aspartat amino-transferase	[redacted]	0,0 %	0,0 %	0,0 %	23MA98	0
Hyponatriæmi	[redacted]	0,0 %	0,0 %	0,0 %	10MA98	1.518
Lymfopeni	[redacted]	0,0 %	0,0 %	0,0 %	16MA98	3.114
Pneumoni	[redacted]	0,0 %	0,0 %	0,0 %	04MA14	25.695
Trombocytopeni	[redacted]	8,0 %	0,7 %	6,0 %	16MA98	3.114
Neutropeni	[redacted]	11,6 %	39,8 %	10,3 %	16MA98	3.114
Anæmi	[redacted]	5,4 %	5,7 %	8,6 %	16MA98	3.114
Pleuraeffusion	[redacted]	0,0 %	0,0 %	0,0 %	04MA09	34.259
Febril neutropeni	[redacted]	2,7 %	10,0 %	3,4 %	16MA98	3.114
Urinvejsinfektion	[redacted]	0,0 %	0,0 %	0,0 %	11MA07	24.431
Leukopeni	[redacted]	8,0 %	12,5 %	13,7 %	16MA98	3.114
Venøs tromboemboli	[redacted]	0,0 %	2,9 %	0,0 %	05MA12	20.946

Medicinrådet accepterer ansøgers tilgang vedr. bivirkningsomkostninger, men vælger at ekskludere nogle enkelte bivirkningsomkostninger.

Testomkostninger

Ansøger har ikke inkluderet omkostninger til test for RET-fusion, men har valgt at udføre en følsomhedsanalyse, hvor testomkostninger inkluderes. I denne følsomhedsanalyse antager ansøger, at patienter bliver testet med en next-generation-sequencing (NGS) test, og at 1,5 % af alle testede patienter vil være RET-fusion-positive. Ansøger takserer en NGS-test med 5.000 DKK. Dermed bliver de gennemsnitlige testomkostninger per patient 333.333 DKK.

Medicinrådets vurdering af ansøgers antagelser vedr. testomkostninger

Fagudvalget vurderer, at det vil være nødvendigt at teste ca. 25 % af patienterne, da den resterende del af patienterne vil være testet med NGS tidligere i udredningsforløbet. Medicinrådet vælger derfor at inkludere testomkostninger for 25 % af patienterne svarende til gennemsnitlige testomkostninger på 83,333 DKK per patient, men vælger også at udføre følsomhedsanalyser, hvor testomkostningerne varieres.

8.2.3 Efterfølgende behandling

Ansøger inkluderer omkostninger til efterfølgende behandling, da OS forventes at afspejle både effekten af interventionen, men også effekten af de efterfølgende behandlinger. Ansøger antager, at 80 % modtager efterfølgende behandling. Af dem har ansøger antaget, at 60 % af patienterne, som progredierer på selpercatinib, vil modtage platinbaseret kemoterapi som efterfølgende behandling, mens 20 % vil modtage strålebehandling, og de sidste 20 % vil modtage BSC. For komparator (platinbaseret kemoterapi) vil 60 % af de progredierede patienter modtage docetaxel, 20 % vil modtage strålebehandling, og 20 % vil modtage BSC. For både docetaxel og platinbaseret kemoterapi takserer ansøger omkostninger ligesom beskrevet ovenfor, mens ansøger antager en engangsomkostning for strålebehandling i form af DRG-takster (5.383 DKK).

Ansøger antager, at den gennemsnitlige behandlingsvarighed for patienter, der efterfølgende behandles med docetaxel, er 11,64 uger, mens det for platinbaseret kemoterapi er 13,05 uger. Ansøger har ikke redegjort for, hvordan disse behandlingslængder er udledt.

Medicinrådets vurdering af ansøgers antagelser vedr. efterfølgende behandling

Fagudvalget fremhæver, at fordelingen blandt de efterfølgende behandlinger samt behandlingslængden er forbundet med stor usikkerhed grundet heterogenitet, men vurderer, at ansøgers antagelser kan være rimelige, selvom ansøger ikke har redegjort eller argumenteret for de respektive behandlingslængder. Usikkerheden vedr. efterfølgende behandling bidrager med usikkerhed til resultatet, men da omkostningerne til efterfølgende behandling er meget små, vælger Medicinrådet at acceptere dette, men foretager en følsomhedsanalyse, hvor efterfølgende behandling ekskluderes.

Medicinrådet accepterer ansøgers tilgang vedr. efterfølgende behandling.

8.2.4 Patientomkostninger

Patientomkostninger er estimeret på baggrund af administrations- og monitoreringsbesøg på hospitalet og inkluderer patientens effektive tid på hospitalet, ventetid og transporttid. Ansøger antager, at både patienttiden og transporttiden udgør én time ved hvert hospitalsbesøg.

Ansøger anvender en enhedsomkostning for patienttid på 179 DKK pr. time og transportomkostninger på 100 DKK pr. besøg, jf. Medicinrådets værdisætning af enhedsomkostninger.

Medicinrådets vurdering af ansøgers antagelser vedr. patient- og transportomkostninger
Medicinrådet accepterer ansøgers tilgang vedr. patient- og transportomkostninger

8.3 Følsomhedsanalyser

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

Ansøger har udarbejdet en lang række følsomhedsanalyser, hvor effekten af variation i forskellige parametre undersøges. Som udgangspunkt varieres modellens parametre til det øvre og nedre konfidensinterval. For parametre uden standardfejl og dermed konfidensinterval antager ansøger en standardfejl på 10 % af punktestimatet. Ansøger har foretaget mange følsomhedsanalyser, men har specifikt fremhævet følgende:

Tabel 24. Ansøgers udvalgte følsomhedsanalyser

Følsomhedsanalyse	Beskrivelse
Variation af diskonteringsrenten	Diskonteringsrenten sættes til hhv. 0 og 6 %.
Variation af administrationsomkostningerne	Omkostningerne sættes til øvre og nedre konfidensinterval, som er konstrueret med antagelsen om en standardfejl på 10 % af punktestimatet.
Variation af monitoreringsomkostningerne	Omkostningerne sættes til øvre og nedre konfidensinterval, som er konstrueret med antagelsen om en standardfejl på 10 % af punktestimatet.
Variation af omkostningerne til efterfølgende behandling	Omkostningerne sættes til øvre og nedre konfidensinterval, som er konstrueret med antagelsen om en standardfejl på 10 % af punktestimatet.

Følsomhedsanalyse	Beskrivelse
Variation i fordelingen mellem efterfølgende behandlinger	Omkostningerne sættes til øvre og nedre konfidensinterval, som er konstrueret med antagelsen om en standardfejl på 10 % af punktestimatet.
Variation i bivirkningsfrekvenserne	Omkostningerne sættes til øvre og nedre konfidensinterval konstrueret med standardfejlen fra de respektive studier.

Medicinrådets vurdering af ansøgers valg af følsomhedsanalyser
Medicinrådet vurderer, at nogle af ansøgers følsomhedsanalyser belyser første-ordens usikkerheder, omend antagelsen om en standardfejl på 10 % af punktestimatet er en anelse arbitrær. Disse følsomhedsanalyser belyser ikke anden-ordens og strukturelle usikkerheder. Medicinrådet vælger derfor at præsentere følsomhedsanalyser (Tabel 25).

Tabel 25. Medicinrådets udvalgte følsomhedsanalyser

Følsomhedsanalyse	Beskrivelse
Ekstrapoleringer	Varierende parametrisk funktion til ekspolering af både PFS og OS
Testomkostninger	Ingen omkostninger til test med NGS
Efterfølgende behandling	Ekskludering af efterfølgende behandling

Medicinrådet vælger kun at præsentere et udsnit af ansøgers følsomhedsanalyser samt at foretage yderligere følsomhedsanalyser af de parametre, Medicinrådet vurderer, bidrager med usikkerhed.

8.4 Opsummering af basisantagelser

I Tabel 26 opsummeres basisantagelserne i henholdsvis ansøgers og Medicinrådets hovedanalyse.

Tabel 26. Basisantagelser for ansøgers og Medicinrådets hovedanalyse

Basisantagelser	Ansøger	Medicinrådet
Tidshorisont	25 år	25 år
Diskonteringsrate	3,5 %	3,5 %

Basisantagelser	Ansøger	Medicinrådet
Inkluderede omkostninger	Lægemiddelomkostninger Hospitalsomkostninger Bivirkningsomkostninger Patient og transportomkostninger	Lægemiddelomkostninger Hospitalsomkostninger Bivirkningsomkostninger Patient og transportomkostninger
Dosering	Selpercatinib: Selpercatinib 160 mg to gange dagligt Platinbaseret kemoterapi: Pemetrexed 500 mg/M^2 hver 3. uge Carboplatin 5mg/ml/min hver 3. uge i maksimal 6 cyklusser Docetaxel: Docetaxel 75 mg/M^2 hver 3. uge Pemetrexed: Pemetrexed 500 mg/M^2 hver 3. uge	Selpercatinib: Selpercatinib 160 mg to gange dagligt Platinbaseret kemoterapi: Pemetrexed 500 mg/M^2 hver 3. uge Carboplatin 5mg/ml/min hver 3. uge i maksimal 6 cyklusser Docetaxel: Docetaxel 75 mg/M^2 hver 3. uge Pemetrexed: Pemetrexed 500 mg/M^2 hver 3. uge
Behandlingslinje	2. linje	2. linje
Behandlingslængder	[redacted]	[redacted]
Intervention:	[redacted]	[redacted]
Docetaxel:	[redacted]	[redacted]
Platinbaseret kemoterapi:	[redacted]	[redacted]
Parametriske funktioner for PFS		
Intervention:	Stratificeret Gompertz	Stratificeret Gompertz
Komparator:	Stratificeret Gompertz	Stratificeret Gompertz
Parametriske funktioner for OS		
Intervention:	Ikke-parametrisk spline fordeling med 1 *knot*	Ikke-parametrisk spline fordeling med 1 *knot*
Komparator:	Ikke-parametrisk spline fordeling med 1 *knot*	Ikke-parametrisk spline fordeling med 1 *knot*
Inkludering af spild	Ja	Ja

Basisantagelser	Ansøger	Medicinrådet
Andre væsentlige antagelser	Ingen testomkostninger	Testomkostninger med NGS for 25 % af patienterne

9. Resultater

9.1 Resultatet af Medicinrådets hovedanalyse

Medicinrådets hovedanalyse bygger på samme antagelser som ansøgers hovedanalyse med undtagelse af de ændringer, der er beskrevet i Tabel 26. Medicinrådets hovedanalyse bygger på samme antagelser som ansøgers hovedanalyse med undtagelse af de ændringer, der er beskrevet i de ovenstående afsnit.

Den gennemsnitlige inkrementelle omkostning pr. patient bliver i Medicinrådets hovedanalyse ca. [redacted] DKK og [redacted] DKK sammenlignet med hhv. platinbaseret kemoterapi (klinisk spørgsmål 3) og docetaxel (klinisk spørgsmål 4). Størstedelen af omkostningerne forekommer dog de første 2 år af behandlingsforløbet.

Er analysen udført med AIP, bliver den inkrementelle omkostning pr. patient ca. 1,3 mio. og 1,6 mio. DKK sammenlignet med hhv. platinbaseret kemoterapi (klinisk spørgsmål 3) og docetaxel (klinisk spørgsmål 4).

Resultaterne fra Medicinrådets hovedanalyse er præsenteret i Tabel 27 og Tabel 28.

Tabel 27. Resultatet af Medicinrådets hovedanalyse ved sammenligning med platinbaseret kemoterapi (klinisk spørgsmål 3), DKK, diskonterede tal

	Selpercatinib	Platinbaseret kemoterapi	Inkrementelle omkostninger
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Hospitalsomkostninger	212.890	309.778	-96.888
Efterfølgende behandling	[redacted]	[redacted]	[redacted]
Patientomkostninger	14.688	10.978	3.710
Testomkostninger	83.333	0	83.333
Terminalomkostninger	0	0	0
Totale omkostninger	[redacted]	[redacted]	[redacted]

Tabel 28. Resultatet af Medicinrådets hovedanalyse ved sammenligning med docetaxel (klinisk spørgsmål 4), DKK, diskonterede tal

	Selpercatinib	Docetaxel	Inkrementelle omkostninger
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Hospitalsomkostninger	212.890	185.693	27.197
Efterfølgende behandling	[redacted]	[redacted]	[redacted]
Patientomkostninger	14.688	8.742	5.946
Testomkostninger	83.333	0	83.333
Terminalomkostninger	0	0	0
Totale omkostninger	[redacted]	[redacted]	[redacted]

9.1.1 Resultatet af Medicinrådets følsomhedsanalyser

Ved samme antagelser som i Medicinrådets hovedanalyse for meromkostninger har Medicinrådet udført en følsomhedsanalyse på parametrene listet i Tabel 29.

Tabel 29. Resultatet af Medicinrådets følsomhedsanalyse sammenlignet med hovedanalysen, DKK

Scenarie		Inkrementelle omkostninger	
		Platinbaseret kemoterapi (klinisk spørgsmål 3)	**Docetaxel (klinisk spørgsmål 4)**
Resultatet af hovedanalysen		[redacted]	[redacted]
Ekstrapolering af PFS for både intervention og komparator	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
Ekstrapolering af OS for både	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]

Scenarie		Inkrementelle omkostninger	
intervention og komparator	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
Ingen testomkostninger		[redacted]	[redacted]
Ekskludering af efterfølgende behandling		[redacted]	[redacted]

10. Budgetkonsekvenser

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

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

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

10.1 Ansøgers estimat af patientantal og markedsandel

Ansøger har antaget, at der vil være ca. 8 og 16 patienter om året med hhv. PD-L1 ≥ 50 og PD-L1 < 50, der ved anbefaling vil være kandidater til behandling med selpercatinib. Ansøgers estimat vedr. markedsoptag for patienter med PD-L1 ≥ 50 er præsenteret i Tabel 30, mens det for patienter med PD-L1 < 50 er præsenteret i Tabel 31.

Tabel 30. Ansøgers estimat vedr. markedsoptag, PD-L1 ≥ 50

	År 1	År 2	År 3	År 4	År 5
			Anbefales		
Selpercatinib	40 %	80 %	80 %	80 %	80 %
Platinbaseret kemoterapi	36 %	12 %	12 %	12 %	12 %
BSC	24 %	8 %	8 %	8 %	8 %
			Anbefales ikke		

	År 1	År 2	År 3	År 4	År 5
Selpercatinib	0 %	0 %	0 %	0 %	0 %
Platinbaseret kemoterapi	60 %	60 %	60 %	60 %	60 %
BSC	40 %	40 %	40 %	40 %	40 %

Tabel 31. Ansøgers estimat vedr. markedsoptag, PD-L1 < 50

	År 1	År 2	År 3	År 4	År 5
			Anbefales		
Selpercatinib	40 %	80 %	80 %	80 %	80 %
Docetaxel	15 %	5 %	5 %	5 %	5 %
Pemetrexed	15 %	5 %	5 %	5 %	5 %
BSC	30 %	10 %	10 %	10 %	10 %
			Anbefales ikke		
Selpercatinib	0 %	0 %	0 %	0 %	0 %
Docetaxel	30 %	30 %	30 %	30 %	30 %
Pemetrexed	30 %	30 %	30 %	30 %	30 %
BSC	40 %	40 %	40 %	40 %	40 %

Medicinrådets vurdering af ansøgers budgetkonsekvensanalyse

Fagudvalget er blevet konsulteret i forhold til både patientantal og markedsoptag, hvis selpercatinib anbefales som mulig standardbehandling, og hvis ikke selpercatinib anbefales. Fagudvalget vurderer, at ansøgers estimat vedr. patientantal er rimeligt og stemmer overens med Medicinrådets protokol vedr. selpercatinib, men fagudvalget vurderer, at selpercatinib vil opnå et højere markedsoptag end antaget af ansøger. Medicinrådet vælger derfor at justere markedsoptaget. Det justerede markedsoptag er præsenteret i Tabel 32 for PD-L1 < 50 og i Tabel 33 for PD-L1 ≥ 50.

Tabel 32. Medicinrådets estimat vedr. markedsoptag, PD-L1 ≥ 50

	År 1	År 2	År 3	År 4	År 5
			Anbefales		
Selpercatinib	42 %	80 %	80 %	80 %	80 %
Platinbaseret kemoterapi	42 %	12 %	12 %	12 %	12 %
BSC	16 %	8 %	8 %	8 %	8 %
			Anbefales ikke		
Selpercatinib	0 %	0 %	0 %	0 %	0 %
Platinbaseret kemoterapi	60 %	60 %	60 %	60 %	60 %
BSC	40 %	40 %	40 %	40 %	40 %

Tabel 33. Medicinrådets estimat vedr. markedsoptag, PD-L1 < 50

	År 1	År 2	År 3	År 4	År 5
			Anbefales		
Selpercatinib	75 %	80 %	80 %	80 %	80 %
Docetaxel	7,5 %	5 %	5 %	5 %	5 %
Pemetrexed	7,5 %	5 %	5 %	5 %	5 %
BSC	15 %	10 %	10 %	10 %	10 %
			Anbefales ikke		
Selpercatinib	0 %	0 %	0 %	0 %	0 %
Docetaxel	30 %	30 %	30 %	30 %	30 %
Pemetrexed	30 %	30 %	30 %	30 %	30 %
BSC	40 %	40 %	40 %	40 %	40 %

Medicinrådet har udført sin egen budgetkonsekvensanalyse, hvor patientantallet er ligesom antaget af ansøger, men markedsoptaget er justeret jf. fagudvalgets vurdering.

10.2 Medicinrådets budgetkonsekvensanalyse

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

- Markedsoptaget er justeret jf. afsnit 10.1
- Inkludering af testomkostninger i budgetkonsekvensanalysen

Medicinrådet estimerer, at anvendelse af selpercatinib vil resultere i budgetkonsekvenser på ca. [redacted] DKK i år 5 sammenlignet med platinbaseret kemoterapi (klinisk spørgsmål 3) og ca. [redacted] sammenlignet med docetaxel (klinisk spørgsmål 4). Resultatet er præsenteret i Tabel 16 og Tabel 35.

Er analysen udført med AIP, bliver budgetkonsekvenserne i år 5 ca. 9,2 mio. DKK sammenlignet med platinbaseret kemoterapi (klinisk spørgsmål 3) og 19,3 mio. DKK sammenlignet med docetaxel (klinisk spørgsmål 4).

Tabel 34. Medicinrådets analyse af totale budgetkonsekvenser (klinisk spørgsmål 3), mio. DKK, ikke-diskonterede tal

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

Tabel 35. Medicinrådets analyse af totale budgetkonsekvenser (klinisk spørgsmål 4), mio. DKK, ikke-diskonterede tal

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

11. Diskussion

Behandling med selpercatinib er forbundet med inkrementelle omkostninger på ca. [redacted] DKK sammenlignet med behandling med platinbaseret kemoterapi og ca. [redacted] DKK sammenlignet med docetaxel. De inkrementelle omkostninger er næsten udelukkende drevet af lægemiddelomkostningerne for selpercatinib, men der er dog betydelig usikkerhed forbundet med estimering af disse omkostninger, og konklusioner skal drages med usikkerhederne in mente.

Datagrundlaget anvendt i analysen er hverken baseret på en direkte eller indirekte sammenligning, men blot en naiv sammenligning af studier, hvoraf RET-fusion status er ukendt for patienter, der indgår i studierne anvendt for komparator. Derfor er effekt- og punktestimaterne anvendt i analysen behæftet med stor usikkerhed, hvilket gør det endelige resultat usikkert.

Ekspoleringerne anvendt i analysen er ligeledes forbundet med usikkerhed. Fagudvalget vurderer, at de anvendte ekspoleringer kan være rimelige til at beskrive behandlingsforløbet, men ekspoleringerne er behæftet med meget usikkerhed, og fagudvalget kan ikke udelukke, at de andre ekspoleringer også er rimelige. I Tabel 29 er det tydeligt, at den anvendte parametriske fordeling har stor betydning for det endelige resultat, som kan variere op til ca. [redacted] DKK, såfremt en anden parametrisk fordeling anvendes.

Der er usikkerhed vedr. de forventede omkostninger til test for RET-fusion. Fagudvalget vurderer, at ca. 25 % af patienter ikke har modtaget en NGS-test i forbindelse med tidligere udredninger og derfor vil kræve en NGS-test. Fagudvalget vurderer dog, at et præcist estimat er vanskeligt at kvantificere. I modellen antages det, at 1,5 % af alle testede patienter vil være RET-fusion-positive, hvilket fagudvalget vurderer kan være realistisk, men fremhæver også, at dette er usikkert. Der er altså både usikkerhed vedr. andelen af patienter, der skal testes, og andelen af patienterne, der vil være RET-fusion-positive. Dette kan have stor betydning for de endelige testomkostninger.

Da analysen er behæftet med stor usikkerhed, skal tolkningen af de endelige resultater ske med forsigtighed.

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13. Versionslog

Versionslog		
Version	**Dato**	**Ændring**
1.0	29. september 2021	Godkendt af Medicinrådet

14. Bilag (TC, MTC)

14.1 Resultatet af ansøgers hovedanalyse

I ansøgers hovedanalyse, hvor der sammenlignes med vandetanib, bliver den inkrementelle omkostning pr. patient [redacted] DKK over en tidshorisont på 25 år. Resultaterne fra ansøgers hovedanalyse er præsenteret i Tabel 36.

Tabel 36. Resultatet af ansøgers hovedanalyse, DKK, diskonterede tal

	Selpercatinib	Vandetanib	Inkrementelle omkostninger
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Hospitalsomkostninger	125.828	136.587	-10.759
Patientomkostninger	5.321	4.435	886
Totale omkostninger	[redacted]	[redacted]	[redacted]

I ansøgers hovedanalyse, hvor der sammenlignes med sorafenib, bliver den inkrementelle omkostning pr. patient ca. [redacted] DKK. Resultaterne fra ansøgers hovedanalyse er præsenteret i Tabel 37.

Tabel 37. Resultatet af ansøgers hovedanalyse, DKK, diskonterede tal

	Selpercatinib	Sorafenib	Inkrementelle omkostninger
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Hospitalsomkostninger	125.828	135.673	-9.845
Patientomkostninger	6.639	7.401	-762
Totale omkostninger	[redacted]	[redacted]	[redacted]

I ansøgers hovedanalyse bliver den inkrementelle omkostning pr. patient ca. [redacted] DKK. Resultaterne fra ansøgers hovedanalyse er præsenteret i Tabel 38.

Tabel 38. Resultatet af ansøgers hovedanalyse, DKK, diskonterede tal

	Selpercatinib	Cabozantanib	Inkrementelle omkostninger
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Hospitalsomkostninger	[redacted]	[redacted]	[redacted]

	Selpercatinib	Cabozantanib	Inkrementelle omkostninger
Patientomkostninger	[redacted]	[redacted]	[redacted]
Totale omkostninger	[redacted]	[redacted]	[redacted]

14.2 Resultatet af ansøgers budgetkonsekvensanalyse

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

Med ovenstående antagelser om patientantal og markedsandel estimerer ansøger, at anvendelse af selpercatinib vil resultere i budgetkonsekvenser på ca. [redacted] DKK i år 5 for TC og for [redacted] DKK for MTC. Ansøgers estimat af budgetkonsekvenserne fremgår af Tabel 39 og Tabel 40.

Tabel 39. Ansøgers hovedanalyse for totale budgetkonsekvenser for TC, mio. DKK, ikke-diskonterede tal

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

Tabel 40. Ansøgers hovedanalyse for totale budgetkonsekvenser for MTC, mio. DKK, ikke-diskonterede tal

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

15. Bilag (NSCLC)

15.1 Resultatet af ansøgers hovedanalyse

I ansøgers hovedanalyse bliver den inkrementelle omkostning pr. patient ca. [redacted] DKK og [redacted] DKK for hhv. klinisk spørgsmål 3 og 4 over en tidshorisont på 25 år. Resultaterne fra ansøgers hovedanalyse er præsenteret i Tabel 41 og Tabel 42.

Tabel 41. Resultatet af ansøgers hovedanalyse klinisk spørgsmål 3, DKK, diskonterede tal

	Selpercatinib	Platinbaseret kemoterapi	Inkrementelle omkostninger
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Hospitalsomkostninger	109.732	253.847	-144.115
Efterfølgende behandling	[redacted]	[redacted]	[redacted]
Patientomkostninger	14.688	10.978	3.710
Testomkostninger	0	0	0
Terminalomkostninger	0	0	0
Totale omkostninger	[redacted]	[redacted]	[redacted]

Tabel 42. Resultatet af ansøgers hovedanalyse klinisk spørgsmål 4, DKK, diskonterede tal

	Selpercatinib	Docetaxel	Inkrementelle omkostninger
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Hospitalsomkostninger	109.732	133.418	-23.685
Efterfølgende behandling	[redacted]	[redacted]	[redacted]
Patientomkostninger	14.688	8.742	5.946
Testomkostninger	0	0	0
Terminalomkostninger	0	0	0
Totale omkostninger	[redacted]	[redacted]	[redacted]

15.2 Resultatet af ansøgers budgetkonsekvensanalyse

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

Med de ovenstående antagelser om patientantal og markedsandel estimerer ansøger, at anvendelse af selpercatinib vil resultere i budgetkonsekvenser på ca. [redacted] DKK og [redacted] DKK i år 5 for hhv. klinisk spørgsmål 3 og 4. Ansøgers estimat af budgetkonsekvenserne fremgår af Tabel 43 og Tabel 44.

Tabel 43. Ansøgers hovedanalyse for totale budgetkonsekvenser (klinisk spørgsmål 3), mio. DKK, ikke-diskonterede tal

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

Tabel 44. Ansøgers hovedanalyse for totale budgetkonsekvenser (klinisk spørgsmål 4), mio. DKK, ikke-diskonterede tal

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

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Forhandlingsnotat

Dato for behandling i Medicinrådet	29.09.2021
Leverandør	Elli Lilly
Lægemiddel	Selpercatinib (Retsevmo)
Ansøgt indikation	Selpercatinib til behandling af RET-forandret kræft i skjoldbruskkirtlen eller ikke-småcellet lungekræft

Forhandlingsresultat

Amgros og leverandøren indgik en aftale i maj 2021 på selpercatinib og har efterfølgende, i forbindelse med vurderingen i Medicinrådet, forhandlet en ny pris. Den nye pris er betinget af en godkendelse på et af de kliniske spørgsmål.

Lægemiddel	Styrke/dosis	Pakningsstørrelse	AIP (DKK)	Nuværende SAIP (DKK)	Forhandlet SAIP (DKK)	Rabatprocent ift. AIP
Selpercatinib	40 mg.	60 stk.	19.950	[redacted]	[redacted]	[redacted]
Selpercatinib	80 mg.	60 stk.	39.900	[redacted]	[redacted]	[redacted]

Vurdering af forhandlingsresultatet

Det er Amgros' vurdering, at vi på nuværende tidspunkt har opnået den bedst mulige pris. Denne vurdering baserer vi på følgende punkter:

- Leverandøren mener, at denne targeterede behandling er "first in class", samt at der er et uopfyldt medicinsk behov til behandling af RET-forandret kræft i skjoldbruskkirtlen og ikke-småcellet lungekræft. Derudover påpeger de, at lægemidlet har en bedre bivirkningsprofil end nuværende behandling.

[redacted]

Konklusion

[redacted]

Relation til markedet

Følgende tabel viser prisen for et års behandling i rene lægemiddelpriser.

Lægemiddel	Indikation	Dosis pr dag	Pris pr. mg SAIP (DKK)	Pris pr dag SAIP (DKK)	Samlet pris SAIP (DKK)
Selpercatinib	RET-forandret kræft	120 mg * 2	[redacted]	[redacted]	[redacted]
Selpercatinib	RET-forandret kræft	160 mg * 2	[redacted]	[redacted]	[redacted]
Cabozantinib*	Kræft i skjoldbruskkirtlen	140 mg	[redacted]	[redacted]	[redacted]
Cabozantinib*.**	Kræft i skjoldbruskkirtlen	70 mg	[redacted]	[redacted]	[redacted]
Osimertinib	EGFR- inhibitor	80 mg	[redacted]	[redacted]	[redacted]
Alectinib	ALK- inhibitor	600 mg * 2	[redacted]	[redacted]	[redacted]

*Cometriq (cabozantinib med indikationen: kræft i skjoldbruskkirtlen)
**Dosisreduktion på 50%

Andre lande

Vurderingen af selpercatinib er fortsat under behandling i både Norge, Sverige og England[1].

[1] Enhertu (trastuzumab deruxtekan) vid HER-2-positiv bröstcancer (janusinfo.se)
Trastuzumab deruxtecan for treating HER2-positive unresectable or metastatic breast cancer after 2 or more anti-HER2 therapies (nice.org.uk)
Trastuzumab derukstekan (Enhertu) (nyemetoder.no)

Høringssvar – Eli Lilly – Vedr. udkast til vurderingsrapport for selpercatinib Herlev, 25-Aug-2021

Kære Hans Christian,

Tak for det tilsendte udkast til vurderingen vedrørende selpercatinib til behandling af RET-forandret kræft i skjoldbruskkirtlen og ikke-småcellet lungekræft.
Eli Lilly har taget udkastet til efterretning, og er glade for at læse fagudvalgets anerkendelse af selpercatinibs fordelagtigt effekt og bivirkningsprofil for disse patienter. Evidensgrundlaget for mindre patientgrupper, såsom patienter med RET-forandret kræft, er oftest udfordret af begrænset antal af patienter og manglende komparative studier. Derfor finder Eli Lily det meget positivt, at fagudvalget i deres deskriptive sammenligninger anerkender at datagrundlaget er meget usikkert, men at selpercatinibs effektestimater og bivirkningsprofil er særdeles fordelagtige, f.eks. at selpercatinib medførte, at enkelte patienter fik komplet respons (2 ud af 22 patienter), hvilket ikke er observeret med andre behandlinger i patienter med RET-forandret, jod-refraktær kræft i skjoldbruskkirtlen.

Eli Lilly er enige i fagudvalgets konklusioner omhandlende den kliniske merværdi og kategorisering, men har i Medicinrådets sundhedsøkonomiske afrapportering svært ved at følge antagelserne omkring dosisintensiteten for komparatorerne sorafenib og vandetanib for RET-forandret kræft i skjoldbruskkirtlen.

Medicinrådet antager i den sundhedsøkonomiske rapport at dosisintensiteten for cabozantinib, vandetanib og sorafenib er 50%, begrundet med at de anvendte estimater, baseret på de kliniske studier, overestimerer dosisintensiteten i forhold til dansk klinisk praksis. Estimatet for dosisintensiteten i det kliniske studie for selpercatinib vurderes at være repræsentativ for dansk klinisk praksis. Medicinrådets antagelse omkring at reducere dosisintensiteten for sorafenib (81,4%) og vandetanib (94,9%) til 50% er ikke supporteret af klinisk evidens. Når Medicinrådet fraviger dosisintensiteten fra de kliniske studier, er det vigtigt at understrege at en dosisændring også påvirker effekt- og safety estimater, da disse estimater er direkte kausale med doseringen af lægemidlerne.
Medicinrådets base case antagelser omkring 50% dosisintensitet er ikke supportereret af evidens og introducerer derfor yderligere usikkerhed i vurderingen af den kliniske effekt, samtidig med at antagelsen tilføjer relativt flere omkostninger til selpercatinib.
Det fremgår af den sundhedsøkonomiske rapport at ændringen ”*vurderes at have stor betydning for analysens resultat, da lægemidlerne udgør en stor del af de samlede omkostninger i analysen*”, hvorfor Medicinrådet har udført en følsomhedsanalyse med en dosisintensitet på 100% for alle lægemidler, hvilket er et mindre ekstremt scenarie end den anvendte base case.

Eli Lilly opfordrer derfor Medicinrådet til i efterfølgende økonomisk forhandling at anvende følsomhedsanalysen omkring dosisintensiteten for sorafenib, vandetanib og cabozantinib beskrevet i tabel 8 i den sundhedsøkonomiske analyse, eller estimater baseret på den tilgængelige evidens fra de pågældende studier. Nuværende antagelser blander estimater fra kliniske studier med ”real-world evidence” baseret på fagudvalgets kliniske erfaring med de ældre lægemidler, og den begrænsede erfaring med selpercatinib, hvilket resulterer i betydelig bias for omkostningsestimaterne i analysen.

Med venlig hilsen

Kasper Dacke
Pricing & Access Manager
Eli Lilly Danmark

Fra: Hans Christian Cederberg Helms
Sendt: 1. september 2021 17:40
Til: Kasper Dacke <dacke_kasper@lilly.com>
Emne: Høringssvar vedr selpercatinib

Kære Kasper

Tak for jeres høringssvar vedr. den sundhedsøkonomiske afrapportering for selpercatinib.
Vi har diskuteret jeres synspunkter ang. dosisintensiteterne for selpercatinib og komparatorerne med fagudvalgsformanden og præsenteret jeres indvendinger for Rådet på dagens rådsmøde.
VI har dog ikke fundet anledning til at ændre i det udkast i tidligere har fået udsendt.

mvh

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Medicinrådet

Medicinrådet

Medicinrådets vurdering vedrørende selpercatinib til behandling af RET-forandret kræft i skjoldbruskkirtlen eller ikke-småcellet lungekræft

Version 1.0

Om Medicinrådet

Medicinrådet er et uafhængigt råd etableret af Danske Regioner.

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

Om vurderingsrapporten

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

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

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

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1. Medicinrådets konklusion

Medicinrådet har vurderet selpercatinib til tre patientgrupper: RET-forandret jod-refraktær kræft i skjoldbruskkirtlen, RET-forandret medullær kræft i skjoldbruskkirtlen og RET-forandret ikke-småcellet lungekræft. Værdien af selpercatinib kan ikke kategoriseres efter Medicinrådets metoder, fordi datagrundlaget for alle tre patientgrupper er meget usikkert. Det skyldes, at vurderingen er baseret på et enkelarmet studie, og der ikke er et tilstrækkeligt datagrundlag for komparatorerne i patientgrupper med kendt RET-forandring.

Medicinrådet kan ikke vurdere effekten af selpercatinib til behandling af RET-forandret jod-refraktær kræft i skjoldbruskkirtlen, men vurderer dog, at selpercatinib har en bedre sikkerhedsprofil end sorafenib og vandetanib.

Medicinrådet vurderer, at selpercatinib kan være en mere effektiv behandling af RET-forandret medullær kræft i skjoldbruskkirtlen end cabozantinib. Datagrundlaget er dog for usikkert til, at Medicinrådet kan vurdere, om selpercatinib giver patienterne en længere overlevelse. Samtidig vurderer Medicinrådet, at selpercatinib har en bedre sikkerhedsprofil end cabozantinib.

Medicinrådet finder, at datagrundlaget ikke er tilstrækkeligt til at vurdere, om selpercatinib er mere effektivt end platinbaseret kemoterapi til behandling af RET-forandret ikke-småcellet lungekræft. Medicinrådet vurderer dog, at selpercatinib kan være mere effektivt end docetaxel og derved være et mere effektivt behandlingsalternativ til patienter, der ikke kan behandles med checkpoint inhibitor-immunterapi eller platinbaseret kemoterapi. Selpercatinib har en bedre sikkerhedsprofil end både platinbaseret kemoterapi og docetaxel.

For alle vurderingerne gælder, at evidensens kvalitet er meget lav.

MEDICINRÅDET KATEGORISERER LÆGEMIDLERS VÆRDI I EN AF FØLGENDE KATEGORIER:

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

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

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

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

2. Begreber og forkortelser

ALK:	Anaplastisk lymfomkinase
CNS:	Centralnervesystemet
CR:	Komplet respons (*Complete response*)
EMA:	Det Europæiske Lægemiddelagentur (*European Medicines Agency*)
EPAR:	*European Public Assessment Report*
EGFR:	*Epidermal growth factor receptor*
EORTC-QLQ-C30:	*European Organisation for Research and Treatment of Cancer Quality-of-life Questionnaire-Core 30*
GRADE:	System til at vurdere evidens (*Grading of Recommendations, Assessment, Development and Evaluation*)
MKRF:	Mindste klinisk relevante forskel
NSCLC:	Ikke-småcellet lungekræft *(Non-small-cell lung cancer)*
ORR:	Objektiv responsrate
OS:	Samlet overlevelse (*Overall survival*)
PR:	Partielt respons (*Partial response*)
PD-L1:	*Programmed death-ligand 1*
PFS:	Progressionsfri overlevelse
RECIST:	*Response Evaluation Criteria in Solid Tumors*
RET:	*Rearranged during transfection*
ROS1:	*ROS proto-onkogene 1 receptor tyrosinkinase*

3. Introduktion

Formålet med Medicinrådets vurdering af selpercatinib til RET-forandret kræft i skjoldbruskkirtlen og ikke-småcellet lungekræft (NSCLC) er at vurdere den værdi, lægemidlet har sammenlignet med dansk standardbehandling.

Vurderingen er udarbejdet, fordi Medicinrådet har modtaget en endelig ansøgning fra Eli Lily. Medicinrådet modtog ansøgningen den 29. april 2021.

De kliniske spørgsmål er:

1. Hvilken værdi har selpercatinib sammenlignet med sorafenib eller vandetanib for voksne med avanceret RET-forandret jod-refraktær kræft i skjoldbruskkirtlen, der er progredieret efter tidligere behandling med en multikinasehæmmer?
2. Hvilken værdi har selpercatinib sammenlignet med cabozantinib for voksne og børn ≥ 12 år med avanceret RET-forandret medullær kræft i skjoldbruskkirtlen, der er progredieret efter tidligere behandling med en multikinasehæmmer?
3. Hvilken værdi har selpercatinib sammenlignet med platinbaseret kemoterapi for voksne med avanceret RET-forandret NSCLC, der er progredieret efter behandling med checkpoint-inhibitor immunterapi?
4. Hvilken værdi har selpercatinib sammenlignet med docetaxel eller pemetrexed for voksne med avanceret RET-forandret ikke-småcellet lungekræft, der er progredieret efter behandling med checkpoint-inhibitor immunterapi og platinbaseret kemoterapi?

De kliniske spørgsmål og relevante komparatorer i forhold til nuværende dansk klinisk praksis er skitseret i Figur 3-2 (afsnit 3.3).

3.1 RET-mutation og -fusioner samt kræft i skjoldbruskkirtlen og ikke-småcellet lungekræft

RET-mutationer og -fusioner

Forandringer i genet *Rearranged during transfection* (RET) ses i forskellige kræftformer bl.a. i skjoldbruskkirtel og lunger. RET-genet koder for en tyrosinkinasereceptor, som har en vigtig rolle i udviklingen i flere væv [1]. RET-mutationer og RET-fusioner er to forskellige mekanismer for forandringer i og medfølgende overaktivering af RET-proteinet, der kan virke som en onkogen driver [1].

RET-mutationer er hyppigst i medullær kræft i skjoldbruskkirtlen, mens RET-fusioner er hyppigst ved papillær kræft i skjoldbruskkirtlen og forskellige former for lungekræft [2]. Samlet set ses RET-forandringer i ca. 0,5-2 % af tumorvæv på tværs af kræftformer [2–4], og i disse tumorer repræsenterer det overaktive RET-protein en genetisk forandring, man kan målrette behandling imod.

Kræft i skjoldbruskkirtlen
I 2019 blev antallet af nye tilfælde af kræft i skjoldbruskkirtlen i Danmark opgjort til at være ca. 420 patienter. Omkring en tredjedel havde kræft i stadie III-IV [5]. Generelt er prognosen god med 5-årsoverlevelser omkring 80-95 %, afhængigt af den histologiske (mikroskopisk anatomi) undertype og kræftstadie på diagnosetidspunktet [6].

Fokus for denne vurdering er papillære og medullære karcinomer, da langt størstedelen af patienter med RET-forandring har en af disse tumorer. Den hyppigst forekommende histologi er papillært karcinom, der udgår fra follikelepitelcellerne og udgør omkring to tredjedele af alle tilfælde. Papillært karcinom udgør, sammen med follikulært karcinom, de differentierede former for kræft i skjoldbruskkirtlen (ca. 85-90 % af alle tilfælde). Derudover udgør udifferentierede og anaplastiske karcinomer omkring 5 % af tilfældene, mens de resterende ca. 7 % udgår fra de parafollikulære celler (C-celler) og betegnes medullært karcinom [6]. RET-forandringer er hyppigt forekommende i sporadisk medullært karcinom (ca. 60 %) og familiært medullært karcinom (100 %) [7], mindre hyppigt i differentieret skjoldbruskkirtelkarcinom (10 %) og meget sjældent i andre histologier [1,2]. Det anslås, at der i Danmark vil være omkring 10 – 20 nydiagnosticerede patienter årligt med RET-forandret kræft i skjoldbruskkirtlen.

De generelt gode prognoser for kræft i skjoldbruskkirtlen skyldes til dels, at patienterne kun udvikler fjernmetastaser i 4-15 % af tilfældene [8]. Ved lokalt avanceret eller metastatisk sygdom ses en 5-årsoverlevelse omkring 40-80 % afhængig af den underliggende histologi. Prognosen kan dog være påvirket yderligere i negativ retning ved medullært karcinom ved den ikke-arvelige form for RET-forandring [7,9]. Det vides ikke, om udviklingen af fjernmetastaser er mere hyppig ved RET-forandrede tumorer i skjoldbruskkirtlen. Det totale antal patienter om året vil dog, uanset hvad, være lavt. Fagudvalget forventer, at omkring henholdsvis 1-2 patienter (differentieret) og 7-9 patienter (medullært) om året vil udvikle RET-forandret lokalt avanceret eller metastatisk kræft i skjoldbruskkirtlen.

Ikke-småcellet lungekræft
Omtrent 4.600 danskere diagnosticeres årligt med lungekræft, og dermed er lungekræft en af de hyppigst forekommende kræftsygdomme i Danmark [10,11]. I slutningen af 2016 levede knap 11.151 personer med lungekræft, mens cirka 3.700 personer årligt dør af lungekræft [11]. Af de diagnosticerede har ca. 80-85 % ikke-småcellet lungekræft (NSCLC) [12]. NSCLC inddeles i planocellulære (ca. 25 %) og ikke-planocellulære tumorer (ca. 75 %).

Omkring 55 % af alle patienter har spredning til ikke-regionale lymfeknuder og/eller fjernmetastaser ved diagnosetidspunktet, hvilket betegnes uhelbredelig NSCLC [12].

Den seneste årsrapport fra Dansk Lunge Cancer Register viser, at 1-årsoverlevelsesraten for patienter med lungekræft udredt i 2017 uanset stadie var 51,4 %, mens 5-årsoverlevelsen for patienter udredt i 2013 var 15,9 % [12].

NSCLC kan drives af forskellige onkogene mutationer, bl.a. aktiverende *epidermal growth factor receptor* (EGFR)-mutationer samt anaplastisk lymfomkinase (ALK)-translokationer [13]. En tredje mutation, som er fundet hos 0,9-2 % af patienter med lungekræft, er translokationer, som involverer genet ROS proto-onkogene 1 receptor tyrosinkinase (ROS1) [14]. RET-forandringer findes næsten udelukkende i ikke-planocellulær NSCLC (hos ca. 1- 5 %), men findes også i andre histologier [2,15,16]. Både EGFR- og ALK-forandringer kan forekomme sammen med RET-forandringer i NSCLC, dog begge med lav sandsynlighed (1-3 % af RET-forandrede) [2]. Derfor vil hovedparten af patienter med diagnosticeret RET-forandring ikke samtidig have targeterbare EGFR- eller ALK-forandringer. Det er et fællestræk for forandringerne, at de hyppigt er årsag til NSCLC hos patienter, der hverken er tidligere eller nuværende rygere [17,18]. Den prognostiske betydning af RET-forandring ved NSCLC er ukendt. Data fra et registerstudie viste, at patienter med RET-forandring samlet set havde en signifikant forbedret overlevelse, men at denne forskel blev statistisk insignifikant efter justering for forskelle mellem populationerne. RET-forandring var således associeret med favorable prognostiske faktorer som ikke-planocellulær histologi, lavere alder, lavere frekvens af rygere og bedre almen tilstand [19]. Fagudvalget forventer, at 20-30 patienter i Danmark årligt vil blive diagnosticeret med uhelbredelig RET-forandret NSCLC, og langt størstedelen af disse vil have ikke-planocellulær-NSCLC uden samtidig ALK eller EGFR-forandring.

3.2 Selpercatinib

Selpercatinib (Retsevmo) er en selektiv hæmmer af RET-proteinet. Selpercatinib hæmmer derved tyrosinkinaseaktiviteten specifikt i væv, der udtrykker RET-protein, hvilket forårsager en hæmning af cellevækst i vævet. Selpercatinib er godkendt af Europakommissionen til indikationerne:

- Voksne med avanceret RET-fusion-positiv kræft i skjoldbruskkirtlen, der kræver systemisk behandling, og som er progredieret efter behandling med en multikinasehæmmer.
- Voksne og børn ≥ 12 år med avanceret RET-muteret medullær kræft i skjoldbruskkirtlen, som kræver systemisk behandling, og som tidligere er behandlet med cabozantinib og/eller vandetanib.
- Voksne med avanceret RET-fusion-positiv ikke-småcellet lungekræft, som kræver systemisk behandling efter tidligere behandling med immunterapi og/eller platinbaseret kemoterapi.

Dosering af selpercatinib er ens for de tre indikationer. Ved vægt under 50 kg er dosis 120 mg oralt to gange dagligt. Ved vægt over 50 kg er dosis 160 mg oralt to gange dagligt. Selpercatinib er hovedsageligt undersøgt i voksne patienter. Kliniske case-studier tyder dog på, at den systemiske eksponering i børn ikke afviger fra eksponeringen i voksne [20].

3.3 Nuværende behandling

Den nuværende behandling for henholdsvis papillær skjoldbruskkirtelkræft, medullær skjoldbruskkirtelkræft og ikke-småcellet lungekræft er beskrevet i de følgende afsnit.

Papillær skjoldbruskkirtelkræft
Standardbehandlingen for papillær skjoldbruskkirtelkræft er kirurgisk resektion (total thyroidektomi). Dette efterfølges af behandling med radioaktivt jod til patienter med et mere fremskredent stadie (vævsinfiltration, residual tumor efter operation eller bestemte aggressive tumortyper) [6]. Patienterne behandles efterfølgende med skjoldbruskkirtelhormon (T4 og T3) for at erstatte den normale produktion af disse, typisk i en højere dosis for at undertrykke stimulation af eventuelt tilbageværende tumorceller.

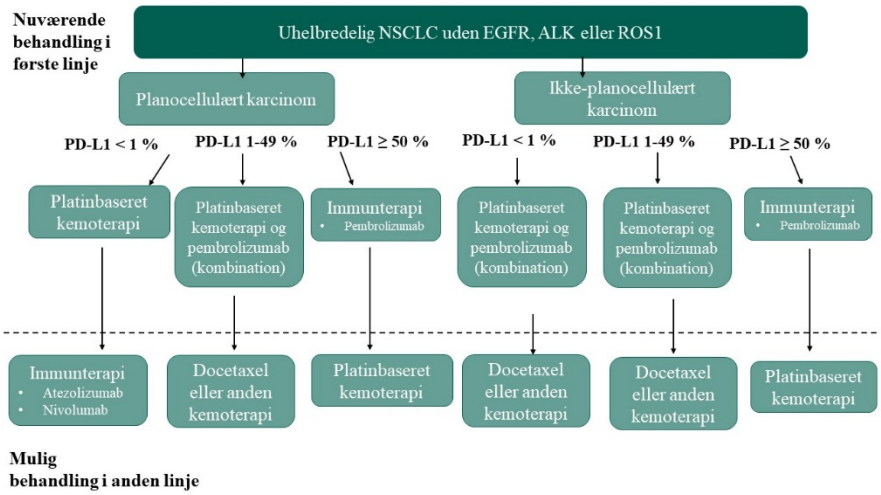
En lille del af patienterne udvikler jod-refraktær metastatisk sygdom, som betragtes som uhelbredelig. Hos disse vurderes behovet for systemisk behandling med multikinasehæmmere. Ifølge DATHYRCA-gruppens behandlingsvejledning behandles disse med lenvatinib i første linje, og efter progression behandles med sorafenib eller vandetanib [6]. Vandetanib er ikke indiceret af EMA til behandling af jod-refraktær kræft i skjoldbruskkirtlen, men anvendes som standard i dansk klinisk praksis. Alle tre lægemidler har vist at kunne forlænge den progressionsfri overlevelse med 5-12 måneder [21-23]. De patienter, der tilbydes behandling med multikinasehæmmere, har progredierende metastatisk sygdom, som er symptomatisk og/eller med truende metastatiske manifestationer, der ikke kan kontrolleres med lokal behandling.

Medullær skjoldbruskkirtelkræft
Standardbehandlingen for medullær skjoldbruskkirtelkræft afviger fra behandlingen for differentieret skjoldbruskkirtelkræft [6]. Der bliver altid udført komplet thyroidektomi, og ofte fjernes også lymfeknuder, da der er stor risiko for lymfeknudemetastaser. I nogle tilfælde gives postoperativ strålebehandling, afhængig af operationsresultatet.

En del af patienterne oplever dog tilbagefald af sygdommen i form af uhelbredelig metastaserende medullær skjoldbruskkirtelkræft. Behandlingen af disse er afhængig af patientens symptomer samt i hvilket væv, metastaserne er lokaliseret. De fleste af disse patienter modtager i dansk klinisk praksis systemisk behandling med multikinasehæmmere, vandetanib i første linje efterfulgt af cabozantinib i anden linje [6]. Disse har begge vist at kunne forlænge den progressionsfri overlevelse med 7-10 måneder [24,25].

Ikke-småcellet lungekræft
Behandlingsmålet for patienter med uhelbredelig NSCLC er symptomlindring og levetidsforlængelse. Patienter med uhelbredelig NSCLC kan få forskellige typer behandling afhængig af tumorkarakteristika. Targeteret behandling er første prioritet for patienter med aktiverende EGFR-mutation eller ALK-translokation. Patienter uden en targeterbar forandring behandles i første linje enten med platinbaseret kemoterapi (oftest carboplatin i kombination med vinorelbin) eller pembrolizumab, der hæmmer bindingen mellem *programmed death-ligand 1* (PD-L1) og dets receptor (checkpoint-inhibitor immunterapi) eller med en kombination af de to modaliteter. Valget af

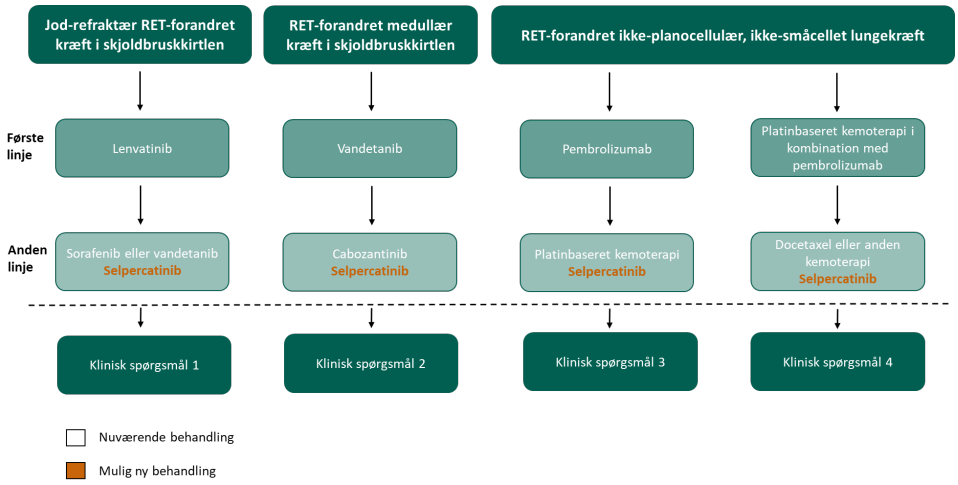
behandling er afhængigt af PD-L1-ekspression og histologisk type af tumoren (planocellulær eller ikke-planocellulær). Patienter med PD-L1-ekspression ≥ 50 % behandles med pembrolizumab monoterapi, uanset histologi. Patienter med PD-L1-ekspression på 1-49 % (uanset histologi) behandles med enten pembrolizumab i kombination med kemoterapi eller platinbaseret kemoterapi, hvis de har for dårlig almen tilstand eller kontraindikationer til kombinationsbehandlingen. Patienter med planocellulær NSCLC og PD-L1-ekspression < 1 % behandles med platinbaseret kemoterapi, mens patienter med ikke-planocellulær NSCLC og PD-L1 ekspression < 1 % kan behandles med pembrolizumab i kombination med platin-baseret kemoterapi. Behandlingen i anden linje er afhængig af, hvad patienten har modtaget i første linje. De mulige behandlinger for uhelbredelig NSCLC er skitseret i figuren nedenfor.



Figur 3-1: Oversigt over anbefalede førstelinjebehandlinger for uhelbredelig ikke-småcellet lungekræft (NSCLC) uden aktiverende EGFR-, ALK- eller ROS1-forandringer samt mulige behandlinger efter progression fra første linje. Figuren er modificeret fra Medicinrådets behandlingsvejledning for uhelbredelig ikke-småcellet lungekræft [13].

Selpercatinibs relation til de nuværende behandlinger

De nuværende første- og andenlinjebehandlinger samt hvorledes selpercatinib kan indplaceres i behandlingsalgoritmerne for RET-forandret, jod-refraktær kræft i skjoldbruskkirtlen, medullær kræft i skjoldbruskkirtlen og RET-forandret NSCLC og de afledte kliniske spørgsmål er skitseret nedenfor.



Figur 3-2: Selpercatinibs indplacering som mulig andenlinjebehandling til RET-forandret-skjoldbruskkirtelkræft (klinisk spørgsmål 1), -medullær skjoldbruskkirtelkræft (klinisk spørgsmål 2) og -ikke-småcellet lungekræft (klinisk spørgsmål 3 og 4). Ved klinisk spørgsmål 1 anvendes både sorafenib og vandetanib som komparator. Dette skyldes, at sorafenib er indiceret af EMA til patientgruppen, mens vandetanib anvendes som standard i dansk klinisk praksis.

4. Metode

Medicinrådets protokol for vurdering vedrørende selpercatinib beskriver sammen med *Håndbog for Medicinrådets proces og metode vedr. nye lægemidler og indikationsudvidelser*, hvordan Medicinrådet vil vurdere lægemidlets værdi for patienterne.

5. Resultater

5.1 Klinisk spørgsmål 1

Klinisk spørgsmål 1 er:

Hvilken værdi har selpercatinib sammenlignet med sorafenib eller vandetanib for voksne med avanceret RET-forandret jod-refraktær kræft i skjoldbruskkirtlen, der er progredieret efter tidligere behandling med en multikinasehæmmer?

5.1.1 Litteratur

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

Ansøger har søgt litteratur med søgestrengen fra protokollen og har udvalgt i alt fem fuldtekstartikler (Tabel 5-1), der beskriver data fra fire forskellige kliniske studier. Ét af selpercatinib og tre af komparatorerne.

Tabel 5-1. Oversigt over studier af patienter med jod-refraktær kræft i skjoldbruskkirtlen og de dertilhørende publikationer

Publikationer	Klinisk forsøg	NCT-nummer	Population	Studietype, Intervention og eventuel komparator	Median opfølgningstid for primært endepunkt
Wirth et al. 2020 [26] EPAR [27] og produktresume for selpercatinib [28]	LIBRETTO-001	NCT03157128	Indeholder en relevant subgruppe med RET-forandring, hvor knap 80 % tidligere er behandlet med multikinase-hæmmer.	Ikke-kontrolleret, fase I/II. Selpercatinib.	16,49 måneder (PFS i største datasæt)
Brose et al. 2014 [21] Worden et al. 2015 [29] EPAR for sorafenib [30]	DECISION	NCT00984282	RET-status ukendt. Størstedelen havde ikke tidligere modtaget systemisk behandling.	Fase III RCT. Sorafenib overfor placebo.	16,2 måneder (PFS)
Kloos et al. 2009 [31]	-	-	RET-status ukendt. Størstedelen var ikke tidligere behandlet med kemoterapi.	Ikke-kontrolleret, fase II Sorafenib.	Ikke angivet
Leboulleux et al. 2012 [22]	-	NCT00537095	RET-status ukendt. Størstedelen havde ikke tidligere modtaget systemisk behandling.	Fase II, RCT. Vandetanib overfor placebo.	18,9 og 19,5 måneder for henholdsvis vandetanib og placebo (PFS)

Selpercatinib er undersøgt i ét klinisk studie (LIBRETTO-001), og data herfra er rapporteret i én fuldtekstartikel [26]. Desuden indeholder EPAR'en [27] og produktresumeet [28] for selpercatinib data fra LIBRETTO-001 ved et senere data cut-off (marts 2020 overfor juni 2019). Endelig har ansøger indsendt 'data on file' fra LIBRETTO-001 fra data cut-off marts 2020.

LIBRETTO-001 er et igangværende ikke-kontrolleret, fase I/II-studie, der undersøger effekten og sikkerheden af selpercatinib i patienter med RET-forandret kræft i skjoldbruskkirtlen, RET-forandret medullær kræft i skjoldbruskkirtlen eller RET-forandret NSCLC. Studiets primære effektmål var objektivt radiologisk respons rate (ORR) ud fra

RECIST-kriterierne. Af relevans for denne vurdering inkluderede studiet PFS, OS og uønskede hændelser som prædefinerede sekundære effektmål samt livskvalitetsmålinger via EORTC QLQ-C30, som eksplorativt effektmål. Studiet indeholder en subgruppe af patienter med RET-forandret, jod-refraktær kræft i skjoldbruskkirtlen, hvor størstedelen tidligere havde modtaget behandling med multikinasehæmmer. Denne patientgruppe er velegnet til at estimere effekten af selpercatinib, jf. klinisk spørgsmål 1. Fagudvalget bemærker dog, at subgruppen kun indeholder 19 patienter i det primære analysesæt og 22 patienter ved data cut-off i marts 2020.

LIBRETTO-001 inkluderede ikke en kontrolarm. Derfor har ansøger søgt efter egnede studier for henholdsvis sorafenib og vandetanib, der er de definerede komparatorer i Medicinrådets protokol (se også Figur 3-2) [32].

Ansøger har inkluderet tre artikler, der rapporterer data fra to forskellige kliniske studier af sorafenib: DECISION og Kloos et al.

DECISION er et randomiseret, dobbeltblindet fase III-studie, der undersøger effekten af sorafenib overfor placebo for patienter med lokalt avanceret eller metastatisk, jod-refraktær differentieret kræft i skjoldbruskkirtlen. Studiets primære effektmål var PFS og OS. ORR samt uønskede hændelser var sekundære effektmål. Langt størstedelen af patienterne havde ikke tidligere modtaget systemisk anti-cancerbehandling. Brose et al. rapporterer data fra studiets primære data cut-off [21], mens Worden et al. rapporterer mere detaljerede data for uønskede hændelser [29]. Data for OS fra DECISION med længere opfølgningstid er desuden tilgængelige i EPAR'en for sorafenib [30].

Kloos et. al rapporterer data fra et ikke-kontrolleret fase II-studie, hvor sorafenibs effekt undersøges i patienter med metastatisk kræft i skjoldbruskkirtlen [31]. Studiets primære effektmål var objektiv responsrate. Størstedelen af patienterne havde ikke tidligere modtaget systemisk anticancerbehandling.

Den sidste artikel af Leboulleux et al., rapporterer data fra ét randomiseret, dobbeltblindet fase II-studie, der undersøger effekten af vandetanib overfor placebo til patienter med lokalt avanceret eller metastatisk differentieret, jod-refraktær kræft i skjoldbruskkirtlen i et randomiseret, dobbeltblindet fase II-studie [22]. Studiets primære endemål var PFS, mens OS, sygdomskontrol (objektivt respons eller stabil sygdom) og uønskede hændelser var sekundære endemål. Overkrydsning til aktiv behandling var tilladt for patienter efter progression. Størstedelen af patienterne havde ikke tidligere modtaget systemisk anticancerbehandling.

For sorafenib vælger fagudvalget at se bort fra data fra Kloos et al., da studiet er uden kontrolarm, og patientgruppen er lille. Derfor anvender fagudvalget udelukkende data fra DECISION til at estimere sorafenibs effekt og data fra Leboulleux et al. til at estimere vandetanibs effekt.

Baselinekarakteristiska for patienterne i LIBRETTO-001, DECISION og Leboulleux et al. er angivet nedenfor.

Tabel 5-2. Baselinekarakteristika

		LIBRETTO-001 selpercatinib*	DECISION sorafenib **	Leboulleux et al. vandetanib **
Patientantal	Intervention	19	207	72
	Komparator	-	210	73
Median alder (range)		54 (25-88)	63 (24-82)	63 (29-81)
Køn, kvinder (%)		10 (53 %)	103 (50 %)	33 (46 %)
ECOG performance status	0	5 (26 %)	130 (63 %)	50 (69 %)
	1	12 (63 %)	69 (33 %)	20 (28 %)
	2	2 (11 %)	7 (3 %)	2 (3 %)
Tumorhistologi	Papillær	13 (68 %)	118 (57 %)	25 (40 %)
	Udifferentieret	3 (16 %)	24 (12 %)	29 (47 %)
	Anaplastisk	2 (11 %)	0 (0 %)	0 (0 %)
	Anden	1 (5 %)	52 (25 %)	8 (13 %)
Fjernmetastaser (%)		19 (100 %)	200 (97 %)	71 (99 %)
Tidligere behandling med multikinasehæmmer (%)		15 (79 %)	0 (0 %)	3 (4 %)

*: Baselinekarakteristika for patienterne i LIBRETTO-001 er kun rapporteret for det primære analysesæt, som indeholder de første 19 inkluderede patienter. Ved det senere data cut-off (marts 2020) var 22 patienter inkluderet, men baselinekarakteriska for de resterende tre er ikke rapporteret. **: For de placebokontrollerede studier rapporteres kun baselinekarakteristika for interventionsarmen. Internt i disse studier er baselinkerakteristika velbalancerede.

Der er væsentlige forskelle i patientpopulationerne i de kliniske studier, der medfører, at en indirekte statistisk sammenligning mellem selpercatinib og sorafenib ikke er mulig.

- Patienterne i LIBRETTO-001 har alle dokumenteret RET-forandring, hvorimod RET-status er ukendt i alle studier af komparatorerne. Den prognostiske betydning af RET-forandring er ukendt.
- Størstedelen af patienterne i LIBRETTO-001 var tidligere behandlet med multikinasehæmmer, hvorimod studierne af komparatorerne hovedsageligt inkluderede kemoterapi- og multikinasehæmmer-naive patienter. Fagudvalget forventer, at dette medfører en dårligere prognose for patienterne i LIBRETTO-001, da de udgør en mere behandlingstung population.
- Patienterne var yngre i LIBRETTO-001, hvilket kan medføre en bedre prognose.

- De repræsenterede histologiske typer af kræft i skjoldbruskkirtlen var forskellige, hvor Leboulleux et al. indeholdt en væsentlig større andel af patienter med udifferentieret kræft i skjoldbruskkirtlen, som umiddelbart har en dårligere prognose.

5.1.2 Databehandling og analyse

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

Ansøger har indsendt data fra alle de ovennævnte studier for effektmålene, OS, PFS, ORR og uønskede hændelser, men ikke for livskvalitet. Pga. forskellene mellem studierne har ansøger ikke lavet en statistisk sammenligning, men foretager i stedet en deskriptiv sammenligning af data fra de enkelte studier.

Medicinrådet er enige i ansøgers tilgang. Manglen på kontrolarm i LIBRETTO-001 og studieforskellene medfører, at der ikke kan laves en meningsfuld statistisk sammenligning. Fagudvalget udfører derfor en deskriptiv sammenligning af selpercatinib med sorafenib og vandetanib.

Fagudvalget anvender data fra LIBRETTO-001 baseret på længst mulig opfølgningstid og størst mulige patientgrupper. For effektmålene, ORR, PFS og uønskede hændelser findes dette i EPAR'en [27]. For uønskede hændelser vælger fagudvalget at anvende data fra den samlede population af patienter med jod-refraktær kræft i skjoldbruskkirtlen, der har modtaget minimum én dosis selpercatinib (n = 42), da denne patientgruppe bedst repræsenterer populationen i det kliniske spørgsmål. OS-data vurderes ud fra ansøgers 'data on file'. Disse data besvarer effektmål i protokollens kliniske spørgsmål og lever op til Medicinrådets principper for anvendelse af upublicerede data, jf. Princippapir for anvendelse af upublicerede data i vurderinger af nye lægemidler og indikationsudvidelser.

5.1.3 Evidensens kvalitet

Da vurderingen af selpercatinib er baseret på en deskriptiv sammenligning med sorafenib og vandetanib, kan Medicinrådet ikke anvende GRADE til at vurdere kvaliteten af evidensen.

Medicinrådet vurderer evidensens kvalitet som meget lav. Medicinrådet bemærker, at den relevante patientgruppe i LIBRETTO-001 blot indeholder 19 eller 22 patienter afhængig af tidspunktet for data cut-off, og at estimater for både PFS og OS er umodne. Medicinrådet finder derfor, at evidensgrundlaget for effekten af selpercatinib er meget usikkert.

Medicinrådet vurderer, at effekten af sorafenib og vandetanib er bedre dokumenteret end selpercatinib, da begge er undersøgt i placebokontrollerede studier. Studierne indeholder dog kun patienter, der ikke tidligere er behandlet med multikinasehæmmer, og hvis RET-status ikke er kendt. Derfor er evidensen for komparatorernes effekt ift. patienter med RET-forandret kræft i skjoldbruskkirtlen, der tidligere er behandlet med multikinasehæmmer, også meget usikker.

5.1.4 Effektestimater og kategorier

I tabellen herunder fremgår effektestimaterne fra de enkelte studier af henholdsvis selpercatinib, sorafenib og vandetanib. Skemaet indeholder ikke nogen estimater af absolutte eller relative forskelle mellem selpercatinib og komparatorerne, da datagrundlaget ikke muliggør statistiske sammenligninger. Værdien af selpercatinib **kan derfor ikke kategoriseres** ved hjælp af Medicinrådets metoder for nogen af effektmålene.

Tabel 5-3. Resultater for klinisk spørgsmål 1

Effektmål	Målenhed (MKRF)	Vigtighed	Selpercatinib	Sorafenib		Vandetanib	
			LIBRETTO-001	DECISION		Leboulleux et al.	
			Selpercatinib n = 19* / 22** / 42***	Sorafenib n = 207	Placebo n = 210	Vandetanib n = 72	Placebo n = 73
Samlet overlevelse (OS)	Median OS (3 måneder)	Kritisk	[redacted]	Ikke nået	36,5 måneder	Ikke nået	Ikke nået
	OS-rate ved 24 måneder (5 %-point)		[redacted]	70 %	70 %	62 %	60 %
Livskvalitet	EORTC-QLQ-C30. Gennemsnitlig ændring i post-basislinje relativt til basislinjen (10 point)	Kritisk	Ingen data	Ingen data	Ingen data	Ingen data	Ingen data
Objektiv responsrate (ORR)	Andel, der opnår komplet eller partielt respons (15 %-point).	Vigtig	77,3 % (54,6; 92,2)**	12,2 %	0,5 %	8 %	5 %
Progressionsfri overlevelse (PFS)	Median PFS (3 måneder)	Vigtig	20,1 måneder (10,8; Ikke nået)**	10,8 måneder (ikke angivet)	5,8 måneder (ikke angivet)	11,1 måneder (7,7; 14,0)	5,9 måneder (4,0; 8,9)
Uønskede hændelser	Andel, der oplever en eller flere uønskede hændelser af grad 3-4 (MKRF: 5 %-point)	Vigtig	59,5 %***	64,3 %	30,1 %	53 %	19 %

	Deskriptiv gennemgang	Se gennemgang	Se gennemgang	Se gennemgang	Se gennemgang	Se gennemgang	Se gennemgang
Konklusion							
Samlet kategori for lægemidlets værdi	Kan ikke kategoriseres. Fagudvalget finder, at selpercatinib udviser en høj objektiv responsrate og en fordelagtig bivirkningsprofil ift. sorafenib og vandetanib.						
Kvalitet af den samlede evidens	Meget lav						

*: Data stammer fra ansøgers 'data-on-file' fra de første 19 patienter (data cut-off marts 2020). **: Data stammer fra EPAR, hvilket inkluderer 22 patienter med minium 6 måneders opfølgningstid (data cut-off 2020). ***: Data stammer fra EPAR, hvilket inkluderer 42 patienter, der alle er behandlet med minimum én dosis selpercatinib (sikkerhedspopulation).

Samlet overlevelse (OS)
Overlevelsesdata for patienter behandlet med selpercatinib er ikke publiceret. I ansøgers 'data-on-file' fremgår det, at patienterne havde [redacted] Fagudvalget vurderer, at der er meget stor usikkerhed omkring effektestimaterne pga. umodne data, en meget lille patientgruppe og manglen på en kontrolarm.

For sorafenib var medianoverlevelsen ikke nået, hvorimod placebokontrollen i sorafenibstudiet viste en median OS på 36,5 måneder. OS-raterne ved 24 måneder var i begge tilfælde ca. 70 % (aflæst fra Kaplan-Meier kurverne).

For vandetanib var medianoverlevelsen ikke nået i hverken vandetanib eller placebokontrollen. OS-raterne ved 24 måneder var i begge tilfælde ca. 60 % (aflæst fra Kaplan-Meier kurverne).

OS-estimaterne for både sorafenib og vandetanib er sandsynligvis påvirket af overkrydsning fra placeboarmene til aktiv behandling efter progression.

Værdien af selpercatinib ift. OS kan ikke kategoriseres overfor hverken sorafenib eller vandetanib. Fagudvalget har vanskeligt ved at vurdere effekten, da:

- OS-data for selpercatinib er umodne.
- Den prognostiske betydning af RET-forandringer er ukendt.
- Restlevetiden med sygdommen generelt er lang.
- Der er væsentlig overkrydsning til aktiv behandling i kontrolstudierne.

Livskvalitet
Ansøger har ikke indsendt data for hverken selpercatinib, sorafenib eller vandetanib. Værdien kan derfor ikke kategoriseres.

Objektiv responsrate (ORR)
Objektiv responsrate (ORR) afspejler interventionens umiddelbare antineoplastiske potentiale. Derfor anser fagudvalget ORR som et vigtigt effektmål.

Ved selpercatinib havde 17 ud af 22 patienter (77,3 %) et objektivt respons. Af disse havde 2 patienter (9,1 %) et komplet respons og 15 patienter (68,2 %) et partielt respons. De resterende 5 patienter havde alle stabil sygdom.

Ved sorafenib havde 24 patienter (12,2 %) et objektivt respons, mens 1 patient (0,5 %) havde objektivt respons i kontrolgruppen. Alle var partielt respons.

Ved vandetanib havde 6 patienter (8 %) et objektivt respons, mens 4 patienter (5 %) havde objektivt respons i kontrolgruppen. Alle var partielt respons.

Værdien af selpercatinib ift. ORR kan ikke kategoriseres overfor hverken sorafenib eller vandetanib. Fagudvalget vurderer, at ORR er høj ved selpercatinib, og lægger vægt på, at 2 patienter (ca. 10 %) havde komplet respons, hvilket ikke er set i tidligere studier af

multikinasehæmmere ved jod-refraktær kræft i skjoldbruskkirtlen. ORR er dog vanskelig at sammenligne på tværs af studierne, da patienternes RET-status er ukendt i både DECISION og Leboulleux et al., og patienter med RET-forandring kunne forventes at respondere bedre, også på komparatorerne.

Progressionsfri overlevelse (PFS)
Fagudvalget vurderer, at PFS er et vigtigt effektmål, som afspejler varighed af sygdomskontrol og giver et direkte indblik i den enkelte behandlings antineoplastiske effekt uden påvirkning fra senere behandlingslinjer eller overkrydsning til aktiv behandling i kliniske studier.

Median PFS for selpercatinib var 20,1 måneder (10,8; ikke nået) med en median opfølgningstid på 16,5 måneder. Fagudvalget vurderer, at der er meget stor usikkerhed omkring estimatet pga. en meget lille patientgruppe, kort opfølgning og manglen på en kontrolarm.

For sorafenib var median PFS 10,8 måneder overfor 5,8 måneder i placebokontrollen.

For vandetanib var median PFS 11,1 måneder (7,7; 14,0) overfor 5,9 måneder (4,0; 8,9) i placebokontrollen.

Værdien af selpercatinib ift. PFS kan ikke kategoriseres overfor hverken sorafenib eller vandetanib. Punktestimatet for median PFS er højere for selpercatinib end for begge komparatorer. PFS er vanskelig at sammenligne på tværs af studierne, da RET-status er ukendt i både DECISION og Leboulleux et al. Derudover medfører det lave patientantal og den korte opfølgningstid i LIBRETTO-001 usikkerhed omkring estimatet for selpercatinib.

Uønskede hændelser
Fagudvalget opgør effektmålet kvantitativt ud fra andelen af patienter, der oplever minimum én uønsket hændelse af grad 3-4, samt kvalitativt ud fra en gennemgang af de enkelte lægemidlers bivirkningsprofiler.

Andelen af patienter, der oplever minimum én uønsket hændelse af grad 3-4
Fagudvalget har anvendt sikkerhedspopulationen i EPAR for patienter med jod-refraktær kræft i skjoldbruskkirtlen, som består af alle inkluderede patienter, der har modtaget minimum én dosis selpercatinib (n = 42). I denne population oplevede 59,5 % minimum én uønsket hændelse af grad 3-4.

For sorafenib oplevede 64,3 % af patienterne minimum én uønsket hændelse af grad 3-4 overfor 30,1 % af patienterne i placebokontrollen.

For vandetanib oplevede 53 % af patienterne minimum én uønsket hændelse af grad 3-4 overfor 19 % af patienterne i placebokontrollen.

Andelen af grad 3-4 uønskede hændelser kan variere betragteligt mellem studier og patientpopulationer. Dette ses eksempelvis i forskellene mellem placeboarmene i sorafenib- og vandetanibstudiet. Derfor kan fagudvalget ikke vurdere, om der er forskelle mellem selpercatinib og de to komparatorer.

Deskriptiv gennemgang af bivirkningsprofilerne
Bivirkningsprofilen for selpercatinib er ikke beskrevet specifikt for populationen med jod-refraktær kræft i skjoldbruskkirtlen. I EPAR'en angives det dog, at 2 patienter (4,8 %) i denne population ophørte behandlingen med selpercatinib pga. uønskede hændelser. Dette var væsentlig færre end for både sorafenib (18,8 %) og vandetanib (33 %).

De mest almindelige uønskede hændelser af grad 3-4 i den samlede selpercatinib sikkerhedspopulation på tværs af indikationer var hypertension (19,2 %), øget alanin aminotransferase (9,8 %), øget aspartat aminotransferase (8,3 %), forlænget QT-interval (4 %) og diarré (3,5 %). Fagudvalgets erfaringer med selpercatinib stemmer overens med den rapporterede bivirkningsprofil. De fleste uønskede hændelser er reversible og kan håndteres ved pausering, dosisreduktion eller ved behandling af den konkrete bivirkning (eksempelvis hypertension). I den samlede sikkerhedspopulation oplevede 3,4 % af patienterne en uønsket hændelse, der førte til død. Ingen af disse blev dog vurderet at være relateret til selpercatinib.

De mest almindelige uønskede hændelser af grad 3-4 for sorafenib var hånd-fod-hudreaktion (20,3 %), hypertension (9,7 %), hypocalcæmi (9,2 %), vægttab (5,8 %), træthed (5,8 %), diarré (5,8 %) og åndenød (4,8 %). Af disse var særligt hånd-fod-hudreaktion, træthed og vægttab årsag til hyppige dosisjusteringer og behandlingsstop, hvilket stemmer overens med fagudvalgets kliniske erfaringer med sorafenib. I den samlede sikkerhedspopulation oplevede 5,8 % af patienterne en uønsket hændelse, der førte til død. Én af disse (0,5 %) blev vurderet at være relateret til sorafenib.

De mest almindelige uønskede hændelser af grad 3-4 for vandetanib var forlænget QT-interval (14 %), diarré (10 %), asteni (7 %) og træthed (5 %). Af disse var særligt forlænget QT-interval og diarré årsag til behandlingsstop. I den samlede sikkerhedspopulation oplevede 2,7 % af patienterne en uønsket hændelse, der førte til død. Disse blev vurderet at være relateret til vandetanib.

Samlet set kan selpercatinibs værdi ift. uønskede hændelser overfor sorafenib og vandetanib ikke kategoriseres. Fagudvalget vurderer, at selpercatinib har en bedre bivirkningsprofil end sorafenib og vandetanib. Dette bygger på, at uønskede hændelser sjældent fører til behandlingsstop ved selpercatinib, samt at selpercatinibs bivirkninger er reversible og kan behandles.

5.1.5 Fagudvalgets konklusion

Den samlede værdi af selpercatinib sammenlignet med sorafenib og vandetanib til patienter med RET-forandret, jod-refraktær kræft i skjoldbruskkirtlen kan ikke kategoriseres efter Medicinrådets metoder grundet manglende komparative data.

Fagudvalget har derfor sammenlignet effekten af selpercatinib med sorafenib og vandetanib ved at foretage en deskriptiv sammenligning af effektestimater fra et ukontrolleret studie af selpercatinib med effektestimater fra randomiserede studier, hvor sorafenib og vandetanib blev sammenlignet med placebo.

Fagudvalget er bevidste om, at datagrundlaget er meget usikkert, men finder alligevel, at den objektive responsrate ved selpercatinib er høj, og bemærker, at behandling med

selpercatinib medførte, at enkelte patienter fik komplet respons (2 ud af 22 patienter), hvilket ikke er observeret med andre behandlinger i lignende patientgrupper. Derudover finder fagudvalget, at selpercatinib har en fordelagtig bivirkningsprofil ift. sorafenib og vandetanib.

5.2 Klinisk spørgsmål 2

Klinisk spørgsmål 2 var:

Hvilken værdi har selpercatinib sammenlignet med cabozantinib for voksne og børn ≥ 12 år med avanceret RET-forandret medullær kræft i skjoldbruskkirtlen, der er progredieret efter tidligere behandling med en multikinasehæmmer?

5.2.1 Litteratur

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

Ansøger har søgt litteratur med søgestrengen fra protokollen og har udvalgt i alt fire fuldtekstartikler (Tabel 5-4), der beskriver data fra to forskellige kliniske studier. Ét studie af selpercatinib og ét studie af komparatoren (cabozantinib).

Tabel 5-4. Oversigt over studier af patienter med medullær kræft i skjoldbruskkirtlen og de tilhørende publikationer

Publikationer	Klinisk forsøg	NCT-nummer	Population	Studietype, intervention og eventuel komparator	Median opfølgningstid for primært endepunkt
Wirth et al. 2020 [26] EPAR [27] og produktresume for selpercatinib [28]	LIBRETTO-001	NCT03157128	Indeholder en relevant subgruppe med RET-forandring, hvor alle tidligere er behandlet med multikinase-hæmmer.	Ikke-kontrolleret, fase I/II. Selpercatinib.	13,9 måneder (PFS i det største datasæt)
Elisei et al. 2012 [24] Sherman et al. 2016 [33] Schlumberger et al. 2017 [34]	EXAM	NCT00704730	Halvdelen havde RET-forandring og 21 % var tidligere behandlet med multikinase-hæmmer.	Fase III, RCT. Cabozantinib overfor placebo.	13,9 måneder (PFS)

Selpercatinib er undersøgt i ét klinisk studie (LIBRETTO-001), og data herfra er rapporteret i én fuldtekstartikel [26]. Desuden indeholder EPAR'en [27] og

produktresumeet [28] for selpercatinib data fra LIBRETTO-001 ved et senere data cut-off (marts 2020 overfor juni 2019).

LIBRETTO-001 er beskrevet under klinisk spørgsmål 1 (afsnit 5.1.1). Til dette kliniske spørgsmål anvendes en subgruppe af patienter med RET-forandret medullær kræft i skjoldbruskkirtlen, som tidligere har modtaget behandling med multikinasehæmmer (cabozantinib og/eller vandetanib). Denne patientgruppe er velegnet til at estimere effekten af selpercatinib for klinisk spørgsmål 2. Studiet indeholdt desuden en subgruppe, der ikke tidligere var behandlet med multikinasehæmmer.

LIBRETTO-001 inkluderede ikke en kontrolarm. Derfor har ansøger søgt efter egnede studier for cabozantinib, der er den definerede komparator i Medicinrådets protokol (se Figur 3-2) [32].

EXAM er et randomiseret, dobbeltblindet fase III-studie, der undersøger effekten af cabozantinib overfor placebo (randomiseret i forholdet 2:1) til patienter med lokalt avanceret eller metastatisk medullær kræft i skjoldbruskkirtlen. Studiets primære endepunkt var PFS, og sekundære endepunkter var bl.a. OS og ORR. Randomiseringen i studiet var stratificeret for tidligere behandling med multikinasehæmmer og alder. Studiet indeholder prædefinerede subgrupper, hvor patienterne inddeles efter RET-status, bl.a. patienter med kendt RET-forandring og patienter med RET-M918T-mutation. Tre fuldtekstartikler rapporterer data fra studiet. Elisei et al. rapporterer den primære analyse af PFS og bivirkninger [24], Sherman et al. rapporterer PFS og ORR fra de prædefinerede subgrupper baseret på RET-forandringer [33], og Schlumberger et al. rapporterer den endelige OS-analyse [34].

Baselinekarakteristika for patienterne i LIBRETTO-001 og EXAM er angivet nedenfor.

Tabel 5-5. Baselinekarakteristika

		LIBRETTO-001 (selpercatinib)*	EXAM	
			Cabozantinib	Placebo
Patientantal		124	219	111
Median alder, år (range)		57,5 (17-90)	55 (20-86)	55 (21-79)
Køn, kvinder (%)		43 (35 %)	68 (31 %)	41 (37 %)
ECOG performance status	0	31 (25 %)	123 (56 %)	56 (50 %)
	1	84 (68 %)	95 (44 %) ***	55 (50 %) ***
	2	9 (7 %)	- ***	- ***
RET-mutation	Positiv	124 (100 %)	101 (46 %)	58 (52 %)
	Negativ	0 (0 %)	36 (14 %)	10 (9 %)
	Ukendt	0 (0 %)	87 (40 %)	43 (39 %)
	M918T	33 (60 %) **	75 (34 %)	43 (39 %)
Fjernmetastaser (%)		122 (98 %)	191 (87 %)	96 (86 %)
Tidligere behandling med multikinasehæmmer (%)		124 (100 %)	44 (20 %)	24 (22 %)

*: Baselinekarakteristika for patienterne i LIBRETTO-001 er kun rapporteret ved data cut-off i december 2019. Her var patientantallet 124, hvorimod 143 patienter indgår ved data cut-off i marts 2020. **: Andelen af patienter med M918T-mutation er ikke angivet for populationen med 124 patienter, men derimod for de første 55 patienter, som var det primære analysesæt i Wirth et al. [26]. ***: ECOG performance status er angivet samlet for status 1-2 i EXAM.

Der er væsentlige forskelle i patientpopulationerne i de kliniske studier.

- Alle patienter i LIBRETTO-001 var tidligere behandlet med multikinasehæmmer, hvilket kun var tilfældet for ca. 20 % i EXAM.
- Væsentlig flere patienter var i performance status 1-2 i LIBRETTO-001 end i EXAM.
- Patienterne i LIBRETTO-001 har alle dokumenteret RET-forandring, hvilket kun er tilfældet for omkring halvdelen af patienterne i EXAM. EXAM indeholder dog en prædefineret subgruppe med kendt RET-forandring.
- Forskellig andel af patienter med RET-M918T-mutation. Patienter med denne mutation reagerer bedre på cabozantinib, men det er uvist, om mutationen har en indflydelse på effekten af selpercatinib.

5.2.2 Databehandling og analyse

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

Ansøger har indsendt data fra de ovennævnte studier for effektmålene, OS, PFS, ORR og uønskede hændelser, som efterspurgt i protokollen. For effektmålet livskvalitet er der kun indsendt data for selpercatinib, og disse er ikke opgjort som beskrevet i protokollen.

Ansøger har lavet en deskriptiv gennemgang af studiedata for både selpercatinib (LIBRETTO-001) og cabozantinib, hvor cabozantinibs effekt sammenlignes med placebokontrollen (EXAM). Derudover har ansøger lavet en ikke-forankret, justeret indirekte sammenligning af selpercatinib og cabozantinib, hvori studiedata for selpercatinib justeres for baselineforskelle mellem LIBRETTO-001 og EXAM. Analysen er ikke publiceret, men ansøger har indsendt tilstrækkelige detaljer om analysen, til at sekretariatet har kunnet vurdere dens anvendelighed.

Den justerede analyse blev foretaget ud fra den samlede population af tidligere behandlede patienter (124) og patienter, der ikke tidligere var behandlet med multikinasehæmmer (88 patienter) fra LIBRETTO-001 (212 patienter i alt). Denne population blev justeret for forskelle i baselinekarakteristika i forhold til populationen med RET-forandring i EXAM (107 patienter for cabozantinib og 62 for placebo). Herved blev effektestimaterne for selpercatinib justeret og derefter sammenholdt med ujusterede data for cabozantinib.

Analysen omfatter justering pba. patienternes alder, vægt, ECOG performance status, køn, rygehistorik, tidligere behandling med multikinasehæmmer og RET-M918T-mutation.

De vægtede baselinekarakteristika er vist nedenfor.

Tabel 5-6. Baselinekarakteristika i LIBRETTO-001 overfor EXAM og vægtning til ansøgers justerede analyse

Karakteristika	Før justering		Efter justering
	LIBRETTO-001, selpercatinib, både tidligere og ikke tidligere behandlet (n = 212)	EXAM, RET-forandrede behandlet med cabozantinib	LIBRETTO-001, selpercatinib, både tidligere og ikke tidligere behandlet (n_{eff} = 167)
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

Karakteristika	Før justering		Efter justering
	LIBRETTO-001, selpercatinib, både tidligere og ikke tidligere behandlet (n = 212)	EXAM, RET-forandrede behandlet med cabozantinib	LIBRETTO-001, selpercatinib, både tidligere og ikke tidligere behandlet (n_{eff} = 167)
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

Analysen omfatter OS- og PFS-data. For OS-data sammenholdes selpercatinib med cabozantinib hos patienter med RET-M918T-mutation, mens det for PFS sammenholdes med cabozantinib hos patienter med RET-forandring generelt.

Sekretariatet finder, at analysen er udført korrekt, og at den kan anvendes som supplerende evidensgrundlag. Analysen medvirker til et bedre datagrundlag til at besvare effektmål i protokollens kliniske spørgsmål og lever op til Medicinrådets principper for anvendelse af upublicerede data, jf. Princippapir for anvendelse af upublicerede data i vurderinger af nye lægemidler og indikationsudvidelser.

Fagudvalget vurderer, at der er usikkerheder omkring analysen, der medfører, at den ikke kan anvendes til en kategorisering af selpercatinibs effekt. En markant svaghed ved analysen er, at selpercatinibs effekt justeres mod en mere behandlingsnaiv population. Dette er ikke i overensstemmelse med populationen i det kliniske spørgsmål og EMAs indikation, som er patienter, der tidligere er behandlet med multikinasehæmmer. Derudover har det ikke været muligt at justere for andre vigtige prognostiske faktorer såsom tumorstørrelse, organer med fjernmetastaser, calcitoninniveau, andre tidligere behandlinger (kirurgi og strålebehandling) og arvelig eller somatisk RET-forandring. Manglen på en fælles komparator i LIBRETTO-001 og EXAM medfører desuden, at det er vanskeligt at vurdere, hvor effektivt justeringen har balanceret prognostiske variable.

Fagudvalget baserer sin vurdering på en deskriptiv sammenligning af selpercatinib og cabozantinib ud fra de ujusterede studiedata. Til dette anvender fagudvalget studiedata fra LIBRETTO-001 baseret på længst mulig opfølgningstid og størst mulige patientgrupper. For effektmålene, OS, ORR, PFS og uønskede hændelser findes dette i EPAR'en (143 patienter med data cut-off marts 2020) [27]. Desuden inddrager fagudvalget effektestimaterne for OS og PFS fra ansøgers justerede analyse.

5.2.3 Evidensens kvalitet

Da vurderingen af selpercatinib er baseret på en deskriptiv sammenligning med cabozantinib og en justeret analyse, hvor det er uvist om prognostiske faktorer er tilstrækkeligt balancerede, kan Medicinrådet ikke anvende GRADE til at vurdere kvaliteten af evidensen.

Samlet set vurderer Medicinrådet, at evidensens kvalitet er meget lav. Medicinrådet vurderer, at effekten af cabozantinib er bedre dokumenteret end selpercatinib, da den er undersøgt i et placebokontrolleret studie (EXAM). EXAM inkluderer dog hovedsageligt patienter, der ikke tidligere er behandlet med multikinasehæmmer, og kun omkring halvdelen af patienterne har kendt RET-forandring. Derfor er cabozantinibs effekt ift. patienter med RET-forandret medullær kræft i skjoldbruskkirtlen, der tidligere er behandlet med multikinasehæmmer, også meget usikker.

Fagudvalget er bekendt med, at der pågår et fase III randomiseret kliniske studie af selpercatinibs effekt som førstelinjebehandling af patienter med RET-forandret medullær kræft i skjoldbruskkirtlen, som vil kunne bidrage med stærkere evidens for selpercatinibs effekt (LIBRETTO-531/NCT04211337). Data herfra forventes dog tidligst i 2025.

5.2.4 Effektestimater og kategorier

I tabellen herunder fremgår effektestimaterne fra de enkelte studier af henholdsvis selpercatinib og cabozantinib. Derudover fremgår effektestimaterne fra ansøgers justerede analyse af selpercatinib overfor cabozantinib. Værdien af selpercatinib **kan ikke kategoriseres** ved hjælp af Medicinrådets metoder for nogen af effektmålene pga. datagrundlaget, og de aggregerede værdier fremgår derfor ikke af skemaet.

Tabel 5-7. Resultater for klinisk spørgsmål 2

Effektmål	Målenhed (MKRF)	Vigtighed	Effektestimater fra studierne			Ansøgers justerede analyse		
			LIBRETTO-001	EXAM		LIBRETTO-001 og EXAM (Ansøgers analyse)		
			Selpercatinib n = 143 / 315*	Cabozantinib n = 219 / 107** / 81***	Placebo n = 111 / 62** / 45***	Selpercatinib n = 167	Cabozantinib n = 107	Forskel
Samlet overlevelse (OS)	Median OS (3 måneder)	Kritisk	33,3 måneder (33,2; ikke nået)	44,3 måneder***	18,9 måneder***	[redacted]	[redacted]	[redacted]
	OS-rate ved 24 måneder (5 %-point)		77,1 % (63,2; 86,3 %)	70 %***	42 %***	[redacted]	[redacted]	[redacted]
Livskvalitet	EORTC-QLQ-C30. Gennemsnitlig ændring i post-basislinje relativt til basislinjen (10 point)	Kritisk	Ikke opgivet som efterspurgt	Ikke angivet	Ikke angivet	Indgår ikke	Indgår ikke	Indgår ikke
Objektiv responsrate (ORR)	Andel, der opnår komplet eller partielt respons (15 %-point).	Vigtig	69,2 % (61,0; 76,7)	32 % **	0 % **	Indgår ikke	Indgår ikke	Indgår ikke
Progressionsfri overlevelse (PFS)	Median PFS (3 måneder)	Vigtig	Ikke nået (20; ikke nået)	13,8 måneder (ikke angivet)	4,6 måneder (ikke angivet)	[redacted]	[redacted]	[redacted]

Uønskede hændelser	Andel, der oplever en eller flere uønskede hændelser af grad 3-4 (MKRF: 5 %-point)	Vigtig	59,7 %*	69 %	33 %	Indgår ikke	Indgår ikke	Indgår ikke
	Deskriptiv gennemgang	Se gennemgang	Se gennemgang	Se gennemgang	Se gennemgang	Indgår ikke	Indgår ikke	Indgår ikke

Konklusion	
Samlet kategori for lægemidlets værdi	Kan ikke kategoriseres. Fagudvalget vurderer, at data indikerer, at selpercatinib er mere effektivt og mindre bivirkningstungt end cabozantinib.
Kvalitet af den samlede evidens	Meget lav

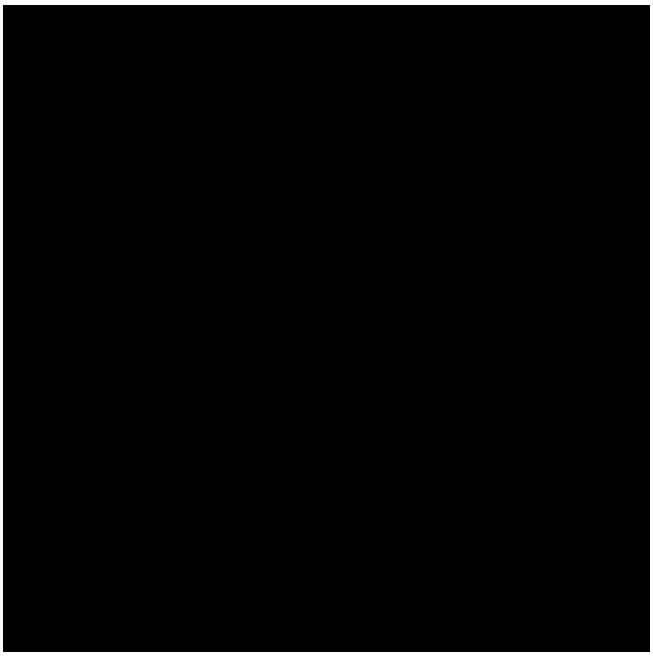
*: Data stammer fra EPAR, hvilket inkluderer 315 patienter med medullær kræft i skjoldbruskkirtlen, der alle er behandlet med minimum én dosis selpercatinib (sikkerhedspopulation). **: Data stammer fra subpopulationen med kendt RET-forandring. ***: Data stammer fra subpopulationen med kendt RET-M918T-mutation, da der ikke findes OS-data fra den samlede population med RET-forandring.

Samlet overlevelse (OS)

Deskriptiv gennemgang
Patienterne behandlet med selpercatinib havde en median overlevelse på 33,2 måneder (33,2; ikke nået) og en 24-måneders OS-rate på 77,1 % (63,2; 86,3 %). Estimaterne er meget usikre, da 82 % af patienterne er censurerede i analysen. Median opfølgningstid var 15,7 måneder.

For cabozantinib var medianoverlevelsen 44,3 måneder overfor 18,9 måneder i placebokontrollen. OS-raterne ved 24 måneder var ca. 70 % for cabozantinib og 42 % for placebokontrollen (aflæst fra Kaplan-Meier kurverne). Effektestimaterne stammer fra subgruppen med RET-M918T-mutation (som udgør ca. 75 % af patienterne med RET-forandring), da der ikke findes estimater fra den samlede gruppe med kendt RET-forandring.

Ansøgers justerede analyse
Nedenstående figur viser de justerede og ujusterede Kaplan-Meier kurver for OS i ansøgers analyse.



[redacted]

[redacted]

Samlet vurdering
Den samlede værdi for OS kan ikke kategoriseres, pga. manglende komparativt datagrundlag og generelt umodne data for selpercatinib. Fagudvalget vurderer, at den justerede analyse indikerer, at selpercatinib medfører en længere overlevelse end cabozantinib, hvilket kommer til udtryk i både 24-måneders OS-raten og hazard ratio. Fagudvalget bemærker, at OS er svært at anvende som effektmål ved denne sygdom, fordi overlevelsen ved denne sygdom generelt er lang, og flertallet vil få tilbudt flere behandlingslinjer efter progression. Desuden er der stor usikkerhed om effektestimaterne for selpercatinib pga. umodne dataestimater.

Livskvalitet
Ansøger har ikke opgjort data for effektmålet, som efterspurgt i protokollen. For selpercatinib er der i stedet indsendt en opgørelse over, hvor mange patienter der oplever en forbedring på minimum 10 point på EORTC QLQ-C30 '*global health scale*' [redacted] Ansøger har dog ikke indsendt data for de resterende patienter, og det er uvist, om de oplevede mindre stigninger, ingen ændringer eller fald i livskvaliteten.

Der er ikke opgjort data ved EORTC QLQ-C30 for cabozantinib.

Værdien ift. livskvalitet kan ikke kategoriseres. Fagudvalget kan ikke vurdere, om selpercatinib samlet set medfører klinisk relevante ændringer i patienternes livskvalitet, da der kun foreligger data for de patienter, der oplevede en stigning på minimum 10 point, mens det er uvist, hvordan de resterende patienter blev påvirket.

Objektiv responsrate (ORR)
Ved selpercatinib havde 99 ud af 143 patienter (69,2 %) et objektivt respons. Af disse havde 6 patienter (4,2 %) et komplet respons og 93 patienter (65,0 %) et partielt respons. Af de resterende 44 patienter havde 31 stabil sygdom, 2 havde sygdomsprogression som bedste scanningsresultat, og 7 kunne ikke vurderes.

Ved cabozantinib havde 34 ud af 107 patienter med RET-forandring (32 %) et objektivt respons (alle partielt respons), mens ingen patienter havde objektivt respons i kontrolgruppen.

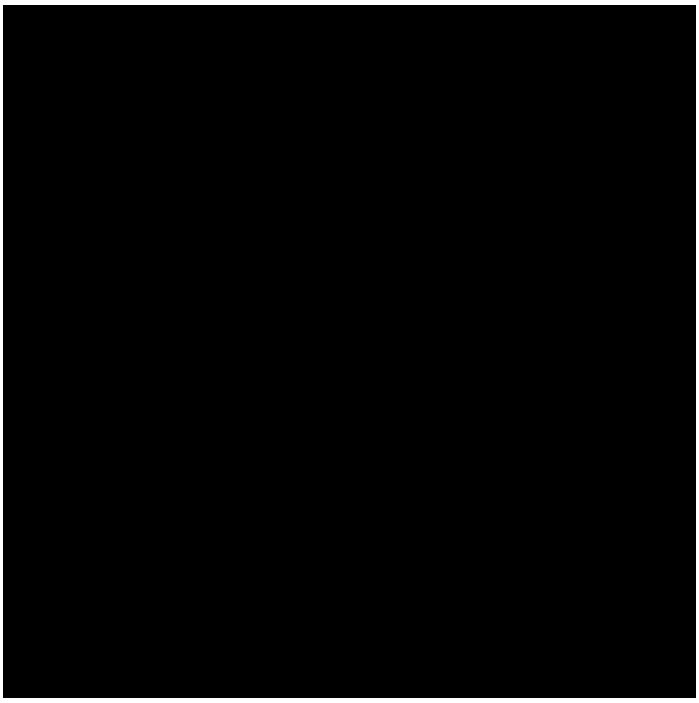
Værdien ift. ORR af selpercatinib kan ikke kategoriseres overfor cabozantinib. Fagudvalget vurderer, at ORR er høj ved selpercatinib, og lægger vægt på, at 6 patienter (ca. 4 %) havde komplet respons, hvilket ikke er set i tidligere studier af multikinasehæmmere ved RET-forandret medullær kræft i skjoldbruskkirtlen.

Progressionsfri overlevelse (PFS)

Deskriptiv gennemgang
Median PFS var ikke nået (20 måneder; ikke nået) for patienter behandlet med selpercatinib efter en median opfølgningstid på 13,9 måneder.

For cabozantinib var median PFS 13,8 måneder overfor 4,6 måneder i placebokontrollen for patienter med kendt RET-forandring.

Ansøgers justerede analyse
Nedenstående figur viser de justerede og ujusterede Kaplan-Meier kurver for PFS i ansøgers analyse.



Figur 5-1: [redacted]

[redacted].

Samlet vurdering
Den samlede værdi ift. PFS kan ikke kategoriseres. Fagudvalget vurderer, at både den deskriptive sammenligning og ansøgers justerede analyser indikerer, at selpercatinib medfører en klinisk relevant længere PFS end cabozantinib.

Uønskede hændelser

Andelen af patienter, der oplever minimum én uønsket hændelse af grad 3-4
Fagudvalget har anvendt sikkerhedspopulationen i EPAR for patienter med medullær kræft i skjoldbruskkirtlen, der har modtaget minimum én dosis selpercatinib (n = 315). I denne population oplevede 59,7 % minimum én uønsket hændelse af grad 3-4.

For cabozantinib oplevede 69 % af patienterne minimum én uønsket hændelse af grad 3-4 overfor 33 % af patienterne i placebokontrollen.

Andelen af grad 3-4 uønskede hændelser kan variere betragteligt mellem studier og patientpopulationer. Derfor kan fagudvalget ikke vurdere, om der er forskelle mellem selpercatinib og cabozantinib.

Deskriptiv gennemgang af bivirkningsprofilerne
Specifikt for populationen med medullær kræft i skjoldbruskkirtlen angives i EPAR'en, at 15 patienter (4,8 %) ophørte behandlingen med selpercatinib pga. uønskede hændelser. 8 patienter (2,4 %) oplevede en uønsket hændelse, der førte til død, men ingen af disse blev vurderet at være relateret til selpercatinib. Bivirkningsprofilen for selpercatinib i øvrigt er beskrevet i afsnit 5.1.4

For cabozantinib oplevede 35 patienter (16 %) uønskede hændelser, der medførte behandlingsstop, mens 17 patienter (7,9 %) oplevede en uønsket hændelse, der førte til død. 9 (4,2 %) af disse blev vurderet at være relateret til cabozantinib.

De mest almindelige uønskede hændelser af grad 3-4 for cabozantinib var diarré (15,9 %), hånd-fod-hudreaktion (12,6 %), træthed (9,3 %), hypertension (8,4 %), asteni (5,6 %), vægttab (4,7 %) og nedsat appetit (4,7 %).

Samlet set kan selpercatinibs værdi ift. uønskede hændelser overfor cabozantinib ikke kategoriseres.

Fagudvalget vurderer, at selpercatinib har en mere gunstig bivirkningsprofil end cabozantinib. Dette bygger på, at uønskede hændelser sjældent fører til behandlingsstop ved selpercatinib, samt at selpercatinibs bivirkninger er reversible og kan behandles.

5.2.5 Fagudvalgets konklusion

Den samlede værdi af selpercatinib sammenlignet med cabozantinib til patienter med RET-forandret medullær kræft i skjoldbruskkirtlen kan ikke kategoriseres efter Medicinrådets metoder grundet manglende komparative data.

Fagudvalget er bekendt med, at der pågår et fase III randomiseret kliniske studie af selpercatinibs effekt som førstelinjebehandling af patienter med RET-forandret medullær kræft i skjoldbruskkirtlen, som vil kunne bidrage med stærkere evidens for selpercatinibs effekt (LIBRETTO-531/NCT04211337). Data herfra forventes dog tidligst i 2025.

I den nuværende vurdering har fagudvalget foretaget en deskriptiv sammenligning af effektestimaterne, fra et ukontrolleret studie selpercatinib med et fase III-randomiseret

studie for cabozantinib, og har desuden anvendt en justeret indirekte sammenligning af selpercatinib og cabozantinib som supplerende datagrundlag. Fagudvalget finder, at de ikke-komparative data indikerer, at selpercatinib er mere effektivt og mindre bivirkningstungt end cabozantinib, fordi:

- Selpercatinib viser længere PFS end cabozantinib. Fagudvalget vurderer, at forskellen er klinisk relevant.
- ORR er dobbelt så høj for selpercatinib som for cabozantinib (69 % overfor 32 %), og enkelte patienter behandlet med selpercatinib havde komplet respons.
- Data, om end meget usikre, indikerer at selpercatinib muligvis kan medføre længere overlevelse.
- Væsentlig færre patienter ophørte behandling med selpercatinib pga. uønskede hændelser i forhold til cabozantinib, og bivirkningerne forbundet med selpercatinib er reversible og kan behandles.

5.3 Klinisk spørgsmål 3

Klinisk spørgsmål 3 er:

Hvilken værdi har selpercatinib sammenlignet med platinbaseret kemoterapi for voksne med avanceret RET-forandret NSCLC, der er progredieret efter behandling med checkpoint-inhibitor immunterapi?

5.3.1 Litteratur

I Medicinrådets protokol for vurdering af selpercatinib er der angivet flere søgestrenge til klinisk spørgsmål 3 [32]. Dette skyldtes, at fagudvalget forventede, at ansøger ikke ville kunne finde kliniske studier af komparatoren, der stemmer overens med populationen i det kliniske spørgsmål. For at opnå det bedst mulige sammenligningsgrundlag opfordrede fagudvalget ansøger til at udføre en sammenligning af data for selpercatinib med observationelle data fra patienter med kendt RET-forandring og/eller patienter, der tidligere havde modtaget immunterapi og dernæst modtog kemoterapi. Formålet med dette var at få indblik i betydningen af henholdsvis RET-forandringer og tidligere behandling med checkpoint inhibitor-immunterapi for effekten af platinbaseret kemoterapi. Derudover ønskede fagudvalget en sammenligning med platinbaseret kemoterapi ud fra randomiserede kliniske studier, hvor platin-baseret kemoterapi var undersøgt som førstelinjebehandling, for at få et mere solidt estimat af effekten af platinbaseret kemoterapi baseret på prospektive studier. I denne søgning har ansøger, efter konsultation med fagudvalget, valgt at definere platinbaseret kemoterapi som carbo- eller cisplatin i kombination med vinorelbin eller pemetrexed. I dansk klinisk praksis behandles de fleste patienter med carboplatin i kombination med vinorelbin, men fagudvalget forventer, at de ovennævnte kombinationer medfører en sammenlignelig effekt.

Ansøger har søgt litteratur med søgestrengene fra protokollen og har fundet ét studie, der undersøger effekten af selpercatinib i RET-forandret NSCLC (LIBRETTO-001) [35].

Derudover har ansøger fundet seks artikler, der omhandler retrospektive studier af effekten af kemoterapi ved enten RET-forandret NSCLC eller i patienter med NSCLC, der tidligere er behandlet med checkpoint inhibitor-immunterapi (Tabel 5-8). Medicinrådet bemærker, at studierne Shen et al. [36] og Tan et al. [37] blev anvendt ved klinisk spørgsmål 4 af ansøger. Medicinrådet vurderer dog, at disse studier egner sig bedre til at besvare klinisk spørgsmål 3, og derfor fremgår de af tabellen nedenfor.

Tabel 5-8. Oversigt over litteratur til at besvare klinisk spørgsmål 3, hvor patienter har kendt RET-fusion og/eller tidligere har modtaget behandling med checkpoint inhibitor-immunterapi

Publikationer	Klinisk forsøg	NCT-nummer	Population	Studietype, Intervention og eventuel komparator	Median opfølgningstid for primært endepunkt
Drilon et al. 2020 [35] EPAR [27] og produktresume for selpercatinib [28]	LIBRETTO-001	NCT03157128	Subgruppe af patienter med RET-forandret NSCLC, hvoraf alle tidligere er behandlet med platinbaseret kemoterapi og halvdelen yderligere med check point inhibitor-immunterapi.	Ikke-kontrolleret, fase I/II. Selpercatinib.	13,9 måneder (PFS i største datasæt)
Studier med kendt RET-forandring					
Gautschi et al. 2017 [17]	-	-	RET-forandret NSCLC, størstedelen med avanceret ikke-planocellulær histologi.	Observationelt studie. Platin-baseret kemoterapi som førstelinje behandling.	Ikke angivet
Shen et al. 2020 [36]	-	-	RET-forandret NSCLC behandlet med pemetrexed og/eller platinbaseret kemoterapi. Langt overvejende asiatisk.	Observationelt studie. Platin i kombination med pemetrexed, som førstelinje-behandling.	Ikke angivet

Publikationer	Klinisk forsøg	NCT-nummer	Population	Studietype, Intervention og eventuel komparator	Median opfølgningstid for primært endepunkt
Tan et. al 2020 [37]	-		RET-forandret NSCLC, der har modtaget forskellige behandlings-regimer, bl.a. pemetrexed-baseret kemoterapi. Langt overvejende asiatisk.	Observationelt studie. Platin i kombination med pemetrexed, hovedsageligt som førstelinje behandling.	20,3 måneder
Studier af platinbaseret kemoterapi efter progression på checkpoint inhibitor-immunterapi					
Bersanelli et al. 2020 [38]	-	-	Avanceret NSCLC, der er progredieret under eller efter førstelinjebe-handling med checkpoint inhibitor-immunterapi, og som efterfølgende har modtaget kemoterapi.	Observationelt studie. Platin-baseret kemoterapi.	10,7 måneder fra opstart på kemoterapi.
Metro et al. 2019 [39]	-	-	Avanceret NSCLC, der er progredieret under eller efter behandling med checkpoint inhibitor-immunterapi, og som efterfølgende har modtaget kemoterapi. Patienter havde ikke EGFR eller ALK mutation.	Observationelt studie. Platin-baseret kemoterapi.	5,7 måneder efter progression på checkpoint inhibitor-immunterapi.

Publikationer	Klinisk forsøg	NCT-nummer	Population	Studietype, Intervention og eventuel komparator	Median opfølgningstid for primært endepunkt
Park et. al 2018 [40]	-	-	Avanceret NSCLC, der er progredieret under eller efter behandling med checkpoint inhibitor-immunterapi, og som efterfølgende har modtaget kemoterapi.	Observationelt studie. Platin-baseret kemoterapi.	Ikke angivet

LIBRETTO-001 er beskrevet overordnet i afsnit 5.1.1. Subgruppen af patienter med RET-forandret NSCLC er alle tidligere behandlet med platinbaseret kemoterapi, og godt halvdelen har yderligere været behandlet med checkpoint inhibitor-immunterapi (sekventielt eller i kombination). Subgruppen indeholder 105 patienter i det primære analysesæt og 214 ved data cut-off i marts 2020. Denne patientgruppe er velegnet til at estimere effekten af selpercatinib for klinisk spørgsmål 3. Dog er populationen i LIBRETTO-001 generelt tungere behandlet end populationen i det kliniske spørgsmål, da alle patienterne i LIBRETTO-001 i forvejen er behandlet med platinbaseret kemoterapi. Dette kan medføre mere konservative effektestimater for selpercatinib.

Ansøger har fundet tre studier, hvor RET-status er kendt (Gautschi et al. [17], Shen et al. [36] og Tan et al. [37]). Alle tre studier er retrospektive og indeholder data fra patienter behandlet med platinbaseret kemoterapi, men disse patienter var ikke tidligere behandlet med checkpoint inhibitor-immunterapi, og størstedelen af patienterne modtog platinbaseret kemoterapi i første behandlingslinje. Derved er effekten af kemoterapien i disse studier muligvis overestimeret i forhold til populationen i det kliniske spørgsmål. Studierne er dog den bedste mulighed for at estimere den prædiktive betydning af RET-status for effekten af platinbaseret kemoterapi.

Gautschi et al. rapporterer data fra det globale RET-Registry (GLORY). Dette indeholder data fra 29 centre fordelt over 12 lande i Europa, Asien og USA. Studiet indeholder data fra i alt 165 patienter med RET-forandret NSCLC, hvoraf 84 har modtaget platinbaseret kemoterapi. Ingen af patienterne modtog selektive RET hæmmere, men 55 af de 165 patienter modtog multikinasehæmmer på et tidspunkt i behandlingsforløbet.

Shen et al. rapporterer data fra 10 hospitaler i Kina. Data fra patienternes behandlinger med kemoterapi og targeterede lægemidler blev indsamlet og patienter med RET-forandringer blev identificeret retrospektivt. Studiet indeholder 22 patienter, der blev behandlet med pemetrexed, og for 19 af disse var det i kombination med carbo- eller cisplatin.

Tan et al. indeholder 64 patienter i Singapore med RET-forandret NSCLC, hvoraf 38 blev behandlet med platinbaseret kemoterapi i kombination med pemetrexed.

De tre andre retrospektive studier indeholder patienter, der tidligere er progredieret efter behandling med checkpoint inhibitor-immunterapi, men RET-status kendes ikke i disse patienter.

Bersanelli et al. rapporterer data fra 20 behandlingscentre i Italien. Studiet indeholder 342 patienter i alt, hvoraf 67 modtog platinbaseret kemoterapi som den første behandlingslinje efter progression på checkpoint inhibitor-immunterapi.

Metro et al. rapporterer data fra 14 centre fra Europa. Studiet indeholder 172 patienter med PD-L1 > 50 %, hvoraf 31 modtog platinbaseret kemoterapi efter progression fra behandling med pembrolizumab.

Park et al. rapporterer data fra et center i Sydkorea. Studiet indeholder 309 patienter, men kun 24 af disse modtog platinbaseret kemoterapi efter progression på checkpoint inhibitor-immunterapi, og størstedelen modtog dette i senere behandlingslinjer.

Udvalgte baselinekarakteristika for patienterne i registerstudierne overfor LIBRETTO-001 er vist i tabellen nedenfor.

Tabel 5-9. Udvalgte baselinekarakteristika for populationen i LIBRETTO og registerstudierne, hvor patienter har kendt RET-fusion og/eller tidligere har modtaget behandling med checkpoint inhibitor-immunterapi

		LIBRETTO-001	Gautschi et al.	Shen et al.	Tan et al.	Bersanelli al.	Metro et al.	Park et al.
Patientantal	I studiet	214	165	62	64	342	42	73
	I relevant arm	214	84	22	38	67	31	24
Alder, median (rækkevidde)		62 (23-81)	61 (28-89)	59 (ikke angivet)	62 (25-85)	66 (34-86)	64 (19-84)	60 (35-83)
Køn (kvinde)		57 %	52 %	47 %	56 %	39 %	36 %	32 %
Ikke-planocellulær histologi (%)		86 %	98 %	100 %	95 %	68 %	69 %	60 %
Ryge-historik	Aldrig	68 %	63 %	60 %	69 %	Ikke angivet	10 %	43 %
	Tidligere eller nuværende	32 %	37 %	40 %	31 %	Ikke angivet	90 %	57 %
ECOG PS	0 - 1	98 %	Ikke angivet	Ikke angivet	Ikke angivet	76 %	57 %	81 %
	2	2 %	Ikke angivet	Ikke angivet	Ikke angivet	23 %	43 %	19 %
Sygdomsstadie IV		92 %	72 %	71 %	78 %	71 %	Ikke angivet	Ikke angivet

Der er væsentlige forskelle i baselinekarakteristika mellem populationerne:

- Der er væsentlig flere patienter, der aldrig har røget i populationerne med RET-forandring, hvilket korrelerer med en væsentlig bedre prognose.
- Patienterne i LIBRETTO har alle tidligere modtaget minimum én behandlingslinje (platinbaseret kemoterapi), mens patienterne i studierne med kendt RET-forandring modtog platinbaseret kemoterapi i første linje.
- Der er næsten ingen patienter med ECOG-performance score på 2 i LIBRETTO, hvorimod 20-40 % af patienterne havde PS = 2 i registerstudierne omhandlende patienter, der tidlige var behandlet med immunterapi. Patienter med ECOG-performance score 2 har generelt en dårligere prognose.
- Næsten alle patienter med RET-forandring havde ikke-planocellulær NSCLC, hvilket kun gjaldt 60-70 % i registerstudierne omhandlende patienter, der tidlige var behandlet med immunterapi. Patienter med ikke-planocellulær NCSLC har generelt en bedre prognose.
- To af de retrospektive studier med kendt RET-forandring (Shen et al. og Tan et al.) er hovedsageligt baseret på en asiatisk population, hvilket korrelerer en bedre prognose.

Derudover indeholder alle seks retrospektive studier meget få patienter, der modtog en relevant behandling i forhold til hvad Medicinrådet efterspurgte i protokollen (19-84), og effektestimaterne er derfor behæftet med stor usikkerhed.

Ansøger har suppleret datagrundlaget med en søgning efter randomiserede kliniske studier, hvor platinbaseret kemoterapi er undersøgt i patienter, der ikke tidligere er behandlet med platin, som efterspurgt af fagudvalget. Ansøger har fundet ti artikler, der beskriver data fra syv randomiserede kliniske studier, hvori effekten af platinbaseret kemoterapi undersøges som første behandlingslinje. Fagudvalget har desuden tilføjet to fuldtekstartikler, der referer fra ét klinisk studie (KEYNOTE-024) (Tabel 5-10).

Tabel 5-10. Oversigt over litteratur til at besvare klinisk spørgsmål 3, hvor effekten af platinbaseret kemoterapi som førstelinjebehandling undersøges i randomiserede kliniske studier

Publikationer	Klinisk forsøg	NCT-nummer	Population	Studietype, Intervention og eventuel komparator	Median opfølgningstid for primært endepunkt
Awad et al. 2021 [41] Borghaei et al. 2019 [42] Langer et al. 2016 [43]	KEYNOTE-021	NCT02039674	Patienter med stadie IIIb-IV NSCLC uden ALK eller EGFR-mutation. Størstedelen med ikke-planocellulær histologi.	Fase II, RCT. Pembrolizumab plus pemetrexed og carboplatin overfor pemetrexed og carboplatin.	49,4 måneder (median tid fra randomisering til data seneste cut-off)

Publikationer	Klinisk forsøg	NCT-nummer	Population	Studietype, Intervention og eventuel komparator	Median opfølgningstid for primært endepunkt
Gadgeel et al. 2020 [44] Garassino et al. 2020 [45]	KEYNOTE-189	NCT02578680	Patienter med stadie IV-ikke-planocellulær NSCLC uden ALK eller EGFR-mutation.	Fase III, RCT. Pembrolizumab plus pemetrexed og carbo- eller cisplatin overfor pemetrexed plus carbo- eller cisplatin.	18,7 måneder (OS)
Scagliotti et al. 2008 [46]	-	-	Patienter med stadie IIIb-IV NSCLC. Halvdelen havde ikke-planocellulær histologi. Studiet indeholder en analyse af subgruppen med ikke-planocellulær histologi og en analyse opdelt efter rygehistorik.	Fase III, RCT. Cisplatin plus pemetrexed overfor cisplatin plus gemcitabin.	Ikke angivet
Kim et al. 2012 [47]	Kyoto Thoracic Oncology Research Group Trial 0902	UMIN-CTR 000002451	Patienter med ikke-planocellulær NSCLC i stadie IIIb/IV.	Ikke-kontrolleret, Fase II. Carboplatin plus pemetrexed.	15,5 måneder
Manegold et al. 2000 [48]	-	-	Patienter med stadie IIIb-IV NSCLC. Halvdelen havde ikke-planocellulær histologi.	Ikke kontrolleret, Fase II. Cisplatin plus pemetrexed.	Ikke angivet

Publikationer	Klinisk forsøg	NCT-nummer	Population	Studietype, Intervention og eventuel komparator	Median opfølgningstid for primært endepunkt
Ohe et al. 2007 [49]	FACS	-	Patienter med stadie IIIb-IV NSCLC. Omkring 75 % havde ikke-planocellulær histologi. Asiatisk population.	Fase III, RCT. Cisplatin plus irinotecan overfor carboplatin plus paclitaxel, cisplatin plus gemcitabine, eller cisplatin plus vinorelbine.	Ikke angivet
Bennouna et al. 2014 [50]	NAVotrial 01	EudraCT: 2009-012001-19	Patienter med ikke-planocellulær NSCLC i stadie IIIb/IV.	Fase II, RCT. Vinorelbin plus cisplatin overfor pemetrexed plus cisplatin.	Ikke angivet
Reck et al. 2016 [51] Reck et al. 2019 [52]	KEYNOTE-024	NCT02142738	Patienter med stadie IV-NSCLC og PD-L1 udtryk > 50 %. Omkring 80 % havde ikke-planocellulær histologi.	Fase III, RCT. Pembrolizumab overfor cisplatin eller carboplatin plus pemetrexed eller gemcitabine.	25,2 måneder (OS)

De inkluderede studier er meget heterogene, fra små ikke-kontrollerede fase II-studier (eksempelvis Manegold et al. [48]) til store fase III-randomiserede studier (eksempelvis Scagliotti et al. [46] og KEYNOTE-189 [44,45]).

KEYNOTE-021 var et randomiseret, ublindet fase 2-studie af pembrolizumab i kombination med platinbaseret kemoterapi sammenlignet med platinbaseret kemoterapi til førstelinjebehandling af uhelbredelig ikke-planocellulær NSCLC. Studiet indeholdt en kohorte (kohorte G) med 63 patienter i kontrolarmen, som blev behandlet med platinbaseret kemoterapi. Studiet rapporterer data fra alle relevante effektmål undtagen livskvalitet. Den endelige analyse af OS og PFS er publiceret i Awad et al. [41].

KEYNOTE-189 var et randomiseret, dobbeltblindet fase III-studie, hvor pembrolizumab i kombination med platinbaseret kemoterapi blev sammenlignet med platinbaseret kemoterapi til førstelinjebehandling af metastatisk ikke-planocellulær NSCLC. Studiet indeholdt 206 patienter i kontrolarmen, som blev behandlet med platinbaseret kemoterapi. Studiets relevante effektmål var overlevelse (OS), behandlingsophør grundet bivirkninger, progressionsfri overlevelse (PFS) og bivirkninger af grad 3-5, som rapporteres i Gadgeel et al. [44], og livskvalitet vha. EORTC QLQ-C30, som rapporteres i Garassino et al. [45].

Scagliotti et al. rapporterer data fra et fase III-randomiseret studie, hvor patienterne modtog cisplatin i kombination med enten pemetrexed eller gemcitabin til førstelinjebehandling af uhelbredelig NSCLC. Den relevante behandlingsarm (cisplatin i kombination med pemetrexed) indeholdt 862 patienter, hvoraf 436 havde ikke-planocellulær histologi. OS- og PFS-data er tilgængelige for denne subpopulation. Studiets primære effektmål var OS, mens PFS, ORR og uønskede hændelser var sekundære effektmål.

Kim et al. rapporterer data fra et ikke-kontrolleret fase II-studie i Japan, hvor 49 patienter med uhelbredelig NSCLC blev behandlet i første linje med carboplatin i kombination med pemetrexed, efterfulgt af vedligeholdelsesbehandling med pemetrexed. Studiets primære effektmål var ORR, mens OS, PFS og uønskede hændelser var sekundære effektmål.

Manegold et al. rapporterer data fra et ikke-kontrolleret multicenter, fase II-forsøg, hvor 36 patienter med uhelbredelig NSCLC blev behandlet med cisplatin i kombination med pemetrexed. Patientpopulationen var delt lige mellem patienter med planocellulær og ikke-planocellulær histologi, og der blev ikke rapporteret data specifikt for populationen med ikke-planocellulær NSCLC. Studiets primære effektmål var ORR, mens OS og PFS var sekundære effektmål.

Ohe et al. rapporterer data fra FACS, som var et randomiseret, fire-armet fase III-studie udført i Japan, hvor carboplatin i kombination med paclitaxel, cisplatin i kombination med gemcitabin og cisplatin i kombination med vinorelbin blev sammenlignet med cisplatin i kombination med irinotecan. Den relevante behandlingsarm (cisplatin i kombination med vinorelbin) indeholdt 145 patienter. Studiets primære effektmål var OS, mens ORR og tid-til-progression, sikkerhed og livskvalitet var sekundære effektmål.

Bennouna et al. rapporterer fra NAVotrial, som var et randomiseret fase II-studie, hvor patienter blev randomiseret 1:2 til enten cisplatin i kombination med pemetrexed (51 patienter) eller cisplatin i kombination med vinorelbin (100 patienter). Studiets primære effektmål var sygdomskontrolrate (objektivt respons plus stabil sygdom), mens ORR, OS, PFS og sikkerhed var sekundære effektmål.

KEYNOTE-024 var et randomiseret fase III-studie, som blev tilføjet af fagudvalget, da dette studie undersøger effekten af pembrolizumab overfor platinbaseret kemoterapi i patienter med PD-L1-udtryk > 50 %. Studiets primære effektmål var PFS, mens OS, ORR og sikkerhed var sekundære effektmål. Reck et al. 2016 rapporterer data for PFS og ORR [51], mens Reck et al. 2019 rapporterer data for OS og sikkerhed med længere opfølgningstid [52].

Der er flere forskelle i baselinekarakteristika mellem studierne, der vanskeliggør en sammenligning. Nogle af de varierende baselinekarakteristika med prognostisk betydning er vist nedenfor (Tabel 5-11).

Tabel 5-11. Udvalgte baselinekarakteristika for populationen i LIBRETTO og studierne af første linje kemoterapi

		LIBRETTO-001	KEYNOTE-21	KEYNOTE-189	Scagliotti et al.	Kim et al.	Manegold et al.	Ohe et al.	NAVotrial01	KEYNOTE-024
Patientantal i relevant arm		184* (218)	63	206	862	49	36	145	100	151
Alder, median (rækkevidde)		62 (23-81)	66 (37-80)	64 (34-84)	61 (29-83)	63 (41-74)	58 (26-73)	61 (28-74)	61 (38-75)	66 (38-85)
Køn (kvinde)		57 %	59 %	47 %	30 %	41 %	19 %	30 %	38 %	37 %
Ikke-planocellulær histologi (%)		86 %**	97 %	96 %	51 %	98 %	47 %	75 %	88 %	82 %
Ryge-historik	Aldrig	68 %	25 %	12 %	15 %	49 %	Ikke angivet	Ikke angivet	60 %	13 %
	Tidligere eller nuværende	32 %	75 %	88 %	73 %	51 %			40 %	87 %
	Ukendt	0 %	0 %	0 %	12 %	0 %			0 %	0 %
Sygdoms-stadie	IIIb	5,4 %	2 %	0 %	23,8 %	20 %	50 %	18 %	8 %	0 %
	IV	92 %	98 %	100 %	76,2 %	80 %	50 %	82 %	88 %	100 %

* Baselinekarakteristika for patienterne i LIBRETTO-001 er fra analysesættet ved data cut off i december 2019 med 184 patienter, som er publiceret i EPAR. Der er ikke publiceret baselinekarakteristika for populationen ved data cut-off i marts 2020, hvor 218 patienter var inkluderet. ** Tumorhistologier er ikke opgivet for datasættet med 184 patienter, men kun for de 105 patienter i det primære analysesæt i Drilon et al. [35].

De største forskelle mellem studierne er:

- Patienterne i LIBRETTO har alle tidligere modtaget minimum én behandlingslinje (platinbaseret kemoterapi), mens patienterne i alle andre studier ikke tidligere har modtaget systemisk behandling for uhelbredelig NSCLC.
- Væsentlige forskelle i andelen af patienter, der er tidligere eller nuværende rygere, hvor populationen i LIBRETTO-001 er karakteriseret ved, at 68 % aldrig har røget. I de største studier af kemoterapi har 88 % (KEYNOTE-189) og 73 % (Scaglioti et al.) røget. Sammenhængen mellem rygestatus og prognose fremgår bl.a. i Scagliotti et al., hvor subgruppen af ikke-rygere har en signifikant længere median overlevelse (15,9 måneder overfor 10,3 måneder) [46].
- Forskelle i andelen af patienter, der har ikke-planocellulær NSCLC. Dette varierer fra 50 % til næsten 100 %. Patienter med ikke-planocellulær NCSLC har generelt en bedre prognose.
- Forskelle i kønsfordelingen, hvor knap 60 % er kvinder i LIBRETTO-001 og KEYNOTE-021, mens det gælder 18-47 % i de andre studier.

5.3.2 Databehandling og analyse

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

Ansøger har indsendt data fra de ovennævnte studier for effektmålene, OS, PFS, ORR og uønskede hændelser. Data for livskvalitet for selpercatinib er dog opgjort på en anden måde end defineret i protokollen. Pga. forskellene mellem studierne har ansøger ikke lavet en statistisk sammenligning, men har i stedet foretaget en deskriptiv sammenligning af data fra de enkelte studier.

Medicinrådet er enige i ansøgers tilgang. Manglen på kontrolarm i LIBRETTO-001 og studieforskellene medfører, at der ikke kan laves en meningsfuld statistisk sammenligning. Fagudvalget udfører derfor en deskriptiv sammenligning af selpercatinib med platinbaseret kemoterapi ud fra tre komparatorgrupper:

- Patienter med RET-forandring (overfor Gautschi et al., Shen et al. og Tan et al.).
- Patienter, der tidligere er progredieret under eller efter behandling med checkpoint inhibitor-immunterapi (Park et al., Metro et al. og Bersanelli et al.).
- Patienter, der er behandlet med førstelinje kemoterapi i prospektive kliniske studier.

Fagudvalget sammenligner effekten af selpercatinib med et samlet kontrolestimat fra hver af de tre ovenstående grupper, som er fremkommet ved at tage medianen af effektestimaterne fra de enkelte studier. Medicinrådet vurderer, at analysen skal tages med store forbehold, pga. forskellene mellem studierne.

Fagudvalget anvender studiedata fra LIBRETTO-001 baseret på længst mulig opfølgningstid og størst mulige patientgrupper. Dette findes i EPAR'en for alle effektmål bortset fra livskvalitet [27]. EPAR'en indeholder data for uønskede hændelser for flere populationer. Fagudvalget vælger at anvende kvantitative data fra den samlede

population af patienter med RET-forandret NSCLC, der har modtaget minimum én dosis selpercatinib (n = 345), mens fagudvalget, ved den deskriptive gennemgang, anvender data fra den samlede sikkerhedspopulation på tværs af indikationer i LIBRETTO-001.

5.3.3 Evidensens kvalitet

Da vurderingen af selpercatinib er baseret på en deskriptiv sammenligning med platinbaseret kemoterapi, kan Medicinrådet ikke anvende GRADE til at vurdere kvaliteten af evidensen.

Forskellene i studiepopulationerne samt manglen på kontrolarm medfører, at Medicinrådet vurderer evidensens kvalitet som meget lav.

Fagudvalget er bekendt med, at der pågår et fase III randomiseret kliniske studie af selpercatinibs effekt overfor platinbaseret kemoterapi alene eller i kombination med pembrolizumab, som førstelinjebehandling af patienter med RET-forandret ikke-planocellulær NSCLC (LIBRETTO-431/NCT04194944). Dette studie vil kunne bidrage med stærkere evidens for selpercatinibs effekt, men data herfra forventes tidligst i 2024.

5.3.4 Effektestimater og kategorier

I tabellen herunder fremgår effektestimaterne fra LIBRETTO-001 og de samlede kontrolestimater fremkommet ved at tage medianen af effektestimaterne fra de enkelte studier. Effektmålene fra de enkelte studier i komparatorgrupperne fremgår i Tabel 11-1 i Bilag 1. Skemaet indeholder ikke estimater af absolutte eller relative forskelle mellem selpercatinib og komparatorerne, da datagrundlaget ikke muliggør sådanne sammenligninger. Værdien af selpercatinib **kan derfor ikke kategoriseres** vha. Medicinrådets metoder for nogen af effektmålene.

Tabel 5-12. Resultater for klinisk spørgsmål 3

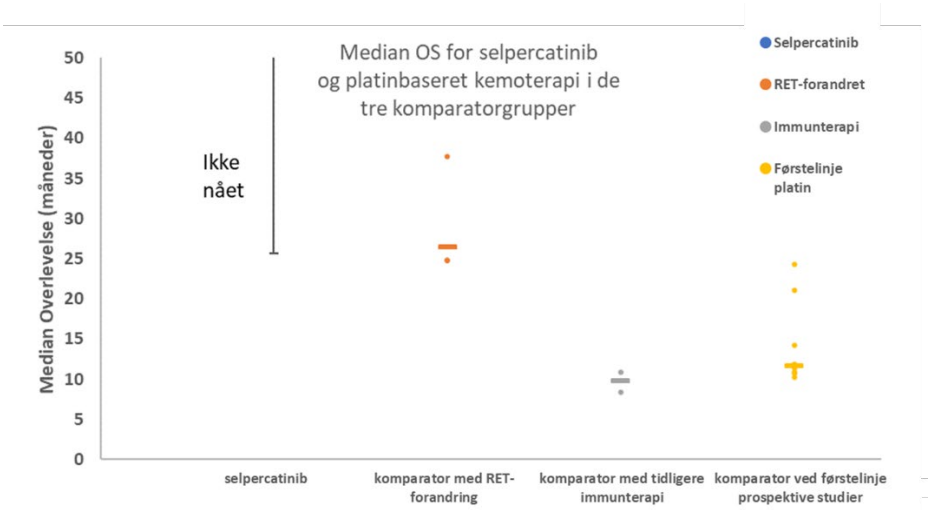
Effektmål	Målenhed (MKRF)	Vigtighed	Selpercatinib (LIBRETTO-001) n = 218 / 345*/23**	Kemoterapi ved RET-forandret NSCLC – samlet kontrol Median (range) 3 studier, n = 19-84	Kemoterapi efter immunterapi - samlet kontrol Median (range) 3 studier, n = 24-67	Førstelinje kemoterapi fra RCT - samlet kontrol Median (range) 8 studier, n = 36-862
Samlet overlevelse (OS)	Median OS (3 måneder)	Kritisk	Ikke nået (25,7; ikke nået)	26,4 måneder (24,8-37,7)	9,7 måneder (8,4-10,9)	11,6 måneder (10,2-24,3)
	OS-rate ved 24 måneder (5 %-point)		67,3 % (55,4; 76,7)	60 % (kun ét estimat)	Ikke angivet	29,9 % (15-51)
Livskvalitet	EORTC-QLQ-C30. Gennemsnitlig ændring i post-basislinje relativt til basislinjen (10 point)	Kritisk	Ikke opgivet som efterspurgt i protokollen	Ikke angivet	Ikke angivet	-2,6 point (kun ét estimat)
Objektiv responsrate (ORR)	Andel, der opnår komplet eller partielt respons (15 %-point)	Vigtig	56,9 % (50,0; 63,6)	51 % (50-54)	42,9 % (22,8-66,7)	31,8 % (19,4-51)
Progressionsfri overlevelse (PFS)	Median PFS (3 måneder)	Vigtig	19,3 måneder (16,5; ikke nået)	7,7 måneder (4,9-7,7)	4,5 måneder (4,5-4,9)	5,7 måneder (4,1-9,9)

Uønskede hændelser	Andel, der oplever en eller flere uønskede hændelser af grad 3-4 (MKRF: 5 %-point)	Vigtig	61,2 %*	Ikke angivet	Ikke angivet	66,8 % (kun ét estimat)
	Deskriptiv gennemgang		Se gennemgang	Ikke angivet	Ikke angivet	Se gennemgang
CNS-progression	Median tid til CNS-progression (3 måneder)	Vigtig	9,36 måneder (6,7; 12,1)**	Ikke angivet	Ikke angivet	Ikke angivet
Konklusion						
Samlet kategori for lægemidlets værdi	Kan ikke kategoriseres. Fagudvalget vurderer, at selpercatinib kan være mere effektivt end platinbaseret kemoterapi, bl.a. pga. effekt på CNS-metastaser. Selpercatinib er mindre bivirkningstungt end platinbaseret kemoterapi. Vurderingen af effekten vanskeliggøres af sammenhængen mellem RET-status og gunstige prognostiske faktorer.					
Kvalitet af den samlede evidens	Meget lav					

* Data stammer fra EPAR, hvilket inkluderer 345 patienter med RET-forandret NSCLC, der alle er behandlet med minimum én dosis selpercatinib (sikkerhedspopulation).**LIBRETTO-001 indeholder 23 patienter med målbare CNS-metastaser ved baseline. Resultatet for effektmålet er angivet som responsvarighed for CNS-metastaser i stedet for tid til CNS-progression.

Samlet overlevelse (OS)

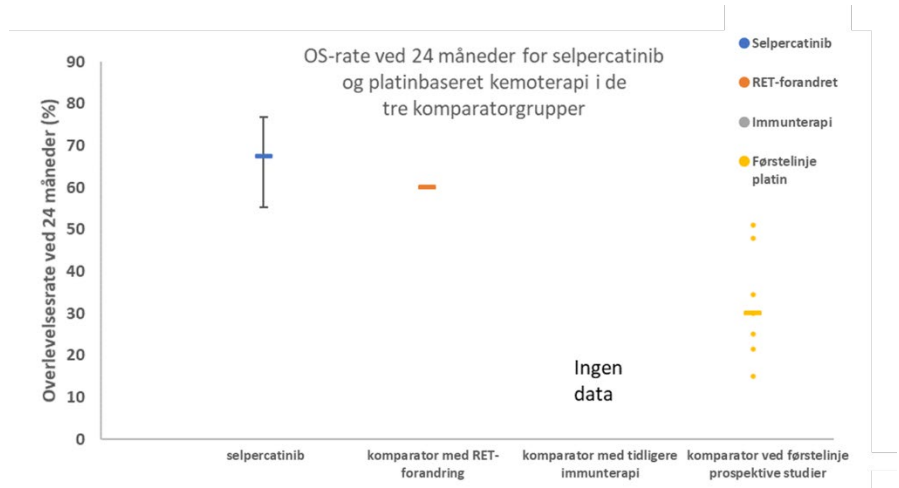
Figuren viser en oversigt over median OS for selpercatinib samt medianen af studieestimaterne for de tre komparatorgrupper.



Figur 5-2: Samlede estimater for selpercatinib og platinbaseret kemoterapi i forhold til median overlevelse. De vandrette streger viser medianerne, fejllinjerne viser 95 % konfidensinterval omkring medianen for selpercatinib, og prikkerne viser estimaterne fra de enkelte studier, der indgår i komparatorgrupperne.

Patienterne behandlet med selpercatinib havde en median overlevelse, der ikke var nået (25,7 måneder; ikke nået) ved en median opfølgningstid på 14,3 måneder. Median OS for komparatorgrupperne var henholdsvis 26,4 måneder (24,8-37,7), 9,7 måneder (8,4-10,9) og 11,6 måneder (10,2-24,3) for grupperne, RET-forandring, tidligere immunterapi og førstelinje RCT.

Overlevelsesraten ved 24-måneder er vist i figuren nedenfor.



Figur 5-3: Samlede estimater for selpercatinib og platinbaseret kemoterapi i forhold til OS-raten ved 24 måneder. De vandrette streger viser punktestimaterne, fejllinjerne viser 95 %

konfidensinterval omkring estimatet for selpercatinib, og prikkerne viser estimaterne fra de enkelte studier, der indgår i komparatorgrupperne.

Patienterne behandlet med selpercatinib havde 24-måneders OS-rate på 67,3 % (55,4; 76,7). Estimaterne er dog meget usikre, da 81 % af patienterne er censurerede i analysen. Der fandtes kun estimater for komparatorgrupperne, RET-forandring og førstelinje RCT. For disse var OS-raten ved 24 måneder henholdsvis 60 % (ingen range, da den kun er angivet i Gautschi et al.) og 29,9 % (15-51).

Selpercatinibs værdi overfor platinbaseret kemoterapi ift. den samlede overlevelse kan ikke kategoriseres pga. manglende komparativt datagrundlag. Fagudvalget vurderer, at overlevelsen ved selpercatinib er længere end ved platinbaseret kemoterapi i patienter uden RET-forandring, men patienter med RET-forandring har formodentlig en bedre prognose end patienter uden. Effekten af selpercatinib i denne patientgruppe kan ikke entydigt skelnes fra effekten af platinbaseret kemoterapi på det nuværende datagrundlag. Fagudvalget bemærker dog, at overlevelsesdata fra komparatorgruppen med RET-forandringer stammer fra førstelinjebehandling, hvorved komparatorestimatet sandsynligvis er overestimeret.

Livskvalitet

Ansøger har ikke opgjort data for effektmålet, som efterspurgt i protokollen. For selpercatinib er der i stedet indsendt en opgørelse over, hvor mange patienter der oplever enten en stigning eller et fald på minimum 10 point på EORTC QLQ-C30 '*global health scale*' [redacted]. Ansøger har ikke indsendt data for de resterende patienter, og det er uvist, om de oplevede mindre stigninger, ingen ændringer eller mindre fald i livskvaliteten.

Kun ét studie på tværs af de tre komparatorgrupper rapporterer data for livskvalitet ved EORTC QLQ-C30 (KEYNOTE-189 [45]). Her sås ingen klinisk relevante ændringer i forhold til baseline. Efter 12 uger var global health scoren på -2,6 (-5,8; 0,5) i forhold til baseline, og efter 21 uger var scoren -4,0 point (-7,7; 0·3)

Værdien ift. livskvalitet kan ikke kategoriseres. Fagudvalget vurderer, at data indikerer, at patienternes livskvalitet øges under behandling med selpercatinib. Fagudvalget lægger særlig vægt på, at omkring halvdelen af patienterne oplevede en klinisk relevant stigning på den overordnede '*global health scale*', hvilket sjældent observeres ved studier af platinbaseret kemoterapi. Fagudvalget bemærker dog, at det er meget vanskeligt at vurdere livskvalitetsdata ud fra ikke-kontrollerede studier.

Objektiv responsrate (ORR)

Objektive responsrater for selpercatinib og komparatorgrupperne er vist i figuren nedenfor.

Figur 5-4: Samlede estimater for selpercatinib og platinbaseret kemoterapi i forhold til objektiv responsrate. De vandrette streger viser punktestimaterne, fejllinjerne viser 95 % konfidensinterval omkring estimatet for selpercatinib, og prikkerne viser estimaterne fra de enkelte studier, der indgår i komparatorgrupperne.

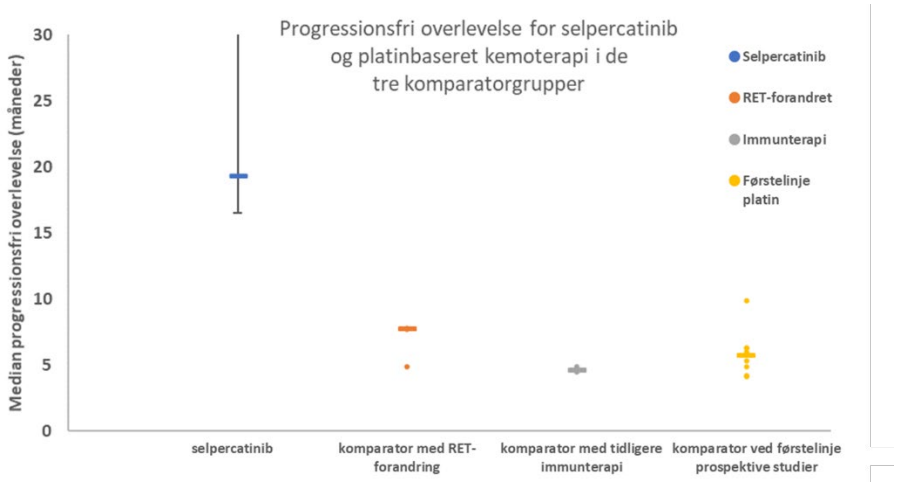
Ved selpercatinib havde 124 ud af 218 patienter (56,9 %) et objektivt respons. Af disse havde 9 patienter (4,1 %) et komplet respons og 115 patienter (52,8 %) et partielt respons. Af de resterende patienter havde 60 (27,5 %) stabil sygdom.

ORR i subgruppen af patienter fra LIBRETTO-001, der tidligere var behandlet med både platinbaseret kemoterapi og checkpoint inhibitor-immunterapi, var 67,2 % (53,7; 79), hvilket indikerer, at ORR for selpercatinib ikke er nævneværdigt påvirket af, om patienterne har modtaget begge behandlinger eller udelukkende platinbaseret kemoterapi.

Den samlede ORR for selpercatinib var ikke markant forskellig fra kemoterapi i komparatorgrupperne, selvom der var store udsving mellem de enkelte studier. Her var median ORR henholdsvis 51 % (50-54), 42,9 % (22,8-66,7) og 31,8 % (19,4-51) for RET-forandring, tidligere immunterapi og førstelinje. Der var enkelte tilfælde af komplette respondere på tværs af studierne, men generelt var dette sjældent (0-3 %).

Selpercatinibs værdi overfor platinbaseret kemoterapi ift. ORR kan ikke kategoriseres. Fagudvalget vurderer, at responsraterne er høje både for selpercatinib og platinbaseret kemoterapi, men ud fra det forhåndenværende data er der ikke klinisk relevant forskel (defineret som en forskel på 15 %-point) på ORR mellem selpercatinib og platin-baseret kemoterapi hos patienter med RET-forandret NSCLC. Fagudvalget bemærker, at ORR kan være overestimeret i komparatorgruppen, da patienterne her ikke var tidligere behandlet, og data fra en lille subgruppe (48 patienter) fra LIBRETTO-001 indikerer, at ORR er endnu højere i patienter, der ikke tidligere er behandlet med platinbaseret kemoterapi (85 %).

Progressionsfri overlevelse (PFS)
Figuren viser en oversigt over median PFS for selpercatinib samt medianen af studieestimaterne for de tre komparatorgrupper.



Figur 5-5: Samlede estimater for selpercatinib og platinbaseret kemoterapi i forhold til median progressionsfri overlevelse. De vandrette streger viser medianerne, fejllinjerne viser 95 % konfidensinterval omkring medianen for selpercatinib, og prikkerne viser estimaterne fra de enkelte studier, der indgår i komparatorgrupperne.

Median PFS for selpercatinib var 19,3 måneder (16,5; ikke nået) med en median opfølgningstid på 13,6 måneder. For komparatorgrupperne var medianerne henholdsvis 7,7 måneder (4,9-7,8), 4,5 måneder (4,5-4,9) og 5,7 måneder (4,1-9,9) for grupperne, RET-forandring, tidligere immunterapi og førstelinje RCT.

Værdien af selpercatinib overfor platinbaseret kemoterapi ift. PFS kan ikke kategoriseres pga. manglende komparative data. Fagudvalget vurderer, at selpercatinib medfører en forlængelse af PFS på ca. 12 måneder, hvilket overstiger den fastsatte mindste klinisk relevante forskel (3 måneder), uagtet hvilken komparatorgruppe man sammenligner med.

Uønskede hændelser

Andelen af patienter, der oplever minimum én uønsket hændelse af grad 3-4
Samlet set oplevede 61,2 % minimum én uønsket hændelse af grad 3-4 ved behandling med selpercatinib. Tallet er baseret på den samlede sikkerhedspopulation med RET-forandret NSCLC.

Ved platinbaseret kemoterapi oplevede 66,8 % minimum én uønsket hændelse i KEYNOTE-189. De andre studier i komparatorgrupperne har ikke rapporteret samlede estimater for grad 3-4 uønskede hændelser.

Fagudvalget kan ikke vurdere, om der er forskelle mellem selpercatinib og platinbaseret kemoterapi, da andelen af grad 3-4 uønskede hændelser kan variere betragteligt mellem studier og patientpopulationer, bl.a. pga. forskelle i behandlingslængde.

Deskriptiv gennemgang af bivirkningsprofilerne
Specifikt for populationen med RET-forandret NSCLC oplevede 25 patienter behandlet med selpercatinib (7,2 %) uønskede hændelser, der medførte behandlingsstop. Ingen patienter døde, som følge af en uønsket hændelse relateret til selpercatinib, mens 13 patienter (3,8 %) oplevede en uønsket hændelse, der førte til død. Bivirkningsprofilen for selpercatinib i øvrigt er beskrevet i afsnit 5.1.4.

De hyppigste bivirkninger ved platinbaseret kemoterapi er hæmatologiske bivirkninger, heriblandt febril neutropeni. Derudover er kvalme, træthed, nyrepåvirkning, neuropati og påvirkning af slimhinder hyppige. Fagudvalget vurderer, at disse bivirkninger kan være generende for patienterne og påvirke deres daglige funktionsniveau. Visse af disse bivirkninger, såsom påvirkning af nyrerne og neuropati, kan være livslange. Fagudvalget gør opmærksom på, at behandling med kemoterapi ofte gives i serier, hvorfor de fleste bivirkninger vil være begrænset til en kortere periode. Det gælder dog ikke for nyrepåvirkning, neuropati og påvirkning af slimhinder.

Samlet set kan selpercatinibs værdi ift. uønskede hændelser overfor platinbaseret kemoterapi ikke kategoriseres. Fagudvalget vurderer, at selpercatinib er mindre bivirkningstungt end platinbaseret kemoterapi, baseret på bivirkningsprofilerne for de to stoffer og fagudvalgets kliniske erfaring med platinbaseret kemoterapi.

CNS-progression
Tid til CNS-progression er et vigtigt effektmål, da CNS-metastaser er hyppigt forekommende ved RET-forandret NSCLC. Effektmålet er ikke angivet, som defineret i protokollen. I stedet har ansøger angivet responsvarigheden efter målbart respons i CNS-metastaser for en lille subgruppe af patienter (se afsnit 5.3.4). Ud af 23 patienter med målbare CNS-metastaser, responderede de 20 på selpercatinib. Den CNS-specifikke responsvarighed var 9,36 måneder (6,7; 12,1) ved en median opfølgningstid på 13 måneder.

Der er ikke rapporteret data for CNS-progression for platinbaseret kemoterapi. Det er fagudvalgets erfaring, at platinbaseret kemoterapi sjældent har effekt på CNS-metastaser.

Selpercatinibs værdi ift. CNS-progression kan ikke kategoriseres. Fagudvalget vurderer, at selpercatinib, modsat platinbaseret kemoterapi, er aktivt overfor CNS-metastaser, men tager forbehold for det sparsomme datagrundlag.

5.3.5 Fagudvalgets konklusion

Den samlede værdi af selpercatinib sammenlignet med platinbaseret kemoterapi til patienter med RET-forandret NSCLC, der er progredieret efter behandling med checkpoint inhibitor-immunterapi, kan ikke kategoriseres efter Medicinrådets metoder.

Fagudvalget er bekendt med, at der pågår et fase III randomiseret kliniske studie af selpercatinibs effekt overfor platinbaseret kemoterapi alene eller i kombination med pembrolizumab, som førstelinjebehandling af patienter med RET-forandret ikke-

planocellulær NSCLC (LIBRETTO-431/NCT04194944). Dette studie vil kunne bidrage med stærkere evidens for selpercatinibs effekt, men data herfra forventes tidligst i 2024.

Vurderingen på det nuværende datagrundlag vanskeliggøres af, at ingen af de tilgængelige studier af platinbaseret kemoterapi indeholder en population, der svarer til det kliniske spørgsmål. Fagudvalget har derfor sammenlignet data for selpercatinib med tre forskellige komparatorgrupper, hhv. registerstudier omhandlende patienter med RET-forandring, registerstudier omhandlende patienter, der modtog platinbaseret kemoterapi efter progression på checkpoint inhibitor-immunterapi og prospektive kliniske studier af førstelinje platinbaseret kemoterapi.

Baseret på det tilgængelige indirekte datagrundlag vurderer fagudvalget, at selpercatinib på nogle effektmål synes ligeværdigt med platinbaseret kemoterapi. Der er således ikke dokumenteret klinisk relevante forskelle på hverken OS eller ORR, når man sammenligner data for selpercatinib med registerstudierne, hvor patienterne har RET-forandring. På andre effektmål indikerer data, at selpercatinib er mere effektivt end platinbaseret kemoterapi, uanset hvilken komparatorgruppe der anvendes. Dette bygger på:

- Væsentlig længere median PFS ved selpercatinib.
- Selpercatinib er mindre bivirkningstung.
- Selpercatinib medfører tilsyneladende øget livskvalitet i en del patienter.
- Selpercatinib har effekt på CNS-metastaser.

5.4 Klinisk spørgsmål 4

Klinisk spørgsmål 4 var:

Hvilken værdi har selpercatinib sammenlignet med docetaxel eller pemetrexed for voksne med avanceret RET-forandret ikke-småcellet lungekræft, der er progredieret efter behandling med checkpoint inhibitor immunterapi og platinbaseret kemoterapi?

5.4.1 Litteratur

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

Ansøger har søgt litteratur med søgestrengene fra protokollen og har udvalgt i alt fire fuldtekstartikler (Tabel 5-13), der beskriver data fra to forskellige kliniske studier og to retrospektive analyser.

Sekretariatet har tilføjet syv fuldtekstartikler, der beskriver data fra yderligere tre kliniske studier (OAK, Checkmate 057 og KEYNOTE-010).

Tabel 5-13. Oversigt over studier og publikationer til besvarelse af klinisk spørgsmål 4

Publikationer	Klinisk forsøg	NCT-nummer	Population	Studietype, intervention og eventuel komparator	Median opfølgningstid for primært endepunkt
Drilon et al. 2020 [35] EPAR [27] og produktresume for selpercatinib [28]	LIBRETTO-001	NCT03157128	Subgruppe med RET-forandret NSCLC, hvoraf alle tidligere er behandlet med platinbaseret kemoterapi og halvdelen yderligere med check point inhibitor.	Ikke-kontrolleret, fase I/II. Selpercatinib.	13,9 måneder (PFS i største datasæt)
Garon et al. 2014 [53]	REVEL	NCT01168973	Patienter med stadium IV NSCLC, der tidligere er progredieret under eller efter behandling med platinbaseret kemoterapi. Subgruppe med patienter med ikke-planocellulær NSCLC. RET-status ukendt.	Fase III, RCT. Ramucirumab plus docetaxel overfor placebo plus docetaxel.	8,8 måneder (OS)
Rittmeyer et al. 2017 [54] Bordoni et al. 2018 [55]	OAK	NCT02008227	Patienter med stadium III-IV NSCLC, der tidligere er progredieret under eller efter behandling med platinbaseret kemoterapi. Subgruppe med patienter med ikke-planocellulær NSCLC. RET-status ukendt.	Fase III, RCT. Atezolizumab overfor docetaxel.	21 måneder (OS)

Publikationer	Klinisk forsøg	NCT-nummer	Population	Studietype, intervention og eventuel komparator	Median opfølgningstid for primært endepunkt
Borghaei et al. 2015 [56] Reck et al. 2018 [57]	Check-mate 057	NCT01673867	Patienter med stadium III-IV, ikke-planocellulær NSCLC, der tidligere er progredieret under eller efter behandling med platinbaseret kemoterapi. RET-status ukendt.	Fase III, RCT. Nivolumab overfor docetaxel.	13,2 måneder (OS)
Herbst et al. 2016 [58] Herbst et al 2020 [59] Barlesi et al. 2019 [60]	KEYNOTE-010	NCT01905657	Patienter med stadium III-IV NSCLC, både planocellulær og ikke-planocellulær histologi, der tidligere er progredieret under eller efter behandling med platinbaseret kemoterapi. RET-status ukendt.	Fase II/III, RCT. Pembrolizumab overfor docetaxel.	42,6 måneder (OS og PFS)
Shen et al. 2020 [36]	-	-	RET-forandret NSCLC behandlet med pemetrexed og/eller platinbaseret kemoterapi.	Observationelt studie. Platin i kombination med pemetrexed, som førstelinje behandling.	Ikke angivet
Tan et. al 2020 [37]	Retrospektivt, observationelt studie.		RET-forandret NSCLC, der har modtaget forskellige behandlingsregimer, bl.a. Pemetrexed-baseret kemoterapi.	Observationelt studie. Platin i kombination med pemetrexed, hovedsageligt som førstelinje - behandling.	20,3 måneder

Selpercatinib er undersøgt i ét klinisk studie (LIBRETTO-001), og data herfra er rapporteret i én fuldtekstartikel [35]. Desuden indeholder EPAR'en [27] og produktresumeet [28] for selpercatinib data fra LIBRETTO-001 ved et senere data cut-off med en større patientpopulation (marts 2020 overfor juni 2019).

LIBRETTO-001 er beskrevet under klinisk spørgsmål 1 (5.1.1), og den relevante population for dette kliniske spørgsmål er beskrevet under klinisk spørgsmål 3 (5.3.1). Populationen i LIBRETTO-001 er relativt tæt på populationen defineret i det kliniske spørgsmål, da alle patienter er behandlet med platinbaseret kemoterapi, og 54 % yderligere er behandlet med checkpoint inhibitor-immunterapi.

Ansøger har søgt efter egnede studier for docetaxel eller pemetrexed, der er de definerede komparatorer i Medicinrådets protokol (se Figur 3-2) [32].

Ansøger har ekskluderet de fleste søgeresultater, da ingen kliniske studier undersøger docetaxel i patienter med RET-forandret NSCLC, som tidligere er behandlet med platinbaseret kemoterapi og checkpoint inhibitor-immunterapi. Ansøger har dog fundet ét relevant klinisk studie (REVEL), som kan anvendes til at estimere effekten af docetaxel i patienter med ikke-planocellulær lungekræft, der tidligere er behandlet med platinbaseret kemoterapi [53].

REVEL var et randomiseret, dobbeltblindet fase III-studie, hvis primære formål var at undersøge effekten af ramucirumab i kombination med docetaxel overfor placebo plus docetaxel (75 mg/m²) i patienter med stadium IV NSCLC, der tidligere var progredieret under eller efter behandling med platinbaseret kemoterapi. Studiet indeholdt en subgruppe med ikke-planocellulær NSCLC (447 patienter i placebo plus docetaxel-armen), som er relevant i denne vurderingsrapport. Studiets primære endemål var OS, og PFS, ORR og uønskede hændelser indgik som sekundære endemål.

Ansøger har yderligere inkluderet to retrospektive, observationelle studier, Shen et al. [36] og Tan et al. [37]. Shen et. al og Tan et al. er beskrevet under klinisk spørgsmål 3 (afsnit 5.3.1). Medicinrådet ser bort fra disse to artikler til besvarelsen af klinisk spørgsmål 4, da der for størstedelen af patienternes vedkommende indgik platin i kemoterapiregimerne, hvorved effektestimaterne ikke er retvisende for en forventet effekt af pemetrexed eller docetaxel alene.

Sekretariatet har tilføjet de tre studier, OAK, Checkmate 057 og KEYNOTE-010. Disse studier er sammenlignelige med REVEL, og effektestimaterne fra docetaxelarmene i studierne kan medføre mere robuste effektestimater end REVEL alene.

OAK var et randomiseret, open-label fase III-studie, hvis formål var at undersøge effekten af atezolizumab overfor docetaxel (75 mg/m^2) til patienter, der tidligere var behandlet med platinbaseret kemoterapi. Studiet inkluderede både patienter med planocellulær og ikke-planocellulær NSCLC, men rapporterer data fra subpopulationen med ikke-planocellulær histologi (315 patienter i docetaxelarmen). Studiets primære effektmål var OS, og PFS, ORR, uønskede hændelser og livskvalitet indgik som sekundære effektmål. Bordoni et al. rapporterer data for livskvalitet [55], mens Rittmeyer et al. rapporterer data fra alle andre effektmål [54].

Checkmate 057 var et randomiseret fase III-studie, hvis formål var at undersøge effekten af nivolumab overfor docetaxel (75 mg/m^2) til patienter med ikke-planocellulær NSCLC, der tidligere var behandlet med platinbaseret kemoterapi. Studiet indeholdt 290 patienter i docetaxel-armen. Studiets primære effektmål var OS, og PFS, ORR, uønskede hændelser og livskvalitet indgik som sekundære effektmål. Reck et al. rapporterer data for livskvalitet [57], mens Borghaei et al. rapporterer de øvrige effektmål [56].

KEYNOTE-010 var et randomiseret, open-label fase II/III-studie, der undersøgte effekten af pembrolizumab i to forskellige doseringer overfor docetaxel (75 mg/m^2) til patienter, der tidligere var behandlet med platinbaseret kemoterapi. Studiet indeholdt 343 patienter i docetaxel-armen. Studiets primære effektmål var OS og PFS, og ORR, uønskede hændelser og livskvalitet var sekundære effektmål. Barlesi et al. rapporterer data for livskvalitet [60], mens Herbst et al. 2016 rapporterer data for de øvrige effektmål [58], og Herbst et al. 2020 rapporterer OS og PFS med længere opfølgningstid [59].

Fælles for alle studierne af docetaxel var, at patienterne ikke tidligere var behandlet med checkpoint inhibitor-immunterapi, hvilket kan medføre, at effekten af docetaxel overestimeres. Fagudvalget vurderer dog, at dette er det bedst tilgængelige datagrundlag til at estimere effekten af docetaxel i klinisk spørgsmål 4. Baselinekarakteristika for disse er oplistet nedenfor.

Tabel 5-14. Baselinekarakteristika

		LIBRETTO-001 Selpercatinib	REVEL Docetaxel***	OAK Docetaxel ***	Checkmate 057 Docetaxel	KEYNOTE-010 Docetaxel
Patientantal	Intervention	184* (218)	-	-	-	-
	Komparator	-	625	425	290	343
Median alder (range)		62 (23-81)	61 (25-86)	64 (34-85)	64 (21-85)	62 (56-69)
Køn, kvinder (%)		105 (57 %)	210 (34 %)	166 (39 %)	132 (42 %)	134 (39 %)
ECOG performance status	0	66 (36 %)	199 (32 %)	160 (38 %)	95 (33 %)	116 (34 %)
	1	114 (62 %)	425 (68 %)	265 (62 %)	193 (67 %)	224 (65 %)
	≥2	4 (2 %)	0 (0 %)	0 (0 %)	0 (0 %)	2 (1 %)
Tumorhistologi	Planocellulær	1 % **	171 (27,5 %)	110 (26 %)	0 (0 %)	66 (19 %)
	Ikke-planocellulær	86 % **	447 (71,5 %)	315 (74 %)	290 (100 %)	240 (70 %)
	Large-cell carcinoma	2 % **	0 (0 %)	0 (0 %)	0 (0 %)	0 (0 %)

		LIBRETTO-001 Selpercatinib	REVEL Docetaxel***	OAK Docetaxel ***	Checkmate 057 Docetaxel	KEYNOTE-010 Docetaxel
	Ikke specificeret	11 % **	7 (1 %)	0 (0 %)	0 (0 %)	37 (11 %)
Sygdomsstadium	III	10 (5,4 %)	0 (0 %)	Ikke angivet	24 (8 %)	Ikke angivet
	IV	170 (92 %)	625 (100 %)	Ikke angivet	266 (92 %)	Ikke angivet
Fjernmetastaser (%)		179 (97 %)	625 (100 %)	Ikke angivet	Ikke angivet	Ikke angivet
Hjernemetastaser		60 (33 %)	Ikke angivet	62 (15 %)	12 %	48 (14 %)
Rygehistorik	Aldrig	125 (68 %)	141 (23 %)	72 (17 %)	60 (21 %)	67 (20 %)
	Tidligere eller nuværende	59 (32 %)	484 (77 %)	353 (83 %)	227 (78 %)	269 (78 %)
	Ukendt	0 (0 %)	1 (< 1 %)	0 (0 %)	3 (1 %)	7 (2 %)
Tidligere behandlinger	Platinbaseret kemoterapi	184 (100 %)	625 (100 %)	425 (100 %)	290 (100 %)	343 (100 %)
	Anti PD-L1 immunterapi	100 (54 %)	0 (0 %)	0 (0 %)	0 (0 %)	0 (0 %)

		LIBRETTO-001 Selpercatinib	REVEL Docetaxel***	OAK Docetaxel ***	Checkmate 057 Docetaxel	KEYNOTE-010 Docetaxel
	Tyrosinkinase-hæmmer	67 (36 %)	14 (2 %)	Ikke angivet	26 (9 %)	Ikke angivet
	Taxaner	0 (0 %)	149 (24 %)	Ikke angivet	0 (0 %)	Ikke angivet
Bedste respons på seneste behandlingslinje	Respons eller sygdomskontrol	87 (47 %)	417 (67 %)	Ikke angivet	164 (56 %)	Ikke angivet
	Progressiv sygdom	55 (30 %)	182 (29 %)	Ikke angivet	116 (40 %)	Ikke angivet
	Ukendt	42 (23 %)	26 (4 %)	Ikke angivet	10 (3 %)	Ikke angivet

* Baselinekarakteristika for patienterne i LIBRETTO-001 er fra analysesættet ved data cut off i december 2019, som er publiceret i EPAR. Der er ikke publiceret baselinekarakteristika for populationen ved data cut-off i marts 2020, hvor 218 patienter var inkluderet. ** Tumorhistologier er ikke opgivet for datasættet med 184 patienter, men kun for de 105 patienter i det primære analysesæt i Drilon et al. [35].*** Baselinekarakteristika er kun tilgængelige for den samlede population, hvoraf ca 70-75 % havde ikke-planocellulær NSCLC.

På de fleste punkter er populationerne i LIBRETTO-001 og komparatorstudierne sammenlignelige. Populationerne adskiller sig dog på visse punkter:

- Væsentlig flere patienter i LIBRETTO-001 har aldrig røget (68 % overfor 17-23 %).
- LIBRETTO-001 indeholdt væsentlig flere kvinder (57 %) end studierne af docetaxel (34-42 %).
- Begge populationer havde modtaget flere tidligere behandlingslinjer udover platinbaseret kemoterapi. I LIBRETTO-001 var halvdelen tidligere behandlet med PD-L1 targeteret antistof og en tredjedel med multikinasehæmmer, hvorimod ingen patienter var behandlet med checkpoint inhibitor-immunterapi og kun et fåtal med tyrosinkinasehæmmere i docetaxelstudierne.
- En væsentlig større andel af patienterne havde CNS-metastaser i LIBRETTO-001 end i komparatorstudierne, hvilket korrelerer med en dårligere prognose.

5.4.2 Databehandling og analyse

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

Ansøger har indsendt data fra de ovennævnte studier for effektmålene, OS, PFS, ORR og uønskede hændelser, hvorimod ansøger kun har indsendt data for livskvalitet for selpercatinib. Pga. forskellene mellem studierne har ansøger ikke lavet en statistisk sammenligning, men foretager i stedet en deskriptiv sammenligning af data fra de enkelte studier.

Medicinrådet er enige i ansøgers tilgang. Manglen af kontrolarm i LIBRETTO-001 og studieforskellene medfører, at der ikke kan laves en meningsfuld statistisk sammenligning. Fagudvalget udfører derfor en deskriptiv sammenligning af selpercatinib med docetaxel.

Datagrundlaget for selpercatinib er vurderet i flere detaljer under klinisk spørgsmål 3.

5.4.3 Evidensens kvalitet

Da vurderingen af selpercatinib er baseret på en deskriptiv sammenligning med docetaxel, kan Medicinrådet ikke anvende GRADE til at vurdere kvaliteten af evidensen.

Forskellene i studiepopulationerne samt manglen på kontrolarm medfører dog, at Medicinrådet vurderer evidensens kvalitet som meget lav. Derudover vurderer Medicinrådet, at effekten af komparatoren er meget usikker, da populationen i docetaxelstudierne adskiller sig fra den forventede population i dansk klinisk praksis.

5.4.4 Effektestimater og kategorier

I tabellen herunder fremgår effektestimaterne fra LIBRETTO-001 og de samlede kontrolestimater fremkommet ved at tage medianen af effektestimaterne fra de enkelte studier af docetaxel. Effektmålene fra de enkelte studier i komparatorgrupperne fremgår i Tabel 11-2 i bilag 2. Skemaet indeholder ikke nogen estimater af absolutte eller relative

forskelle mellem selpercatinib og docetaxel, da evidensen ikke muliggør sådanne sammenligninger. Den aggregerede værdi **kan derfor ikke kategoriseres** for nogen af effektmålene.

Tabel 5-15. Resultater for klinisk spørgsmål 4

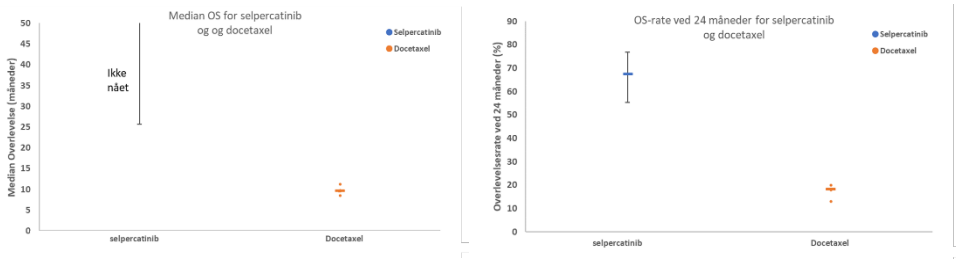
Effektmål	Målenhed (MKRF)	Vigtighed	Selpercatinib (LIBRETTO-001)	Docetaxel - samlet kontrol Median (range)
			n = 218 / 345*/ 23**	4 studier, n = 290 / 625
Samlet overlevelse (OS)	Median OS (3 måneder)	Kritisk	Ikke nået (25,7; ikke nået)	9,6 måneder (8,4-11,2)
	OS-rate ved 24 måneder (5 %-point)		67,3 % (55,4; 76,7)	16,5 % (13-20)
Livskvalitet	EORTC-QLQ-C30. Gennemsnitlig ændring i post-basislinje relativt til basislinjen (10 point)	Kritisk	Ikke opgivet som efterspurgt i protokollen	-2,6 (kun 1 studie)
Objektiv responsrate (ORR)	Andel, der opnår komplet eller partielt respons (15 %-point)	Vigtig	56,9 % (50,0; 63,6)	12,5 % (9,3-14,5)
Progressionsfri overlevelse (PFS)	Median PFS (3 måneder)	Vigtig	19,3 måneder (16,5; ikke nået)	4,1 måneder (3,7-4,2)
Uønskede hændelser	Andel, der oplever en eller flere uønskede hændelser af grad 3-4 (MKRF: 5 %-point)	Vigtig	61,2 %*	67 % (54-71)
	Deskriptiv gennemgang		Se gennemgang	Se gennemgang
CNS-progression	Median tid til CNS-progression (3 måneder)	Vigtig	9,4 måneder (6,7; 12,1)**	Ikke angivet
Konklusion				

Samlet kategori for lægemidlets værdi	Kan ikke kategoriseres. Fagudvalget vurderer, at data indikerer, at selpercatinib er mere effektivt og mindre bivirkningstungt end docetaxel.
Kvalitet af den samlede evidens	Meget lav

* Data stammer fra EPAR, hvilket inkluderer 345 patienter med RET-forandret NSCLC, der alle er behandlet med minimum én dosis selpercatinib (sikkerhedspopulation). ** LIBRETTO-001 indeholder 23 patienter med målbare CNS-metastaser ved baseline. Resultatet for effektmålet er angivet som responsvarighed for CNS-metastaser i stedet for tid til CNS-progression.

Samlet overlevelse (OS)
Patienterne behandlet med selpercatinib havde en median overlevelse, der ikke var nået (25,7 måneder; ikke nået) og en 24-måneders OS-rate på 67,3 % (55,4; 76,7). Estimaterne er dog meget usikre, da 81 % af patienterne er censurerede i analysen.

For docetaxel var medianoverlevelsen 9,6 måneder (8,4-11,2) i den samlede kontrolgruppe, og OS-raten ved 24 måneder var ca. 16,5 % (13-20).



Figur 5-6: Samlede estimater for selpercatinib og docetaxel i forhold til median overlevelse (venstre) og OS-raten ved 24 måneder (højre). De vandrette streger viser punktestimaterne for medianerne/OS-raterne, fejllinjerne viser 95 % konfidensinterval omkring medianen for selpercatinib, og prikkerne viser estimaterne fra de enkelte studier, der indgår i komparatorgruppen.

Værdien af selpercatinib overfor docetaxel ift. OS kan ikke kategoriseres. Fagudvalget vurderer, at selpercatinib medfører en væsentlig længere overlevelse end docetaxel, hvilket tydeliggøres af, at den nedre grænse for konfidensintervallet omkring median OS for selpercatinib er væsentlig højere end den øvre grænse for estimatet omkring median OS for docetaxel. Fagudvalget bemærker dog, at patienter med RET-forandring samlet set har en forbedret prognose, og derved kan det ikke konkluderes, om forskellene mellem grupperne hovedsageligt skyldes behandlingen eller den prognostiske effekt af RET-status.

Livskvalitet
Ansøger har ikke opgjort data for effektmålet, som efterspurgt i protokollen. For selpercatinib er der i stedet indsendt en opgørelse over, hvor mange patienter, der oplever enten en stigning eller et fald på minimum 10 point på EORTC QLQ-C30 '*global health scale*' [redacted]. Ansøger har ikke indsendt data for de resterende patienter, og det er uvist, om de oplevede mindre stigninger, ingen ændringer eller mindre fald i livskvaliteten.

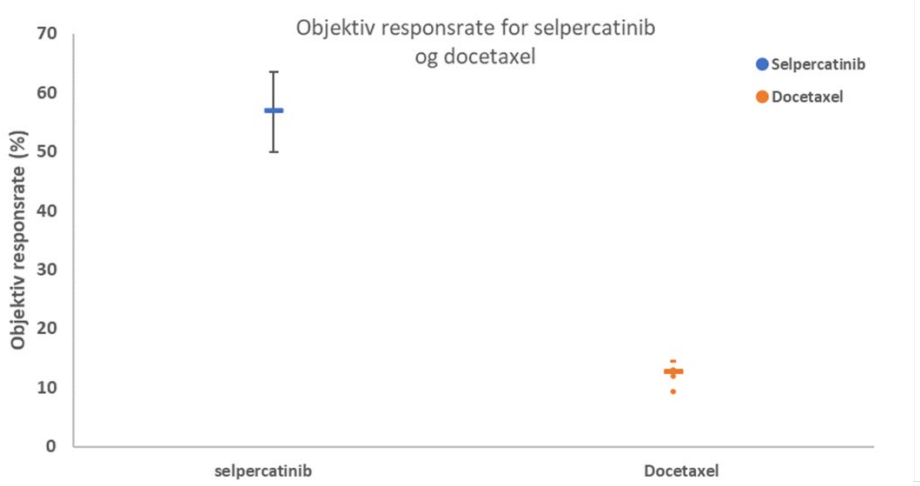
Livskvalitet ved behandling med docetaxel er opgjort med EORTC QLC-C30 i to af komparatorstudierne (OAK [55] og KEYNOTE-010 [60]). I KEYNOTE-010 opgøres data på samme måde som for selpercatinib, hvorved data herfra er mest sammenlignelige. Ved docetaxelbehandling oplevede 25 % af patienterne en forbedring (minimum 10 point), og

33,4 % havde oplevet en forværring (minimum 10 point). Samlet set oplevede patienterne et fald på 2,6 point på '*global health scale*'.

Værdien ift. livskvalitet kan ikke kategoriseres. Fagudvalget vurderer, at flere patienter oplever en stigning i livskvalitet ved behandling med selpercatinib end ved behandling med docetaxel, og at selpercatinib overordnet set påvirker livskvaliteten i positiv retning. Fagudvalget bemærker dog, at det er meget vanskeligt at vurdere livskvalitetsdata ud fra ikke-kontrollerede studier.

Objektiv responsrate (ORR)
Ved selpercatinib havde 124 ud af 218 patienter (56,9 %) et objektivt respons. Af disse havde 9 patienter (4,1 %) et komplet respons og 115 patienter (52,8 %) et partielt respons. Af de resterende patienter havde 60 (27,5 %) stabil sygdom.

Ved docetaxel havde 12,5 % (9,3-14,5) et objektivt respons i den samlede kontrolgruppe. Komplette respondere var meget sjældne i docetaxelstudierne (I alt 4 ud af 1683 patienter).

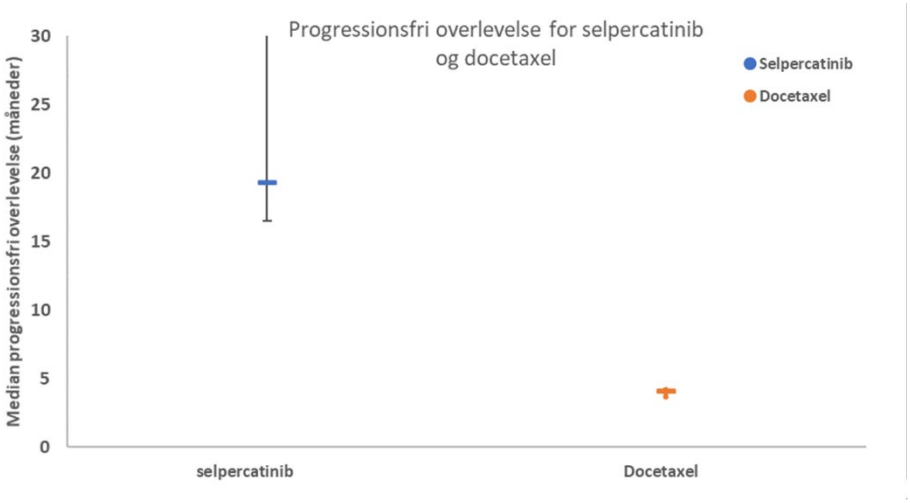


Figur 5-7: Samlede estimater for selpercatinib og docetaxel i forhold til objektiv responsrate. De vandrette streger viser punktestimaterne, fejllinjerne viser 95 % konfidensinterval omkring estimatet for selpercatinib, og prikkerne viser estimaterne fra de enkelte studier, der indgår i komparatorgruppen.

Værdien af selpercatinib overfor docetaxel ift. ORR kan ikke kategoriseres. Fagudvalget vurderer, at ORR er væsentlig højere ved selpercatinib end ved docetaxel, og at forskellene klart overstiger den mindste klinisk relevante forskel (15 %-point).

Progressionsfri overlevelse (PFS)
Median PFS for selpercatinib var 19,3 måneder (16,5; ikke nået) ved en median opfølgningstid på 13,6 måneder.

For docetaxel var median PFS 4,1 måneder (3,7-4,2).



Figur 5-8: Samlede estimater for selpercatinib og docetaxel i forhold til median progressionsfri overlevelse. De vandrette streger viser medianerne, fejllinjerne viser 95 % konfidensinterval omkring medianen for selpercatinib, og prikkerne viser estimaterne fra de enkelte studier, der indgår i komparatorgruppen.

Værdien af selpercatinib overfor docetaxel ift. PFS kan ikke kategoriseres. Fagudvalget vurderer, at selpercatinib medfører en forlængelse af PFS på ca. 12 måneder, hvilket overstiger den fastsatte mindste klinisk relevante forskel (3 måneder).

Uønskede hændelser

Andelen af patienter, der oplever minimum én uønsket hændelse af grad 3-4
Samlet set oplevede 61,2 % minimum én uønsket hændelse af grad 3-4 ved behandling med selpercatinib (se afsnit 5.3.4 for yderligere beskrivelser af uønskede hændelser).

For docetaxel oplevede 67 % (54-71) af patienterne minimum én uønsket hændelse af grad 3-4.

Fagudvalget kan ikke vurdere, om der er forskelle mellem selpercatinib og docetaxel, da andelen af grad 3-4 uønskede hændelser kan variere betragteligt mellem studier og patientpopulationer.

Deskriptiv gennemgang af bivirkningsprofilerne
Bivirkningsprofilen for selpercatinib ved NSCLC er beskrevet i afsnit 5.3.4.

For docetaxel oplevede 55 patienter (8,9 %) uønskede hændelser, der medførte behandlingsstop, mens 31 patienter (5,0 %) oplevede en uønsket hændelse, der førte til død. 9 (1 %) af disse blev vurderet at være relateret til docetaxel. De mest almindelige uønskede hændelser af grad 3-4 for docetaxel var neutropeni (38,8 %), leukopeni (11,8 %), træthed (10 %), febril neutropeni (9,5 %), åndenød (8 %), anæmi (5,7%), venøs tromboemboli (3,4 %) og hypertension (2,9 %). Det er fagudvalgets erfaring, at docetaxel samlet set giver anledning til en betydelig bivirkningspåvirkning og udtrætning af patienter med NSCLC.

Samlet set kan selpercatinibs værdi overfor docetaxel ift. uønskede hændelser ikke kategoriseres. Fagudvalget vurderer dog, at selpercatinib er mindre bivirkningstungt end docetaxel baseret på bivirkningsprofilerne for de to stoffer og fagudvalgets kliniske erfaring med docetaxel.

CNS-progression
Tid til CNS-progression er ikke angivet, som defineret i protokollen. I stedet har ansøger angivet responsvarigheden målbart respons i CNS-metastaser for en lille subgruppe af patienter (se afsnit 5.3.4). Ud af 23 patienter med målbare CNS-metastaser responderede de 20 på selpercatinib. Den CNS-specifikke responsvarighed var 9,36 måneder (6,7; 12,1) med en median opfølgningstid på 13 måneder.

Der er ikke rapporteret data for CNS-progression for docetaxel. Det er fagudvalgets erfaring, at docetaxel sjældent har effekt på CNS-metastaser.

Selpercatinibs værdi ift. CNS-progression kan ikke kategoriseres. Fagudvalget vurderer, at selpercatinib, modsat docetaxel, er aktivt overfor CNS-metastaser, men tager forbehold for det sparsomme datagrundlag.

5.4.5 Fagudvalgets konklusion

Den samlede værdi af selpercatinib sammenlignet med docetaxel til patienter med RET-forandret NSCLC, der er progredieret efter behandling med checkpoint inhibitor-immunterapi og platinbaseret kemoterapi, kan ikke kategoriseres efter Medicinrådets metoder.

Fagudvalget har sammenlignet effekten af selpercatinib med docetaxel ved at foretage en deskriptiv sammenligning af effektestimater fra et ukontrolleret studie af selpercatinib med effektestimater fra forskellige randomiserede studier, hvor docetaxel indgik som kontrolarm. Det har ikke været muligt at estimere docetaxels effekt i den definerede population, da patienterne i studierne ikke tidligere er behandlet med immunterapi. Derudover er RET-status ukendt hos patienterne behandlet med docetaxel. Disse to faktorer forventes at påvirke effektestimaterne i hver sin retning og medfører stor usikkerhed i vurderingen. På trods af dette vurderer fagudvalget, at data indikerer, at selpercatinib er en mere effektiv behandling end docetaxel på baggrund af:

- Væsentlig længere overlevelse ved selpercatinib både bedømt ud fra median overlevelse og OS-raten ved 24 måneder.
- Væsentlig længere median PFS ved selpercatinib.
- Objektive responsrater, der er ca. tre gange større ved selpercatinib end ved docetaxel.
- Selpercatinib er væsentlig mindre bivirkningstung end docetaxel.
- Selpercatinib medfører tilsyneladende øget livskvalitet i en del patienter.
- Selpercatinib har effekt på CNS-metastaser.

6. Andre overvejelser

Påvirkning af efterfølgende behandlingslinjer ved anbefaling af selpercatinib
En eventuel anbefaling af selpercatinib som standardbehandling kan medføre ændringer i de nuværende behandlingslinjer.

Ved jod-refraktær kræft i skjoldbruskkirtlen vil selpercatinib kunne indtræde som andenlinjebehandling i stedet for vandetanib eller sorafenib. Det er fagudvalgets erfaring, at der ikke er krydsresistens mellem multikinasehæmmere ved kræft i skjoldbruskkirtlen. Derfor vil selpercatinib rykke de nuværende behandlingsmuligheder til en senere behandlingslinje, men ikke nødvendigvis erstatte dem. Det samme vil gøre sig gældende for medullær kræft i skjoldbruskkirtlen, hvor en anbefaling af selpercatinib i praksis vil flytte cabozantinib til tredje behandlingslinje.

Ved NSCLC vil selpercatinib ligeledes udskyde den nuværende kemoterapi til en senere behandlingslinje. Fagudvalget forventer ikke, at selpercatinib vil påvirke effekten af eventuel efterfølgende kemoterapi. Fagudvalget forventer dog et frafald på ca. 30 % af patienterne mellem hver behandlingslinje, hvorved væsentlig færre patienter vil modtage kemoterapi, hvis det udskydes til en senere behandlingslinje.

Selpercatinibs effekt i patienter med planocellulær NSCLC
RET-forandringer optræder næsten udelukkende i ikke-planocellulær NSCLC, hvilket er tydeliggjort i både de anvendte registerstudier [17,36,37] og i LIBRETTO-001 [35]. Pga. sjældenheden af RET-forandring ved planocellulær NSCLC vurderer fagudvalget, at man ikke bør teste denne patientgruppe for RET-forandring som en del af standard klinisk praksis. Fagudvalget har ikke grund til at forvente, at effekten af selpercatinib ved planocellulær NSCLC afviger markant fra effekten ved ikke-planocellulær NSCLC.

7. Relation til behandlingsvejledning

Der findes ikke en relevant behandlingsvejledning for kræft i skjoldbruskkirtlen.

Den nuværende behandlingsvejledning for uhelbredelig ikke-småcellet lungekræft dækker kun førstelinjebehandling og omfatter ikke RET-forandret NCSLC.

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9. Sammensætning af fagudvalg og kontaktinformation til Medicinrådet

Medicinrådets fagudvalg vedrørende tværgående kræftlægemidler

Sammensætning af fagudvalg	
Formand	**Indstillet af**
Lars Henrik Jensen *Overlæge*	Lægevidenskabelige Selskaber
Medlemmer	**Udpeget af**
Morten Ladekarl *Professor, overlæge, dr.med.*	Region Nordjylland
Anni Ravnsbæk Jensen *Ledende overlæge*	Region Midtjylland
Pernille Wendtland *Overlæge*	Region Midtjylland
Karin Holmskov Hansen *Overlæge*	Region Syddanmark
Eckhard Schomerus *Overlæge (pædiatri)*	Region Syddanmark
Karen Julie Gehl *Professor, overlæge, dr.med.*	Region Sjælland
Martin Højgaard *Afdelingslæge*	Region Hovedstaden
Lisa Sengeløv *Ledende overlæge, dr.med.*	Region Hovedstaden
Troels K. Bergmann *Overlæge, klinisk lektor (speciallæge i klinisk farmakologi)*	Dansk selskab for klinisk farmakologi
Torben Steiniche *Professor, overlæge, dr.med.*	Dansk Patologiselskab
Karsten Nielsen *Overlæge, lektor, dr.med.*	Dansk Patologiselskab

Sammensætning af fagudvalg	
Simone Møller Hede *Patient/patientrepræsentant*	Danske Patienter
Diana Kristensen *Patient/patientrepræsentant*	Danske Patienter
Lars Bastholt *Overlæge*	Inviteret af formanden

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10. Versionslog

Versionslog		
Version	**Dato**	**Ændring**
1.0	1. september 2021	Godkendt af Medicinrådet

11. Bilag

Bilag 1. Effektestimater fra studier til klinisk spørgsmål 3

Tabel 11-1. Oversigt over effektestimater fra alle studier, der indgår i besvarelsen af klinisk spørgsmål 3

Studie	Median OS	OS-rate ved 24 måneder	Objektiv responsrate	Median PFS	Grad 3-4 uønskede hændelser
LIBRETTO-001 [27]	Ikke nået (25,7; ikke nået)	67,3 % (55,4; 76,7 %)	56,9 % (50,0; 63,6)	19,3 måneder (16,5; ikke nået)	61,2 %
Observationelle studier med kendt RET-forandring					
Gautschi et al. [17]	24,8 måneder (13,6; 32,3 måneder)	Ikke angivet	51 % (38,1; 63,4 %)	7,8 måneder (5,3; 10,2 måneder)	Ikke angivet
Shen et al. [36]	26,4 måneder	60 %	50 %	4,9 måneder	Ikke angivet
Tan et al. [37]	37,7 måneder	Ikke angivet	54 %	7,7 måneder	Ikke angivet
Median for RET-forandret [17,36,37]	26,4 måneder (range = 24,8-37,7 måneder)	60 % (kun ét studie angiver dette)	51 % (range = 50-54 %)	7,7 måneder (range = 4,9-7,8 måneder)	Ikke angivet

Studie	Median OS	OS-rate ved 24 måneder	Objektiv responsrate	Median PFS	Grad 3-4 uønskede hændelser
Observationelle studier af platinbaseret kemoterapi efter progression på checkpoint inhibitor-immunterapi					
Bersanelli et al. [38]	8,4 måneder (5,2; 11,6 måneder)	Ikke angivet	22,8 %	4,9 måneder (3,8; 6,0 måneder)	Ikke angivet
Metro et al. [39]	Ikke angivet	Ikke angivet	42,9 % (25,5; 67,0 %)	4,5 måneder (3,1; 6,5 måneder)	Ikke angivet
Park et al. [40]	10,9 måneder	Ikke angivet	66,7 %	4,5 måneder	Ikke angivet
Median for platin efter immunterapi [38–40]	9,65 måneder (range = 8,4-10,9 måneder)	Ikke angivet	42,9 % (range = 22,8-66,7 %)	4,5 måneder (range = 4,5-4,9 måneder)	Ikke angivet
Studier af platinbaseret kemoterapi som førstelinjebehandling					
KEYNOTE-021 [41]	21,1 måneder (14,9; 35,6 måneder)	48 %	33 % (22; 46 %)	9,9 måneder (6,2; 15,2 måneder)	Rapporterer kun frekvens for grad 3-4 bivirkninger (31 %).
KEYNOTE-189 [44]	10,7 måneder (8,7; 13,6 måneder)	29,9 %	19,4 %	4,9 måneder (4,7; 5,9 måneder)	66,8 %

Studie	Median OS	OS-rate ved 24 måneder	Objektiv responsrate	Median PFS	Grad 3-4 uønskede hændelser
Scagliotti et al. [46]	11,8 måneder (10,4; 13,2 måneder)	25 %	30,6 %	5,3 måneder (4,8; 5,7 måneder)	Rapporterer kun frekvens for grad 3-4 bivirkninger enkeltvis. Intet samlet estimat. Højeste enkeltstående var 15,1 %.
Kim et al. [47]	24,3 måneder (18,7; 29,9 måneder)	51 %	51 % (37; 66 %)	6,3 måneder (4,0; 8,6 måneder)	Rapporterer kun data for uønskede hændelser enkeltvis. Intet samlet estimat. Højeste enkeltstående var 33 %.
Manegold et al. [48]	10,9 måneder (6,8; 16,9 måneder)	Ikke angivet	39 % (23; 57 %)	6,3 måneder (2,9; 14,1 måneder)	Rapporterer kun data for uønskede hændelser enkeltvis. Intet samlet estimat. Højeste enkeltstående var 31 %.
Ohe et al. [49]	11,4 måneder	21,4 %	33,1 %	4,1 måneder	Rapporterer kun data for uønskede hændelser enkeltvis. Intet samlet estimat. Højeste enkeltstående var 72 %.

Studie	Median OS	OS-rate ved 24 måneder	Objektiv responsrate	Median PFS	Grad 3-4 uønskede hændelser
NAVotrial 01 [50]	10,2 måneder	15 %	24,0 %	4,2 måneder	Rapporterer kun data for uønskede hændelser enkeltvis. Intet samlet estimat. Højeste enkeltstående var 44 %
KEYNOTE-024 [51,52]	14,2 måneder (9,8; 19,0 måneder) [52]	34,5 % (26,7; 42,4 %) [52]	27,8 % (20,8; 35,7 %) [51]	6,0 måneder (4,2; 6,2 måneder) [51]	Rapporterer kun frekvens for grad 3-4 bivirkninger (53 %) [52]
Median for førstelinje platinbaseret kemoterapi [41–52]	11,6 måneder (range = 10,2-24,3 måneder)	29,9 % (range = 15-51 %)	31,8 % (range = 19,4-51 %)	5,7 måneder (range = 4,1-9,9 måneder)	66,8 % (kun ét studie angiver dette)

Bilag 2. Effektestimater fra studier til klinisk spørgsmål 4

Tabel 11-2. Oversigt over effektestimater fra alle studier, der indgår i besvarelsen af klinisk spørgsmål 4

Studie	Median OS	OS-rate ved 24 måneder	Objektiv responsrate	Median PFS	Grad 3-4 uønskede hændelser
LIBRETTO-001 [27]	Ikke nået (25,7; ikke nået)	67,3 % (55,4; 76,7 %)	56,9 % (50,0; 63,6)	19,3 måneder (16,5; ikke nået)	61,2 %
Studier af docetaxel					
Checkmate 057 [56]	9,4 måneder (8,1; 10,7)	13 %	12 % (9; 17)	4,2 måneder (3,5; 4,9)	67 %
KEYNOTE 010 [58,59]	8,4 måneder (7,6; 9,5) [59]	15 % [59]	9,3 % [58]	4,1 måneder (3,8; 4,5) [59]	Rapporterer kun frekvens for grad 3-4 bivirkninger (35 %) [58]
OAK [54]	11,2 måneder (9,3; 12,6)	20 %	13 %	4,0 måneder (3,3; 4,2)	54 %
REVEL [53]	9,7 måneder (8,5; 10,6)	18 %	14,5 % (11,4; 18,2)	3,7 måneder (2,8; 4,1)	71 %
Median for docetaxel	9,55 måneder (range = 8,4-11,2 måneder)	16,5 % (range = 13-20 %)	12,5 % (range = 9,3-14,5 %)	4,1 måneder (range = 3,7-4,2 måneder)	67 % (range = 54-71 %)

Application for the assessment of Retsevmo (selpercatinib) for treatment of RET-altered thyroid cancer or non-small cell lung cancer

Contents

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Overview of the pharmaceutical	
Proprietary name	Retsevmo®
Generic name	selpercatinib
Marketing authorization holder in Denmark	Eli Lilly Denmark
ATC code	L01EX22
Pharmacotherapeutic group	RET receptor tyrosine kinase inhibitor
Active substance(s)	selpercatinib
Pharmaceutical form(s)	Oral capsules
Mechanism of action	Selpercatinib is a first-in-class, orally available, highly selective small molecule inhibitor of the proto-oncogene rearranged during transfection (RET) tyrosine kinase receptor. Administration of selpercatinib inhibits cell growth in tumour cells that exhibit increased RET activity due to genomic alternations, i.e. fusion or mutation.
Dosage regimen	Oral 160 mg (2 x 80 mg capsules) BID if ≥ 50 kg and Oral 120 mg (1 x 80 mg + 1 x 40 mg capsules) BID if <50 kg.

Overview of the pharmaceutical	
Therapeutic indication relevant for assessment (as defined by the European Medicines Agency, EMA)	Retsevmo as monotherapy is indicated for the treatment of adults with: • advanced RET fusion-positive non-small cell lung cancer (NSCLC) who require systemic therapy following prior treatment with immunotherapy and/or platinum-based chemotherapy • advanced RET fusion-positive thyroid cancer who require systemic therapy following prior treatment with sorafenib and/or lenvatinib. Retsevmo as monotherapy is indicated for the treatment of adults and adolescents 12 years and older with advanced RET mutant medullary thyroid cancer (MTC) who require systemic therapy following prior treatment with cabozantinib and/or vandetanib.
Other approved therapeutic indications	NA
Will dispensing be restricted to hospitals?	Yes
Combination therapy and/or co-medication	NA
Packaging – types, sizes/number of units, and concentrations	60 hard capsule container of 80 mg or 40 mg
Orphan drug designation	NA

2. Abbreviations

EMA	European Medicines Agency
NA	Not applicable
MTC	medullary thyroid cancer
NSCLC	Non-small cell lung cancer
TC	Thyroid carcinoma
TEAEs	Treatment-emergent adverse events
ORR	Objective response rate
ALK	Anaplastic lymphoma kinase
EGFR	Epidermal growth factor receptor
RCT	Randomized controlled trials
DMC	Danish Medicines Agency
PK	pharmacokinetics
IRC	independent review committee
RECIST	Response Evaluation Criteria in Solid Tumors
ECOG	Eastern Cooperative Oncology Group
OS	overall survival
TTP	time to progression
PR	partial response
DCR	disease control rate
SD	stable disease
DTC	differentiated thyroid cancer
MKI	Multikinase inhibitors
VEGF	vascular endothelial growth factor
Tg	thyroglobulin
IQR	interquartile range
PFS	progression-free survival
NE	Not estimated
CI	Confidence interval
EORTC-QLQ-C30	European Organization for Research and Treatment of Cancer quality of life questionnaire.
HFSR	Hand-Foot Skin Reaction
HR	Hazard ratio
OR	Odds ratio
PAS	Primary analysis set
IAS	Integrated analysis set
SAS	Supplemental analysis set
MAIC	matching-adjusted indirect comparisons
SCAI	Salvage chemotherapy administered after immunotherapy

3. Summary

There are currently no targeted therapeutic options available for REarranged during Transfection (RET*)* fusion-positive non-small cell lung cancer (NSCLC) or *RET* fusion-positive thyroid cancer (TC) and *RET*-mutant medullary thyroid cancer (MTC) patients in the second line setting. For TC there are other options for second line – cabozantinib – this is not a selective RET-inhibitor but a multikinase inhibitor (MKI).
Selpercatinib has demonstrated clinical benefit by directly targeting *RET* as an underlying driver of disease amongst patients with *RET* fusion-positive NSCLC, *RET* fusion-positive TC and *RET*-mutant MTC. The magnitude, durability and speed of the response rate observed in the LIBRETTO-001 trial represents a therapeutic innovation, with the potential to prolong patient quality of life.

The efficacy of selpercatinib in *RET* fusion-positive NSCLC and TC has been demonstrated in LIBRETTO-001, a first in-human Phase I/II open-label trial [1]. Clinical efficacy and safety evidence from LIBRETTO-001 demonstrates that treatment with selpercatinib is well-tolerated and provides a clinically meaningful impact on the lives of patients with advanced *RET* fusion-positive NSCLC and TC. The high rates of durable response to selpercatinib treatment observed in LIBRETTO-001, paired with clinically meaningful PFS and OS, and self-reported improvements in patients' quality of life, support the case for the use of selpercatinib in patients with *RET* fusion-positive NSCLC and TC who require systemic therapy in Denmark.

In LIBRETTO-001, selpercatinib was well tolerated across all tumour types studied. The safety profile was characterised by recognisable and addressable toxicities. As a result, permanent discontinuation of selpercatinib due to TEAEs was infrequent, meaning patients could consistently benefit from the highly efficacious anti-tumour activity of selpercatinib.

A key limitation of the evidence base was that no randomised clinical trial evidence was available for selpercatinib with which to compare efficacy and safety to relevant comparators, with the single-arm LIBRETTO-001 trial representing the primary source of evidence for selpercatinib in *RET* fusion-positive NSCLC, *RET* fusion-positive TC and *RET*-mutant MTC. This necessitated the use of advanced ITC techniques to make comparisons to interventions relevant to the comparison with cabozantinib in *RET*-mutant MTC patients, where data were available. For the remaining comparators no clinical trial or observational evidence were available that allowed for the formal indirect comparisons, hence naïve narrative comparisons were applied.

Targeted therapy is now considered the preferred initial treatment for patients with actionable mutations and consequently molecular profiling of NSCLC and TC tumours is recommended by international consensus guidelines as part of routine evaluation in newly diagnosed patients [2].
Introduction of selpercatinib into routine clinical practice in Denmark will encourage accelerated and increased tumour testing for genetic abnormalities, including RET, enabling patients to access personalised treatment for their cancer. [3]
Overall, with clinically meaningful ORRs across lines of therapy and a well-tolerated, clinically manageable, safety profile, selpercatinib demonstrates a favourable benefit-risk profile for use in patients with *RET* fusion-positive NSCLC and TC who require systemic therapy and another important step towards the establishment of targeted treatment as standard of care, as previously seen with the introduction of other targeted therapies such as therapies targeting ALK and EGFR.

[redacted]

Selpercatinib is the first selective RET kinase inhibitor to be available in Denmark and would fulfil an unmet need for a highly effective, targeted treatment for patients with advanced NSCLC and TC whose cancers are driven by an oncogenic *RET* rearrangement.

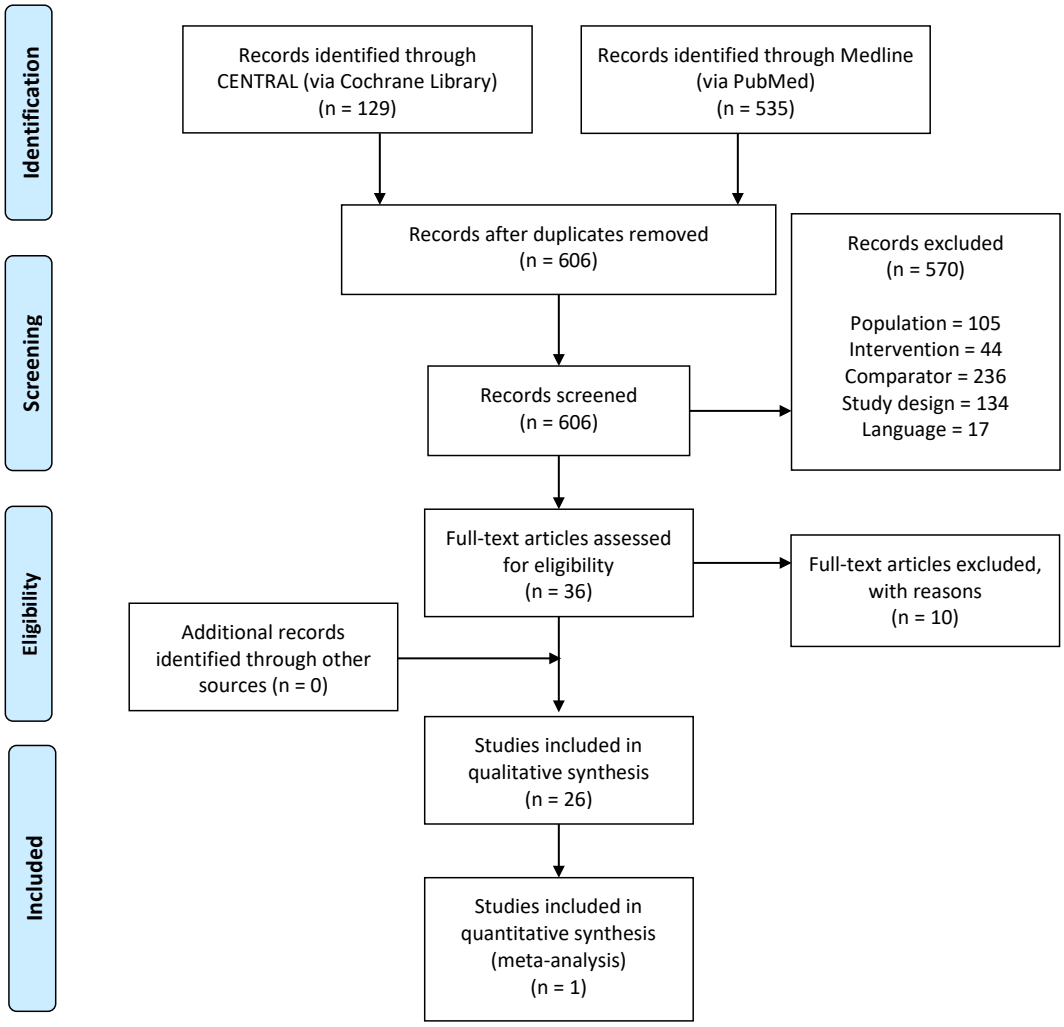
4. Literature search

The DMC requested a systematic literature review to identify evidence, that would allow for comparative analysis, including both RCTs and observational studies. For NSCLC the DMC protocol requests evidence for patients without RET alterations and for comparison versus platinum-based chemotherapy studies conducted in the first line setting. The following electronic databases were searched 08.02.2021 as by the search protocol provided by the DMC for randomized controlled trials (RCT) studies: MEDLINE via PubMed and CENTRAL via Cochrane Library, and for observational studies for platinum-based chemotherapy via PubMed. The search strategy was carried out with inclusion and exclusion criteria as defined in the DMC protocol and no date limit was applied to the electronic searches. Search strategy and results of the searches are documented by screenshots.

Primary screening was performed by two reviewers who independently reviewed each reference (title and abstract) identified by the literature search, applied study selection criteria, and decided on whether to include or exclude the reference at that stage. Secondary screening included obtaining the full-text articles for potentially relevant studies identified by primary screening of titles and abstracts. These were independently reviewed by two reviewers against each eligibility criterion.

The systematic database searches identified 664 records in total. A de-duplication step was performed to remove studies that overlapped across the databases; 58 of the studies were identified as duplicates and excluded. The remaining 606 studies were screened based on the information reported in their titles and/or abstracts. Of these, 570 records were excluded, and 36 records were included for full-text screening. The records were further assessed for eligibility for this review by full-text screening, which resulted in exclusion of 11 publications and inclusion of 26 publications. Eli Lilly furthermore consulted EMA's relevant scientific discussion, both with regards to the new medicine and the comparator for any references or data, but no additional records were identified through other sources. Thus, a total of 26 articles were included.

Figure 1 PRISMA diagram



4.1 Relevant studies

Table 1 Relevant studies included in the assessment for clinical question 1

Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)	Relevant for clinical question
Efficacy of Selpercatinib in RET-Altered Thyroid Cancers, Wirth et al., NEJM, 2020[4]	LIBRETTO-001	NCT03157128	Start date: May 9, 2017 Expected study completion date: March 2022	Clinical question 1
Sorafenib in radioactive iodine-refractory, locally advanced or metastatic differentiated thyroid cancer: a randomised, double-blind, phase 3 trial, Brose et al., Lancet, 2014[5]	DECISION	NCT00984482	Start date: October 15, 2009 Study completion date: August 30, 2017	Clinical question 1

Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)	Relevant for clinical question
Safety and tolerability of sorafenib in patients with radioiodine-refractory thyroid cancer, Worden et al., Endocr Relat Cancer, 2015[6]				
Phase II trial of sorafenib in metastatic thyroid cancer, Kloos et al., J Clin Oncol, 2009[7]	NA	NA	Start date: October 2004 Study completion date: June, 2007	Clinical question 1
Vandetanib in locally advanced or metastatic differentiated thyroid cancer: a randomised, double-blind, phase 2 trial, Leboulleux et al., Lancet Oncol, 2012 [8]	NA	NCT00537095	Start date: October 2004 Study completion date: June, 2007	Clinical question 1

Table 1 Relevant studies included in the assessment for clinical question 2

Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)	Relevant for clinical question
Efficacy of Selpercatinib in RET-Altered Thyroid Cancers, Wirth et al., NEJM, 2020[4]	LIBRETTO-001	NCT03157128	Start date: May 9, 2017 Expected study completion date: March 2022	Clinical question 2
Cabozantinib in Progressive Medullary Thyroid Cancer, Elisei et al., J Clin Oncol, 2013[9]	EXAM	NCT00704730	Start date: June 2008 Study completion date: October 2011	Clinical question 2
Correlative analyses of RET and RAS mutations in a phase 3 trial of cabozantinib in patients with progressive, metastatic medullary thyroid cancer, Sherman et al., Cancer, 2016[10]				
Overall survival analysis of EXAM, a phase III trial of cabozantinib in patients with radiographically progressive medullary thyroid carcinoma, Schlumberger et al., Ann Oncol, 2017[11]				

Table 2 Relevant studies included in the assessment for clinical question 3

Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)	Relevant for clinical question
Platinum based chemotherapy after previous immunotherapy				
Efficacy of Selpercatinib in RET Fusion-Positive Non-Small-Cell Lung Cancer, Drilon et al., The New England journal of medicine, 2020[1]	LIBRETTO-001	NCT03157128	Start date: May 9, 2017 Expected study completion date: March 2022	Clinical question 3
Increased Response Rates to Salvage Chemotherapy Administered after PD-1/PD-L1 Inhibitors in Patients with Non-Small Cell Lung Cancer, Park et al., Journal of thoracic oncology, 2018[12]	NA	NA Observational study	Start: October 2013 End: May 2017	Clinical question 3
Outcomes from salvage chemotherapy or pembrolizumab beyond progression with or without local ablative therapies for advanced non-small cell lung cancers with PD-L1 ≥50% who progress on first-line immunotherapy: real-world data from a European cohort, Metro et al., Journal of thoracic disease, 2019[13]	NA	NA Observational study	Start: January 2017 End: March 2019	Clinical question 3
Chemotherapy in non-small cell lung cancer patients after prior immunotherapy: The multicenter retrospective CLARITY study, Bersanelli et al., Lung cancer, 2020[14]	NA	NA Observational study	Start: November 2013 End: July 2019	Clinical question 3
Targeting RET in Patients With RET-Rearranged Lung Cancers: Results From the Global, Multicenter RET Registry; Gautschi et al., Journal Of Clinical Oncology, 2017[15]	NA	NA Register study	Start: June 2015 End: April 15 2016	Clinical question 3

Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)	Relevant for clinical question
1L platinum-based chemotherapy				

Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)	Relevant for clinical question
Long-Term Overall Survival From KEYNOTE-021 Cohort G: Pemetrexed and Carboplatin With or Without Pembrolizumab as First-Line Therapy for Advanced Nonsquamous NSCLC, Awad et al., Journal of thoracic oncology, 2021[16]	KEYNOTE-21	NCT02039674	Start date: February 21, 2014 End date: November 7, 2016	Clinical question 3
24-Month Overall Survival from KEYNOTE-021 Cohort G: Pemetrexed and Carboplatin with or without Pembrolizumab as First-Line Therapy for Advanced Nonsquamous Non-Small Cell Lung Cancer, Borghaei et al., Journal of thoracic oncology, 2019[17]				
Carboplatin and pemetrexed with or without pembrolizumab for advanced, non-squamous non-small-cell lung cancer: a randomised, phase 2 cohort of the open-label KEYNOTE-021 study, Langer et al., The Lancet Oncology, 2016[18]				
Updated Analysis From KEYNOTE-189: Pembrolizumab or Placebo Plus Pemetrexed and Platinum for Previously Untreated Metastatic Nonsquamous Non-Small-Cell Lung Cancer, Gadgeel et al., Journal of clinical oncology, 2020[19]	KEYNOTE-189	NCT02578680	Start date: January 15, 2016 End date: November 8, 2017	Clinical question 3
Patient-reported outcomes following pembrolizumab or placebo plus pemetrexed and platinum in patients with previously untreated, metastatic, non-squamous non-small-cell lung cancer (KEYNOTE-189): a multicentre, double-blind, randomised, placebo-controlled, phase 3 trial, Garassino et al., The Lancet, 2020[20]				
Oral vinorelbine plus cisplatin as first-line chemotherapy in nonsquamous non-small-cell lung cancer: final results of an International randomized phase II study (NAVotrial 01), Bennouna et al., Clinical lung cancer, 2014[21]	NA	EudraCT: 2009-012001-19	Start date: May 10, 2009 End date: October 13, 2012	Clinical question 3

Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)	Relevant for clinical question
Phase II study of carboplatin and pemetrexed in advanced non-squamous, non-small-cell lung cancer: Kyoto Thoracic Oncology Research Group Trial 0902, Kim et al., Cancer chemotherapy and pharmacology, 2012[22]	Kyoto Thoracic Oncology Research Group Trial 0902	NA	Start date: November 2009 End date: March 2011	Clinical question 3
Front-line treatment of advanced non-small-cell lung cancer with MTA (LY231514, pemetrexed disodium, ALIMTA) and cisplatin: a multicenter phase II trial, Manegold et al., Annals of oncology, 2000[23]	NA	NA	Start date: November 1997 End date: March 1998	Clinical question 3
Randomized phase III study of cisplatin plus irinotecan versus carboplatin plus paclitaxel, cisplatin plus gemcitabine, and cisplatin plus vinorelbine for advanced non-small-cell lung cancer: Four-Arm Cooperative Study in Japan, Ohe et al., Annals of oncology, 2007[24]	NA	NA	Start date: October 2000 End date: June 2002	Clinical question 3
Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naive patients with advanced-stage non-small-cell lung cancer, Scagliotti et al., Journal of clinical oncology, 2008[25]	NA	NA	Start date: July 2004 End date: December 2005	Clinical question 3

Table 3 Relevant studies included in the assessment for clinical question 4

Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)	Relevant for clinical question
Efficacy of Selpercatinib in RET Fusion-Positive Non-Small-Cell Lung Cancer, Drilon et al., The New England journal of medicine, 2020[1]	LIBRETTO-001	NCT03157128	Start date: May 9, 2017 Expected study completion date: March 2022	Clinical question 4
Association Between RET Fusions and Efficacy of Pemetrexed-based Chemotherapy for Patients With Advanced NSCLC in China: A Multicenter Retrospective Study, Shen et al., Clinical lung cancer, 2020[26]	NA	NA Retrospective analysis	Start date: 2011 End date: 2018	Clinical question 4

Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)	Relevant for clinical question
Molecular Characterization and Clinical Outcomes in RET-Rearranged NSCLC, Tan et al., Journal of thoracic oncology, 2020[27]	NA	NA Retrospective analysis	Start date: April 2014 End date: March 2020	Clinical question 4
Ramucirumab plus docetaxel versus placebo plus docetaxel for second-line treatment of stage IV non-small-cell lung cancer after disease progression on platinum-based therapy (REVEL): a multicentre, double-blind, randomised phase 3 trial, Garon et al., Lancet, 2014[28]	REVEL	NCT01168973	Start date: December 2010 End date: December 2013	Clinical question 4

4.2 Main characteristics of included studies

As the included studies diverge quite substantially due to the scope of the clinical questions and the specified search strings from the DMC protocol, the descriptions of the included studies are provided in section 5, and in section 8.2.

5. Clinical questions

5.1 Clinical question 1: What is the value of selpercatinib compared to sorafenib or vandetanib in adults with iodine refractory advanced RET-altered thyroid cancer previously progressed after treatment with a multikinase inhibitor?

Adults with advanced RET-altered iodine-refractory thyroid cancer, which require systemic treatment and who have previously progressed after treatment with a multikinase inhibitor.

5.1.1 Presentation of relevant studies

5.1.1.1 LIBRETTO-001

LIBRETTO-001 is a phase 1–2 clinical trial evaluating the safety, tolerability, pharmacokinetics (PK) and preliminary anti-tumour activity of selpercatinib in adolescent and adult patients with advanced solid tumours, including RET-fusion-positive solid tumours, medullary thyroid cancer (MTC) and other tumours with RET activation [4].

Selpercatinib was administered orally continuously, in 28-day cycles, until disease progression, death, unacceptable toxic effects, or withdrawal of consent. Patients who were enrolled in the phase 1 dose escalation portion of the trial received selpercatinib at doses ranging from 20 mg once daily to 240 mg twice daily. All patients who were enrolled in the phase 2 portion of the trial received the recommended dose of 160 mg twice daily [4].

The primary endpoint was objective response (a complete or partial response), as determined by an independent review committee of expert radiologists (IRC), according to the Response Evaluation Criteria in Solid Tumors (RECIST). Assessments were conducted at baseline and every eight weeks for a year, and every twelve weeks thereafter [4].

Eligible subjects were twelve years of age or older (in areas where this criterion was allowed by regulatory authorities; otherwise the patients were eighteen or older) and had received a diagnosis of advanced metastatic solid tumour. Patients were required to have a prospectively identified RET alteration (fusion or mutation) after they had reached dose level 2 (20mg of selpercatinib twice daily). Other inclusion criteria included an Eastern Cooperative Oncology Group (ECOG) performance status score of zero to two (on a scale from 0 to 5, with higher scores indicating greater disability), adequate organ function, and a corrected QT interval of 470 msec or less [4].

A total of 162 patients were treated across the three efficacy analysis cohorts. Of these patients, 55 had RET-mutant medullary thyroid cancer previously treated with vandetanib, cabozantinib, or both; 88 had RET-mutant medullary thyroid cancer not previously treated with vandetanib or cabozantinib; and 19 had RET fusion–positive previously treated thyroid cancer (TC) [4]. Only the 19 RET-positive TC patients are in scope of clinical question 1.
19 patients received a prior systemic therapy other than radioactive iodine and represented four different thyroid histological subtypes including: papillary (n=13), poorly differentiated (n=3), anaplastic (n=2), and Hürthle cell (n=1).

5.1.1.2 DECISION

DECISION is a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. Patients were randomised 1:1 to either sorafenib 400 mg or matching placebo, both given orally twice daily (taken 12 hours apart without food, ≥1 hour before or 2 hours after a meal). A total of 417 patients were randomized to sorafenib (n=207) or placebo (n=210)[5].

The primary endpoint was PFS, assessed every 8 weeks by central independent blinded review using modified RECIST. Secondary endpoints included overall survival (OS), time to progression (TTP), objective response rate (ORR; complete or partial response [PR]), disease control rate (DCR; complete or PR and stable disease [SD] ≥4 weeks [or ≥6 months via post-hoc analysis]), and duration of response[5].

Eligible study subjects were eighteen or older and had received a diagnosis of locally advanced or metastatic RAI-refractory differentiated thyroid cancer (DTC) (papillary, follicular [including Hürthle cell], and poorly differentiated) progressing within the past 14 months according to RECIST. Patients who had received prior targeted therapy, thalidomide, or chemotherapy for thyroid cancer were excluded; low dose chemotherapy for radio sensitization was allowed[5]. Therefore, the patients included in DECISION provides indirect evidence compared to the clinical question and PICO as only ≈ 3 % of patients had any prior systemic anti-cancer treatment and none had prior MKI-treatment. The patients included in DECISION are expected to have a better prognosis compared to patients included in LIBRETTO-001.

5.1.1.3 Kloos et al. 2009

Based on the pivotal role of Ras-Raf MAP-ERK signalling and vascular endothelial growth factor (VEGF) in papillary thyroid cancer (PTC), the purpose of this study was to conduct a phase II clinical trial of sorafenib targeting RAF and VEGF receptor kinases in PTC. Using a Simon minimax two-stage design, 16 or 25 chemotherapy-naïve metastatic PTC patients were to be enrolled in arm A (accessible tumour for biopsy). Arm B patients had other subtypes of thyroid carcinoma or prior chemotherapy, and did not require tumour biopsies [7].
Therefore, the patients in Kloos et al. provides indirect evidence compared to the clinical question and PICO as the patients included were not previously exposed to MKI-treatment.

The primary end point was the objective response rate. Secondary end points included response correlation with serum thyroglobulin (Tg); functional imaging; tumour genotype; and signalling inhibition in tumour biopsies [7].

Patients were required to be eighteen with adequate performance status and measurable disease. Chemotherapy or radiation therapy was not allowed within 4 weeks before entry. Iodine-131 (131I) therapy was not allowed within 24 weeks before entry (4 weeks if negative post-treatment scan). Leukocytes ≥ 3,000/L, absolute neutrophil count ≥ 1,500/L, platelets ≥ 100,000/ L, serum bilirubin, AST/ALT, and creatinine 1.5 ≥upper limit of normal were required [7].

5.1.1.4 Leboulleux et al. 2012

The objective of the study conducted by Leboulleux et al [8] was to assess efficacy of vandetanib in patients with locally advanced or metastatic DTC in a randomised phase 2 setting [8].

In this randomised, double-blind, phase 2 trial, adult patients were diagnosed with advanced or metastatic differentiated thyroid carcinoma (papillary, follicular, or poorly differentiated) at 16 European medical centres. Eligible patients were sequentially randomised in a 1:1 ratio with a standard computerised scheme to receive either vandetanib 300 mg per day (vandetanib group) or matched placebo (placebo group) [8].

The randomised phase of study treatment ended after patients had objective disease progression or 12 months of stable disease; patients were then given the option to either discontinue study treatment or begin open-label treatment with vandetanib 300 mg. Patients treated with vandetanib were allowed to remain on therapy at the end of the randomised phase if the investigator believed that they were obtaining a clinical benefit or until they received another anticancer treatment.
The primary analysis was carried out in the intention-to-treat population (vandetanib n=72, placebo n=73), and the safety population consisted of 73 patients in the vandetanib group and 72 patients in the placebo group because one patient randomly allocated placebo received vandetanib in error at visit 8 (table 3) and was therefore included in the vandetanib safety analysis. The median duration of follow-up was 18.9 months (IQR 14.8–21.5) for patients randomly allocated vandetanib and 19.5 months (15.1–21.8) for patients in the placebo group.

Response was assessed with RECIST at baseline and then every 12 weeks until progression. The primary endpoint was progression-free survival (PFS) in the intention-to-treat population based on investigator assessment [8]. For those patients who crossed over, PFS was censored at the date of last evaluable RECIST assessment before the first dose of open-label treatment. Secondary endpoints were the proportion of patients who achieved disease control (complete response, partial response, or stable disease at 6 months), the proportion of patients who achieved an objective response (complete response or partial response), overall survival, and safety and tolerability.

5.1.2 Results per study

5.1.2.1 LIBRETTO-001

For LIBRETTO-001 the following data cut-offs (DCO) are presented: 16th December 2019, which is used in the indirect comparisons and the health economic models, and a later DCO at 30th March 2020. In the following section data from the 30th March 2020 DCO will be presented in order to provide data with the longest follow-up, except for quality of life and safety estimates as only 16th December 2019 analyses are available at the time of submission.

Outcome	Data cut-off	Population
Median OS	30th March 2020	RET-fusion positive previously treated (n=19)
OS rate at 24 months	30th March 2020	RET-fusion positive previously treated (n=19)
Quality of life	NA	RET-fusion positive previously treated (n=19)
Objective response rate	30th March 2020	RET-fusion positive previously treated (n=19)
Median PFS	30th March 2020	RET-fusion positive previously treated (n=19)
Adverse events	16th December 2019	RET-mutant MTC safety population (n=299)

Measures of mortality

Median OS

Overall survival data was not mature in publication. At the 30th March 2020 data cut-off for previously treated *RET* fusion-positive thyroid cancer patients, the median OS was [redacted]).

OS rate at 24 months

At the 30th March 2020 data cut-off the OS rate at 24 months was 82.3 among the patients with RET fusion–positive previously treated TC estimated based on visual inspection of Kaplan-Meier curve, hence no confidence interval is available[redacted]. At 12 months, the OS rate was 94.7% [redacted]

Quality of life

Mean change from baseline in EORTC-QLQ-C30.

Not available

Objective response rate

Among the 19 patients with RET fusion–positive previously treated TC, the percentage with the IRC determined objective response was 78.9% (95% CI: 54.4-93.9) at the 30th March 2020 data cut-off.[29] The activity was seen across multiple histologic types of thyroid cancers, including papillary, poorly differentiated, Hürthle-cell, and anaplastic carcinomas.

Table 4 Objective Response and Duration of Response – 30 March 2020 data cut-off[29]

Primary Analysis Set IRC Assessment	
n	19
Objective Response (CR + PR)	
n (%)	78.9
95% CI	(54.4-93.9)
Complete response n (%)	2 (10.5)
Partial response n (%)	13 (68.4)
Duration of Response (months)*	
Median	18.4

95% CI	(7.6-NE)

*Median duration of follow-up was 20.27 months (25th, 75th percentile: 12.9, 25.4) for the first 19 patients.

Progression-free survival

Median PFS was not mature at the time of analysis.

For the previously treated *RET* fusion-positive thyroid cancer patients followed for at least 6 months from first dose, the median PFS by IRC was 20.07 months (95% CI: 10.8-NE) with a median follow-up of 16.5 months at the 30th March 2020 data cut-off.[29] At 1 year 68.6% (95% CI: 42.7-84.6) of the patients were progression-free.[29]

Adverse events

Proportion of patients with a grade 3-4 adverse events

The proportion of patients experiencing a grade 3-4 event was not reported specifically for RET-positive TC patients. Few patients with RET-positive TC were included in the study (n=19), and safety did not differ between patient with RET-positive TC and patients MTC RET-Mutant or the safety profile in a broader safety set of 531 patients treated with selpercatinib (with RET-altered MTC and of those with non-medullary thyroid cancer).

The most common grade 3 or 4 adverse events reported in 162 patients with RET-Mutant MTC or RET Fusion–Positive Thyroid Cancer were hypertension (in 21% of the patients), increased alanine aminotransferase level (in 11%), increased aspartate aminotransferase level (in 9%), hyponatremia (in 8%), and diarrhoea (in 6%). Five grade 5 adverse events (haemoptysis, post procedure haemorrhage, sepsis, cardiac arrest, and cardiac failure) (in 3% of the patients) were observed, all deemed by the investigators to be unrelated to selpercatinib. The adverse-event profile of selpercatinib in patients with RET-altered TC was broadly similar to the overall safety profile in all 531 patients treated with selpercatinib[4].

Summary tables of grade 3-4 adverse events for RET-Mutant MTC and/or RET Fusion–Positive Thyroid Cancer has been presented in clinical question 2 concerning RET-Mutant MTC as most of the patients are RET-Mutant MTC (Table 11 and Table 12).

Narrative assessment of adverse events

As above, please see the data presented in clinical question 2 concerning RET-Mutant MTC.

5.1.2.2 DECISION

Measures of mortality

Median OS

Median OS had not been reached at the time of primary analysis. A total of 150 (71.4%) patients receiving placebo crossed over to receive open-label sorafenib at progression, compromising the survival analysis.

OS rate at 24 months

The OS rate at 24 months is not reported in the publication by Brose et al. 2014, although the rate can be roughly estimated from the Kaplan-Meier curve to approximately 73%.

Quality of life

Mean change from baseline in EORTC-QLQ-C30

Not reported.

Objective response rate

Proportion of patients with complete and partial response

ORR was 12.2% (n=24/196) versus 0.5% (n=1/201) with sorafenib versus placebo, respectively (P < 0.0001), all PR.

Progression-free survival

Median PFS

The study met its primary endpoint, showing significant improvement in PFS for sorafenib compared with placebo (HR: 0.59; 95%CI: 0.45–0.76; P<0.0001); median 10.8 vs 5.8 months, respectively, with a 41% reduction in the risk of progression or death during the double-blind period.

Adverse events

Proportion of patients with a grade 3-4 adverse events

Worden et al. 2015 reports grade 3-4 treatment-emergent AEs for sorafenib in 133 patients (64.3%).[6] The most common grade 3 or 4 adverse events were Hand-foot skin reaction in 42 (20.3%) of the patients in the sorafenib arm versus 0 in the placebo arm; Hypertension in 20 (9.7%) of the patients in the sorafenib arm versus 5 (2.4%) in the placebo arm, and weight loss in 12 (5.8%) of the patients in the sorafenib arm versus 2 (1.0%) in the placebo.

Narrative assessment of adverse events

Median treatment duration was 10.6 months (range: 0.07–31.1) with sorafenib, and 6.5 months (range: 0.4–30.4) with placebo. Mean (standard deviation) daily dose was 651 (159) mg with sorafenib and 793 (26) mg with placebo. AEs occurred in 204 (98.6%) patients receiving sorafenib during the double-blind period and in 183 (87.6%) patients receiving placebo. AEs were predominantly grades 1 or 2 and tended to occur early in treatment. The most common AEs in the sorafenib arm were: hand–foot skin reaction (HFSR), diarrhoea, alopecia, rash/desquamation, fatigue, weight loss, and hypertension. Increase in serum TSH level >0.5mIU/L was reported in 33.3% (n=69/207) of patients, and hypocalcaemia in 18.8% (n=39/207) of patients in the sorafenib arm.

Dose interruptions, reductions, or withdrawals due to AEs occurred in 66.2% (n=137/207), 64.3% (n=133/207), and 18.8% (n=39/207) of patients, respectively, receiving sorafenib, and in 25.8% (n=54/209), 9.1% (n=19/209), and 3.8% (n=8/209) of patients, respectively, receiving placebo. HFSR was the most common reason for sorafenib dose interruptions, reductions, and withdrawals (26.6% [n=55/207], 33.8% [n=70/207], and 5.3% [n=11/207], respectively).

Serious AEs occurred in 77 (37.2%) patients receiving sorafenib and 55 (26.3%) patients receiving placebo. Serious AEs occurring in 2% of patients receiving sorafenib were secondary malignancy (4.3% [n=9/207]), dyspnoea (3.4% [n=7/207]), and pleural effusion (2.9% [n=6/207]); corresponding rates with placebo were 1.9% [n=4/209], 2.9% [n=6/209], and 1.9% [n=4/209], respectively. In the sorafenib group, secondary malignancies occurred in nine patients, including seven with squamous cell carcinomas (SCC) of the skin (one patient also had melanoma) and one each with acute myeloid leukaemia and bladder cancer. In the placebo group, there were single cases of bladder cancer, colon carcinoma, pulmonary carcinoid, and gastric cancer. There were 12 deaths by the end of the 30-day safety follow-up period in the sorafenib group and six in the placebo group; sorafenib: seven deaths due to underlying disease, two to unknown causes, and one each to lung infection, chronic obstructive lung disease, and myocardial infarction; placebo: four due to underlying disease and one each for pulmonary embolism and subdural haematoma. One death in each arm was attributed to study drug: myocardial infarction (sorafenib) and subdural haematoma (placebo).

5.1.2.3 Kloos et al. 2009

Measures of mortality

Median OS

For PTC chemotherapy-naïve patients (n = 33), median OS is 23 months with 95% CI of 18 to 34). For PTC patients with prior chemotherapy, median OS is 37.5 months with 95% CI of 4 to 42.5. Using log-rank test to compare the curves for OS, no statistically significant difference (P = .4787) was found in OS between PTC groups.

OS rate at 24 months

The OS rate at 24 months is not reported in the publication, although the rate can be roughly estimated from the Kaplan-Meier curve.

For PTC chemotherapy-naïve patients the OS rate at 24 months is approx. 45%

For PTC patients with prior chemotherapy the OS rate at 24 months is approx. 62%.

Quality of life

Mean change from baseline in EORTC-QLQ-C30

Not reported in the publication.

Objective response rate

Proportion of patients with complete and partial response

ORR was 15% (n=5/33) in the PTC chemotherapy-naïve patients and 13% (n=1/8) among PTC patients with prior chemotherapy, all were PR.

Progression-free survival

Median PFS

Kaplan-Meier analysis of progression-free survival (PFS) among all PTC patients (n = 41) who received at least one dose of sorafenib showed that PTC chemotherapy-naïve patients (n = 33), the median PFS is 16 months with 95% CI of 8 to 27.5. For PTC patients with prior chemotherapy (n = 8), the median PFS is 10 months with 95% CI of 4 to 28. Using log-rank test to compare the curves for PFS, no statistically significant difference (P = .8627) was found in PFS between PTC groups.

Adverse events

Proportion of patients with a grade 3-4 adverse events

The most common adverse events of Grade 3 were Hyponatremia in three (16%) of patients in Arm A and zero patients in Arm B; Fatigue in two (11%) of patients in Arm A and seven (19%) of patients in arm B; Hand-Foot skin reaction in two (11%) of patients in Arm A and two (5%) in Arm B; Hand or Foot pain in six (16%) of patients in Arm B and one (5%) of patients in Arm A; Arthralgia in five (14%) of patients in Arm B and one (5%) in Arm B.

Narrative assessment of adverse events

Sorafenib was generally well tolerated. However, a dose reduction was necessary to improve tolerance in 52% of patients. The most common (≥ 5% frequency) grade 3 AEs included hand or foot pain (12%), arthralgia (11%), fatigue (16%), HFSR (7%), musculoskeletal chest pain (7%), and asymptomatic hyponatremia (5%). Grade 4 AEs were rare and included pericardial effusion (2%) and reversible neutropenia (4%). The grade 5 event of sudden death (n=1) was unlikely attributed to sorafenib in a 68-year-old man with follicular variant of PTC who had metastasis to the lungs and paratracheal lymph nodes who died at 21 months on the study. The patient achieved PR on the study and had required dose reduction to 400 mg per day of sorafenib because of grade 3 HFSR. The patient who developed acute myeloid leukaemia had received 523 mCi ^{131}I and radiation to his neck mass. Aspergillus pneumonia occurred in a patient who had received multiple chemotherapies and was on 30 mg of oral prednisone daily for 3 years.

5.1.2.4 Leboulleux et al. 2012

At data cut-off on Dec 2, 2009, all patients had discontinued randomised treatment. The main reasons for discontinuation were disease progression, 12 months of stable disease, and adverse events. 28 (39%) of 72 patients were randomly allocated to vandetanib and 59 (81%) of 73 patients were randomly allocated to placebo received open-label treatment.

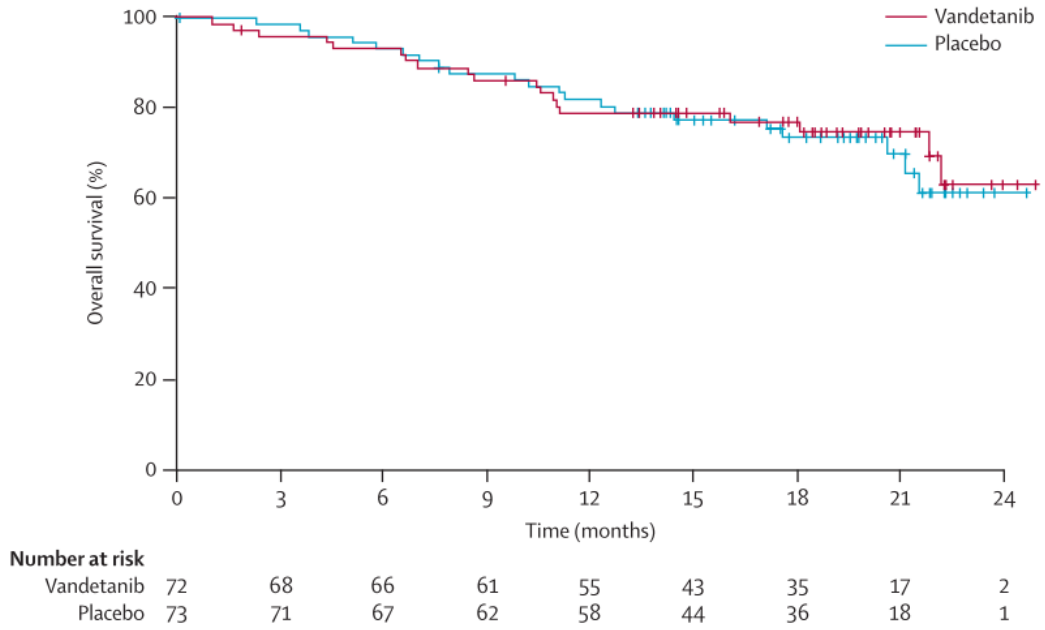
At data cut-off for the primary analysis, 113 (78%) patients had progressed (52 [72%] in the vandetanib group and 61 [84%] in the placebo group) and 40 (28%) had died (19 [26%] patients in the vandetanib group and 21 [29%] in the placebo group); the median duration of follow-up was 18.9 months (IQR 14.8–21.5) for patients randomly allocated to vandetanib and 19.5 months (15.1–21.8) for patients in the placebo group.

Measures of mortality

Median OS

At data cut-off, overall survival did not differ between treatment groups (HR: 0.92 [99.24% CI 0.4–2.15]; p=0.80), although data were immature.

Figure 2 Kaplan-Meier estimates of overall survival (investigator assessed)



OS rate at 24 months

The OS rate at 24 months is not reported in the publication by Leboulleux et al. 2012 but based on visual inspection of the Kaplan-Meier curves the OS rate can be estimated to approximately 60% for placebo and approximately 62% for vandetanib.

Quality of life

Mean change from baseline in EORTC-QLQ-C30

EORTC-QLQ-C30 was not reported in the study.

Objective response rate

In the investigator RECIST assessments, six (8%) of 72 patients in the vandetanib group and four (5%) of 73 in the placebo group had an objective response (odds ratio [OR] 1.57, 95% CI 0.42–5.81; p=0.501). All responses were partial and started during randomised treatment.

Independent central review confirmed only one partial response in a patient randomly allocated vandetanib. 41 (57%) of 72 patients in the vandetanib group and 31 (42%) of 73 in the placebo group achieved disease control at 6 months (OR: 1.79 [95% CI: 0.93–3.46]; p=0.082). This difference in favour of vandetanib reached statistical significance after independent central review: 40 (56%) patients in the vandetanib group versus 26 (36%) in the placebo group (OR: 2.26 [95% CI: 1.16–4.40]; p=0.017)

Progression-free survival

Median PFS

PFS for patients treated with vandetanib was longer than it was for patients treated with placebo (HR: 0.63 [60% CI: 0.54–0.74], one-sided p=0.008; 95% CI: 0.43–0.92, two-sided p=0.017). Median PFS was 11.1 months (95% CI: 7.7–14.0) in the vandetanib group and 5.9 months (4.0–8.9) in the placebo group. The improvement in PFS for patients treated with vandetanib was confirmed by independent central review (HR: 0.49 [95% CI: 0.32–0.74], two-sided p=0.0007).

For patients with papillary thyroid cancer, median PFS was 16.2 months (95% CI: 8.4–22.6) in the vandetanib group and 5.9 months (3.0–11.5) in the placebo group. For patients with follicular thyroid cancer or poorly differentiated carcinoma, median PFS was 7.7 months (3.3–11.1) in the vandetanib group and 5.6 months (2.8–10.6) in the placebo group.

Adverse events

Proportion of patients with a grade 3-4 adverse events

The incidence of grade 3 or worse adverse events was higher in the vandetanib group (39 [53%] of 73 patients) than in the placebo group (14 [19%] of 72 patients).

Narrative assessment of adverse events

During randomised treatment, the median duration of exposure was 192 days (IQR 89–343) for vandetanib and 175.5 days (85.5–336) for placebo. 16 (22%) patients who received vandetanib and two (3%) who received placebo had dose reductions to one tablet of vandetanib 300 mg or placebo every other day. Dose interruptions were required for 28 (38%) patients in the vandetanib group (median duration 18.5 days [IQR 12–21.5 days], maximum duration 51 days) and 11 (15%) in the placebo group (5 days [3–15 days], 22 days). All dose reductions were permanent. Common adverse events occurring with a more than 10% increased incidence in the vandetanib group compared with placebo group were diarrhoea, hypertension, QTc prolongation, rash, acne, and decreased appetite.

The incidence of grade 3 or worse adverse events was higher in the vandetanib group (39 [53%] of 73 patients) than in the placebo group (14 [19%] of 72 patients), with QTc prolongation and

diarrhoea being most common. Grade 3 or worse photosensitivity reactions occurred in three (4%) patients in the vandetanib group.
Adverse events leading to discontinuation of randomised treatment were higher in the vandetanib group (24 patients [33%]) than the placebo group (four patients [6%]). The most common adverse events leading to discontinuation of vandetanib were QTc prolongation (five patients [7%]) and diarrhoea (four patients [5%]). We noted no cardiac complications linked to the prolongation of the QTc. Serious adverse events resulting in death occurred in two patients in the vandetanib group (haemorrhage from skin metastases and pneumonia) and one patient in the placebo group (pneumonia). All three events were regarded as related to treatment by the masked study investigators.

5.1.3 Comparative analyses

For patients with advanced *RET* fusion-positive TC, sorafenib is the only comparator defined in the DMC protocol with clinical evidence for patients with DTC. The approved EMA label of vandetanib does not include treatment for DTC.

No head-to-head trials are available comparing selpercatinib to relevant comparators, with evidence for the efficacy and safety of selpercatinib provided by the single-arm LIBRETTO-001 trial. Therefore, in order to estimate the comparative effectiveness of selpercatinib versus relevant comparators, the evidence identified in the SLR was reviewed for the purposes of conducting an ITC.
No RCT data were identified in patients with *RET* fusion. It is unclear whether data for patients with TC is generalisable to *RET* fusion-positive TC. In the absence of data for *RET* fusion-positive TC patients, one trial was identified that included a placebo arm that could be considered a reasonable proxy for BSC: DECISION and Kloos et al. 2009.

DECISION was a Phase 3, double-blind, parallel-group RCTs. DECISION included patients with locally advanced or metastatic radioactive iodine-refractory DTC progressing within the previous 14 months according to RECIST. Patients received sorafenib 400 mg, orally BID, or a matching placebo. The placebo arm of this trial represents the best available data for the efficacy of BSC in patients with *RET* fusion-positive TC who have received prior TKIs, although DECISION did not report the *RET* fusion-positive proportion of patients or had previously been treated with multikinase inhibitors.

Kloos et al. 2009 divided the patients in treatment naïve and treatment experienced, but none of the patients had previously been treated with a multikinase inhibitor, as in line with the clinical question.
In summary, the evidence for the comparator regimes in RET fusion-positive TC are limited to proxy estimates based on non-RET populations and populations not previously treated with a multikinase inhibitor.
Table 5 provides an overview of the results reported in the identified studies for selpercatinib, sorafenib and vandetanib. The data reported for the outcomes defined in the protocol are very limited, but the results on ORR and PFS indicates better efficacy of selpercatinib compared to sorafenib and vandetanib, despite the more heavily pre-treated patient population in LIBRETTO-001. At 12 months 64% of patients treated with selpercatinib were still progression-free compared to median PFS for sorafenib and vandetanib of 10.8 and 11.1, respectively. Selpercatinib reported an ORR of 79% versus 12.2% and 8% for sorafenib and vandetanib, respectively.
MKIs have non-selective mechanisms of action and thus can be associated with off-target effects, As a results, they are associated with a significant toxicity profile that frequently leads to dose reductions and discontinuations, subjecting patients to considerable side effect profiles.[30, 31] For

patients who do not respond to, or do not tolerate treatment with MKIs, there are no further tolerable and effective treatment options for TC. Therefore, patients who discontinue these treatments due to side effects can only be treated palliatively with BSC. There is therefore an unmet need for tolerable and effective treatment alternatives for thyroid cancer patients following MKI therapy.

Table 5: Overview of study results for narrative comparison between selpercatinib vs. sorafenib and vandetanib

Study	Intervention	Tumour biology	Median OS (mo)	OS at 24 months	ORR	Median PFS (mo)	Grade 3-4 AEs
LIBRETTO-001	Selpercatinib	RET fusion-positive TC	[redacted])	82.3% (52.9-94.2)	78.9% (15/19)	20.07 (10.8-NE)	56.2%*
DECISION	Sorafenib	Non-RET fusion-positive TC	NR	73%	12.2% (24/196)	10.8	64.3%
Kloos et al	Treatment naïve Sorafenib	Non-RET fusion-positive TC	23 (18 – 34)	45%	15% (5/28)	16 (8-27.5)	NA
	Treatment experienced Sorafenib		37.5 (4 -42.5)	62%	13% (1/8)	10 (4-28)	NA
Leboulleux et al. 2012	Vandetanib	Non-RET fusion-positive TC	NR	62%	8% (6/72)	11.1	53% (39/ 73)

NA: not available, NR: not reached; NE: not estimated
*MTC safety analysis

5.2 Clinical question 2: What is the value of selpercatinib compared to cabozantinib in adults and children ≥ 12 years of age with advanced RET-altered thyroid cancer previously progressed after treatment with a multikinase inhibitor?

5.2.1 Presentation of relevant studies

5.2.1.1 LIBRETTO-001

LIBRETTO-001 is a phase 1–2 clinical trial evaluating the safety, tolerability, pharmacokinetics (PK) and preliminary anti-tumour activity of selpercatinib in adolescent and adult patients with advanced solid tumours, including RET-fusion-positive solid tumours, medullary thyroid cancer (MTC) and other tumours with RET activation [4]. Further details have been presented in section 5.1.1.1.

The primary reporting of LIBRETTO-001 included two efficacy analysis cohorts for RET-MTC patients (Wirth 2020). 55 had RET-MTC previously treated with vandetanib, cabozantinib, or both; and 88 patients who had RET-MTC not previously treated with vandetanib or cabozantinib. The 55 patients correspond to the scope of the assessment. An additional updated integrated analysis set (IAS) is available for the RET-MTC population previously treated with vandetanib, cabozantinib n = 124. Data is presented from both analysis sets.

The data from the comparator cabozantinib, which will be used to establish relative efficacy and safety stems from the EXAM trial where 81/219 (37.0%) patients had received prior systemic therapy for MTC (cabozantinib arm). However, clinical effectiveness results are not reported separately for treatment-naïve and pre-treated patients.

Therefore, to provide results for selpercatinib, that can meaningfully be compared to the results of the EXAM trial (no reporting based on prior lines), the comparative analysis is based on all RET-MTC patients included in LIBRETTO-001 and EXAM regardless of exposure to prior treatment.

For full transparency in the section below the results from LIBRETTO is given for the three main individual analysis populations in the LIBRETTO-001;

- **Primary analysis (PAS, n = 55):** the first 55 patients enrolled in Phase-I and Phase-II who had prior exposure to prior therapy of cabozantinib or vandetanib.
- **Integrated analysis set (IAS, n = 124):** Fulfilled the same criteria as the PAS, but included patients enrolled after the 55th patient before the 16 December 2019 data cut-off date.
- **Supplemental analysis set (SAS, n = 88**): cabozantinib and vandetanib naïve but could have other prior treatments

As mentioned above the EXAM trial, which was used for relative efficacy had reporting separately for treatment-naïve and pre-treated patients. Therefore, **comparative analysis** is based on the combined dataset for the IAS and SAS1 hereafter; **any-line LIBRETTO-001 population.**

Table 6: Overview of analysis sets available in LIBRETTO-001

Trial name	LIBRETTO-001
***RET*-mutant MTC**	
Primary analysis set (PAS) (n=55)	The first *RET*-mutant MTC patients enrolled in Phase I and Phase 2 who met the following criteria: 1. Evidence of a protocol-defined qualifying and definitive *RET*-mutation prospectively identified on the basis of a documented CLIA-certified (or equivalent ex-US) molecular pathology report. Patients with a *RET* mutation co-occurring with another oncogenic driver, as determined at the time of study enrolment by local testing, were included. 2. Measurable disease[a] by RECIST 1.1 by investigator assessment 3. Received 1 or more lines of prior therapy of cabozantinib or vandetanib 4. Received 1 or more doses of selpercatinib The PAS provides evidence for the clinically meaningful efficacy of selpercatinib in patients with *RET*-mutant MTC who have received prior systemic therapy.
Integrated analysis set (IAS) (n=143*)	All *RET*-mutant MTC patients treated in LIBRETTO-001 by the data cut-off date who met PAS criteria 1–4 Included all PAS patients and those treated after the 55th patient but on or before the data cut-off This IAS provides further evidence for the efficacy of selpercatinib in patients with *RET*-mutant MTC who have received prior systemic therapy in a larger number of patients, providing increased confidence in the PAS results.

Supplementary analysis set (SAS) **N = 88**	All other RET-mutant MTC patients (e.g., not part of the PAS/IAS) who were treated in LIBRETTO-001 as of the data cut-off date. SAS (Cabozantinib and vandetanib naïve) (n=88) Could have received therapies other than cabozantinib or vandetanib
Any-line LIBRETTO-001 population **(n = 212) – used for MAIC**	Integrated analysis set (IAS) (n=124) + Supplementary analysis set (SAS = 88)

***At 30 March 2020 data cut-off**

5.2.1.2 EXAM

EXAM is an International, randomized, double-blinded, phase 3 efficacy study of cabozantinib (n = 219) versus placebo (n =111) in subjects with unresectable, locally advanced, or metastatic MTC.

Patients were required to have documented radiographic disease progression per RECIST guidelines version 1.0 at screening compared with images obtained within the prior 14 months. No limit was placed on number of prior therapies, including MKIs. The primary end point was PFS. Key secondary end points were objective response rate (ORR) and OS and assessment of the relationship between RET mutation status and efficacy of cabozantinib. Mutations in the RET gene (exons 10, 11, and 13–16) were identified from blood and archival tumour samples using Sanger and next-generation sequencing methods.

Patients were randomized to receive cabozantinib or placebo (2:1) stratified by age (65 and >65 years) and prior MKI treatment (yes, no). Patients received cabozantinib (140 mg/day) or placebo administered orally until intolerable toxicity or disease progression per RECIST version 1.0.

For the RET-mutation positive population the OS results are only reported for the M918T point mutation. 81 patients with RET M918T point mutation were treated with cabozantinib and 45 with placebo. 107 patients with RET-mutant population were treated with cabozantinib and 62 with placebo.

5.2.2 Results per study

5.2.2.1 LIBRETTO-001

For LIBRETTO-001 the following data cut-offs (DCO) are presented: 16th December 2019, which is used in the indirect comparisons and the health economic models, and a later DCO at 30th March 2020. In the following section data from the 30th March 2020 DCO will be presented in order to provide data with the longest follow-up, except for quality of life and safety estimates as only 16th December 2019 analyses are available at the time of submission.

Outcome	Data cut-off	Population(s)
Median OS	30th March 2020	RET-mutant MTC: IAS (n=143) and PAS (n=55)
OS rate at 24 months	30th March 2020	RET-mutant MTC: IAS (n=143) and PAS (n=55)
Quality of life	16th December 2019	RET-mutant MTC (n=193)

Objective response rate	30th March 2020	RET-mutant MTC: IAS (n=143) and PAS (n=55)
Median PFS	30th March 2020	RET-mutant MTC: IAS (n=143) and PAS (n=55)
Adverse events	16th December 2019	RET-mutant MTC safety population (n=299)

Measures of mortality

Median OS

At the 30th March 2020 data cut-off the median OS was 33.3 (95% CI: 33.2 - NE) for both the PAS and the IAS populations, with a median follow-up of 22.1 months in the PAS and 15.7 for the IAS population.[29]

OS rate at 24 months

At the 30th March 2020 data cut-off the OS-rate at 24 months was 77.1% (95% CI: 63.1-86.3) and 76.7% (95% CI: 66.8-84.0) for the PAS and IAS populations, respectively.[29]

Table 7: Summary table of OS in RET-mutant MTC in LIBRETTO-001 - Patients Enrolled by 30 March 2020[29]

	PAS (a subset of IAS) N=55	IAS Prior cabozantinib /vandetanib N=143
Duration of overall survival (months)		
Median	33.3	33.3
95% CI	33.2 - NE	33.2 - NE
Rate (%) of OS		
24 months	77.1	76.7
95% CI	63.1-86.3	66.8-84.0
Duration of follow-up (months)		
Median	22.1	15.7

Quality of life

Mean change from baseline in EORTC-QLQ-C30

Mean change from baseline was not available. The study reported proportion of patients experiencing a clinically meaningful improvement, which was defined as 10-point difference from the baseline value. This metric provides more meaningful results than the mean change from baseline, as this proportion will directly translate into how many patients experienced an improved HRQoL. As seen selpercatinib provides meaningful improvements in quality of life of approximately 34-42 % of patients after cycle 3-9 (28 days cycles) ([redacted]).

Table 8: Summary table of proportion of patients experiencing a ≥ 10 points improvement in the Global Health Status/QoL

QLQ-C30 Subscale, n (%)		*RET*-mutant MTC N=193			
		Cycle 3	Cycle 5	Cycle 7	Cycle 9
Global Health Status/QoL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Objective response rate (ORR)

At the 30th March 2020 data cut-off the ORR was 69.1 (55.2 - 80.9) and 69.2 (61.0- 76.7) in the PAS and IAS population, respectively. Of these 10.9% and 4.2 % were complete responses (CR) and 58.2% and 65.0% were partial responses (PR) in the PAS and IAS population, respectively. Across both analysis sets, the majority of patients treated with selpercatinib experienced at least a partial response, reflecting the high efficacy expected by targeting the RET oncogenic driver.

Table 9: Summary table of best overall responses observed for PAS and IAS population - Patients Enrolled by 30 March 2020

	PAS (a subset of IAS) N=55	IAS Prior cabozantinib /vandetanib N=143
Best overall response, n (%)		
Complete response	6 (10.9)	6 (4.2)
Partial response	32 (58.2)	93 (65.0)
Stable disease	14 (25.5)	35 (24.5)
Progressive disease	1 (1.8)	2 (1.4)
Not evaluable	2 (3.6)	7 (4.9)
Objective response rate (CR + PR)		
n (%)	38 (69.1)	99 (69.2)
95% CI	55.2 - 80.9	(61.0- 76.7)

Progression-free survival

Median PFS

At the 30th March 2020 data cut-off the median PFS was not reached for both the PAS and IAS populations with NE (24.4-NE) and NE (20.0-NE). The follow-up time was 16.7 months and 11.7 months, respectively.[29]

The 12-month PFS Kaplan-Meier estimates were: 12 months 82.3 % (95 % CI: 68.7-90.4) and 76.9 (95% CI: 67.9-83.7) in the PAS and IAS populations, respectively.[29]

Table 10: Summary table of PFS in RET-mutant MTC in LIBRETTO-001 - 30th March 2020 data cut-off[29]

	PAS N = 55	IAS N = 143
Duration of PFS (months)		
Median	NE	NE
95% CI	24.4-NE	20.0-NE
Duration of follow-up (months)		
Median	16.7	11.7

Adverse events

Proportion of patients with a grade 3-4 adverse events.

In the MTC safety analysis group (N = 299 patients), Grade 3 or 4 TEAEs were reported 168 (56.2%) patients, irrespective of relatedness to study drug. The most common Grade 3–4 events were: hypertension (18.4%), ALT increase (7.0%), AST increase (6.0%), hyponatremia (4.0%).

Table 11: RET-mutant MTC (safety analysis cohort). Eli Lilly Data on File (16th December 2019 data cut-off

Preferred term	*RET*-mutant MTC N = 299, incidence (%)
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Narrative assessment of adverse events

As requested in the DMC protocol, a full list of adverse events reported in the trial is given below for those that occurred at any grade in at least 15% of the patients both RET-mutant MTC or Fusion-positive Thyroid Cancer including both MTC patients with and without prior exposure to MKI.

The safety is not likely to be different between these populations. The SmPC of both selpercatinib and cabozantinib provides an additional reference for the narrative assessment of safety.

Table 12: Adverse events in 162 patients with RET-mutant MTC or Fusion-positive Thyroid Cancer (AEs occurred at any grade in at least 15% of the patients, regardless of attribution)

Table 3. **Adverse Events in 162 Patients with *RET*-Mutant MTC or *RET* Fusion–Positive Thyroid Cancer Who Received Selpercatinib.***

Adverse Event	Adverse Events, Regardless of Attribution					Treatment-Related Adverse Events		
	Grade 1	Grade 2	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4	Any Grade
	number of patients (percent)							
Any adverse event	9 (6)	42 (26)	95 (59)	11 (7)	162 (100)	45 (28)	3 (2)	153 (94)
Dry mouth	69 (43)	5 (3)	0	0	74 (46)	0	0	63 (39)
Hypertension	10 (6)	25 (15)	34 (21)	0	69 (43)	19 (12)	0	49 (30)
Diarrhea	44 (27)	8 (5)	9 (6)	0	61 (38)	4 (3)	0	27 (17)
Fatigue	35 (22)	24 (15)	2 (1)	0	61 (38)	1 (1)	0	41 (25)
Increased aspartate aminotransferase level	37 (23)	6 (4)	13 (8)	1 (1)	57 (35)	12 (7)	1 (1)	45 (28)
Nausea	44 (27)	13 (8)	0	0	57 (35)	0	0	25 (15)
Constipation	44 (27)	11 (7)	1 (1)	0	56 (35)	0	0	26 (16)
Increased alanine aminotransferase level	26 (16)	7 (4)	17 (10)	1 (1)	51 (31)	16 (10)	1 (1)	42 (26)
Headache	36 (22)	11 (7)	4 (2)	0	51 (31)	1 (1)	0	21 (13)
Peripheral edema	42 (26)	5 (3)	1 (1)	0	48 (30)	0	0	29 (18)
Increased blood creatinine level	27 (17)	12 (7)	0	0	39 (24)	0	0	22 (14)
Abdominal pain	25 (15)	8 (5)	5 (3)	0	38 (23)	0	0	6 (4)
Arthralgia	25 (15)	10 (6)	0	0	35 (22)	0	0	8 (5)
Vomiting	26 (16)	8 (5)	1 (1)	0	35 (22)	0	0	12 (7)
Hypocalcemia	14 (9)	13 (8)	6 (4)	1 (1)	34 (21)	0	0	5 (3)
Back pain	19 (12)	10 (6)	2 (1)	0	31 (19)	0	0	1 (1)
QT interval prolonged on electrocardiography	11 (7)	16 (10)	4 (2)	0	31 (19)	3 (2)	0	21 (13)
Cough	25 (15)	4 (2)	0	0	29 (18)	0	0	2 (1)
Rash	25 (15)	3 (2)	0	0	28 (17)	0	0	13 (8)
Dizziness	25 (15)	2 (1)	0	0	27 (17)	0	0	9 (6)
Abdominal distension	18 (11)	7 (4)	0	0	25 (15)	0	0	12 (7)
Hypothyroidism	14 (9)	11 (7)	0	0	25 (15)	0	0	12 (7)
Weight increased	11 (7)	9 (6)	5 (3)	0	25 (15)	1 (1)	0	8 (5)

* The adverse events listed here are those that occurred at any grade in at least 15% of the patients, regardless of attribution. The relatedness of adverse events to treatment was determined by the investigators. The total percentage for any given adverse event may be different than the sum of the individual grades because of rounding. In total, five patients had grade 5 adverse events including hemoptysis, postprocedure hemorrhage, sepsis, cardiac arrest, and cardiac failure (one patient each), all deemed by the investigators to be unrelated to selpercatinib.

5.2.2.2 EXAM

Three separate publications have reported data from the EXAM trial. Here efficacy data is presented from two publications reporting data on the RET-mutant subgroup of the EXAM trial, and data from these publication are used in the MAIC analysis (Sherman et al. 2016, Schlumberger et al. 2017). The data from Elisei et, 2013 is only used to report on safety on the total MTC-population as the efficacy data is from an early and redundant data-cut and not used for the comparative analysis.

The three publications used for reporting results from EXAM are:

- Sherman et al. 2016; RET-mutant population receiving cabozantinib (n=107) or placebo (n=62)
    - Used for PFS, ORR and safety
- Schlumberger et al. 2017; RET M918T-positive receiving cabozantinib (n=81) or placebo (n=45)
    - Used for survival
- Elisei 2013 et al. cabozantinib (n = 219) or placebo (n = 111)
    - Safety in MTC population, not restricted to RET-mutation positive

Measures of mortality

Median OS

The median OS for the RET M918T mutation–positive population was 44.3 months with cabozantinib and 18.9 months with the placebo (HR: 0.60 [95% CI: 0.38-0.94] P <0.03).
The median OS for the RET mutation–positive population was not reported, but the HR was reported as 0.79 (95% CI: 0.54-1.17).

OS rate at 24 months

OS Kaplan-Meier curves were reported in Schlumberger et al. 2017 for the RET M918T mutation–positive population showing an OS rate of approx. 70% at 24 months.

Quality of life

Mean change from baseline in EORTC-QLQ-C30 was not reported.

Objective response rate

The overall response rate was 32 % in the RET mutation–positive patients treated with cabozantinib[32] and 34% for the RET M918T–positive subgroup[11].

Progression-free survival

Median PFS

The median PFS for the RET mutation–positive population was 60 weeks with cabozantinib and 20 weeks with the placebo (HR: 0.23 [95% CI: 0.14-0.38] P < 0.0001).[32]

The median PFS was 13.9 months for the RET M918T mutation–positive population, with a HR of 0.15 (95% CI: 0.08-0.28).[11]

Adverse events

The proportion of patients with a grade 3-4 adverse event

Grade 3 or 4 AEs were reported in 69% (148 of 214) and 33% (36 of 109) of patients in the cabozantinib and placebo groups, respectively (both RET-positive and negative, safety was not different based on RET-mutational status). The median time of follow-up was 13.9 months (range, 3.6 to 32.5 months)[9]

Narrative assessment of adverse events

As requested, a full list of adverse events have been inserted below in Table 13. Data in EXAM trial was reported for AEs (any grade), that occurred in ≥ 10 % of cabozantinib patients[9]. The SmPC of both selpercatinib and cabozantinib provides an additional reference for the narrative assessment of safety.

Table 13: AEs (any grade), that occurred in ≥ 10 % of cabozantinib patients in EXAM[9]. Reported for all grade and grade ≥ 3

Table 2. AEs Occurring in ≥ 10% of Cabozantinib-Treated Patients, by Maximum Severity Reported

	Cabozantinib (n = 214)				Placebo (n = 109)			
	All Grades		Grade ≥ 3		All Grades		Grade ≥ 3	
AE	No.	%	No.	%	No.	%	No.	%
Diarrhea	135	63.1	34	15.9	36	33.0	2	1.8
Palmar-plantar erythrodysesthesia*	107	50.0	27	12.6	2	1.8	0	
Decreased weight	102	47.7	10	4.7	11	10.1	0	
Decreased appetite	98	45.8	10	4.7	17	15.6	1	0.9
Nausea	92	43.0	3	1.4	23	21.1	0	
Fatigue	87	40.7	20	9.3	31	28.4	3	2.8
Dysgeusia	73	34.1	1	0.5	6	5.5	0	
Hair color changes	72	33.6	1	0.5	1	0.9	0	
Hypertension	70	32.7	18	8.4	5	4.6	1	0.9
Stomatitis	62	29.0	4	1.9	3	2.8	0	
Constipation	57	26.6	0		6	5.5	0	
Hemorrhage	54	25.2	7	3.3	17	15.6	1	0.9
Vomiting	52	24.3	5	2.3	2	1.8	1	0.9
Mucosal inflammation	50	23.4	7	3.3	4	3.7	0	
Asthenia	45	21.0	12	5.6	16	14.7	2	1.8
Dysphonia	43	20.1	0		10	9.2	0	
Rash	41	19.2	2	0.9	11	10.1	0	
Dry skin	41	19.2	0		3	2.8	0	
Headache	39	18.2	1	0.5	9	8.3	0	
Oropharyngeal pain	38	17.8	1	0.5	5	4.6	0	
Abdominal pain	36	16.8	6	2.8	7	6.4	1	0.9
Alopecia	35	16.4	0		2	1.8	0	
Pain in extremity	33	15.4	3	1.4	12	11.0	1	0.9
Back pain	32	15.0	5	2.3	12	11.0	1	0.9
Dyspnea	29	13.6	5	2.3	19	17.4	11	10.1
Arthralgia	29	13.6	2	0.9	8	7.3	0	
Dizziness	29	13.6	1	0.5	8	7.3	0	
Oral pain	29	13.6	1	0.5	1	0.9	0	
Dry mouth	28	13.1	0		9	8.3	0	
Dysphagia	27	12.6	9	4.2	7	6.4	1	0.9
Cough	26	12.1	1	0.5	14	12.8	0	
Muscle spasms	26	12.1	1	0.5	5	4.6	0	
Dyspepsia	24	11.2	0		0		0	
Insomnia	23	10.7	0		7	6.4	0	
Erythema	23	10.7	2	0.9	2	1.8	0	
Glossodynia	22	10.3	3	1.4	0		0	

NOTE. Laboratory abnormalities are not included.
Abbreviation: AE, adverse event.
*Hand-foot syndrome.

5.2.3 Comparative analyses

No head-to-head trials are available comparing selpercatinib to cabozantinib, with evidence for the efficacy and safety of selpercatinib provided by the single-arm LIBRETTO-001 trial. Therefore, in order to estimate the comparative effectiveness of selpercatinib versus relevant comparator cabozantinib, the evidence identified in the SLR (EXAM-trial) was reviewed for the purposes of conducting an ITC.

Feasibility assessment of an indirect treatment comparison (ITC)

Comparison of study characteristics and endpoints

The LIBRETTO-001 and EXAM trials were considered in the feasibility assessment presented in this submission. The characteristics of these trials and a summary of the key trial outcomes is presented in section 5.2.2. The definition and ascertainment of study endpoints were similar among the trials.

Comparison of baseline characteristics and prognostic factors

The baseline characteristics of the trial populations are presented in section 5.2.1. For the EXAM placebo arm, the baseline characteristics of the *RET*-mutant subgroups were not available. Key differences in the patient population characteristics include the following:

- The LIBRETTO-001 trial (any-line) population receiving selpercatinib is slightly older (median age 58 years) than patients in either the cabozantinib or placebo arm (median age 55 and 55 years, respectively) of the EXAM trial
- The percentage of male patients in LIBRETTO-001 (any-line; 65.5%) was slightly higher than the placebo arm of the EXAM trial (63.1%) except for the cabozantinib arm (68.2%)A higher proportion of patients had performance status 1 or 2 in the LIBRETTO-001 trial than in the EXAM trial population
- A lower proportion of patients had performance status 0 in the LIBRETTO-001 trial (any-line; 34.9%) than in either the cabozantinib or placebo arm of the EXAM trial (61.7% and 50.5% had an ECOG performance status of 0, respectively)
- The proportion of patients with prior anticancer therapy was substantially higher in LIBRETTO-001 (66.0%, any-line dataset) than in the EXAM trial placebo arm (42.3%)
- The proportion of patients with prior TKI therapy was higher in LIBRETTO-001 (61.8%, any-line dataset) than either the cabozantinib or placebo arm in the EXAM trial (21.5% and 21.6%, respectively).
- The proportion of patients who never smoked was higher in the LIBRETTO-001 trial (61.3%, any-line dataset) than the cabozantinib arm in the EXAM trial (51.4%).

The populations appear to be similar for other reported characteristics.

Prognostic factors and predictive factors (treatment-effect modifiers) in patients with MTC were identified in the SLR and were validated with a clinical expert experienced in the treatment of thyroid cancer. The findings are summarised in appendix B, along with a comparison of the trial populations for each of these factors.

Many of the identified prognostic factors were not reported among the three trials. Based on the reported prognostic factors, outcomes in the LIBRETTO-001 trial may be expected to be somewhat worse than those in the EXAM trial, due to older age, worse performance status, and higher proportion of patients with prior therapy (i.e., lower proportion of treatment-naive patients). The proportion of patients who were female and who never smoked was higher in LIBRETTO-001; however, sex and smoking status were not identified as prognostic factors for MTC in the SLR for the NICE submission, which was confirmed by clinical expert feedback.

Given the LIBRETTO-001 trial does not include a control arm, it was not possible to conduct a network meta-analysis (NMA) or anchored indirect treatment comparison to estimate relative efficacy versus relevant comparators. As such, a matching-adjusted, unanchored, indirect treatment comparison versus the EXAM trial was explored to generate relative efficacy estimates

versus cabozantinib and placebo (which can be considered a proxy for BSC). It was considered most feasible to compare selpercatinib with placebo and versus cabozantinib in the RET-mutation positive and RET M918T subgroups from the EXAM trial. An unweighted naïve comparison was also conducted as a supplementary analysis.

Matching-adjusted indirect comparison (MAIC)

Methodology of the MAIC

An unanchored adjusted ITC was conducted using individual patient-level data from the any-line population from LIBRETTO-001 (IAS and SAS1; n=212) and summary statistics from EXAM. Specifically, MAICs were conducted for PFS and OS whereby outcomes in LIBRETTO-001 were adjusted using a PSW approach, in accordance with the methodology proposed in the NICE Decision Support Unit (DSU) Technical Support Document (TSD). [33, 34,35] The LIBRETTO-001 and EXAM trials included both treatment-naïve and pre-treated patients. In the LIBRETTO-001 trial, patients enrolled in the IAS (n=124) had received 1 or more lines of prior cabozantinib or vandetanib. Patients enrolled in the SAS1 (n=88) were cabozantinib and vandetanib naïve. In the RET-mutant subgroup of the EXAM trial (cabozantinib arm), 81/219 (37.0%) patients had received prior systemic therapy for MTC. However, clinical effectiveness results are not reported separately for treatment-naïve and pre-treated patients. It must be noted that comparing pre-treated patients from one trial (LIBRETTO-001 IAS) with a mix of naïve and pre-treated patients from another (EXAM) is likely to be biased.

No Kaplan–Meier curves were available for OS for the RET-mutation positive subgroup treated with cabozantinib or placebo from the EXAM trial. As such, the unweighted curves for the RET M918T positive receiving cabozantinib or placebo in the EXAM trial were digitised from Schlumberger et al. (2017)[11] and compared to the weighted curve for the any-line LIBRETTO-001 population. The PS matching was performed using the LIBRETT0-001 any-line analysis set (IAS and SAS1) and the EXAM trial data, such that the LIBRETT0-001 outcomes were adjusted to reflect the EXAM trial population characteristics for the RET-mutation positive subgroup treated with cabozantinib.

For PFS, the unweighted curves for the RET-mutation positive population receiving cabozantinib (n=107) or placebo (n=62) in the EXAM trial were digitised from Sherman et al. (2016)[32] was compared to the weighted curve for the any-line LIBRETTO-001 population. The PS matching was performed using LIBRETTO-001, any-line dataset, and EXAM, RET-mutation positive subgroup treated with cabozantinib.

The MAIC adjusted for baseline characteristics with known or suspected associations with the efficacy outcomes were reported in both the LIBRETTO-001 trial and EXAM trial publication. Re-weighting of selpercatinib data (LIBRETTO-001 trial, any-line) was based on baseline characteristics of cabozantinib arm (EXAM trial, RET-mutation positive subgroup) only. However, a comparison of adjusted selpercatinib outcomes data was done both with placebo and cabozantinib arm separately. Baseline characteristics between LIBRETTO-001 and EXAM before and after matching were obtained from a logistic regression model. These included age, weight, ECOG performance status, sex, smoking status, prior TKI therapy, and RET M918T mutation status.

To balance the baseline characteristics between LIBRETTO-001 and EXAM, the any-line data set from LIBRETTO-001 patients were assigned weights such that:

- Weighted mean baseline characteristics in the any-line data set from LIBRETTO-001 patients exactly matched those reported for patients in EXAM (RET-mutation positive subgroup treated with cabozantinib)

- The weight for each patient was equal to the patient's estimated propensity weight of being in LIBRETTO-001 (any-line data set) versus EXAM (RET-mutation positive subgroup treated with cabozantinib).

- Weights meeting these conditions were obtained from a logistic regression model for the propensity of inclusion in the LIBRETTO-001 trial (any-line data set) versus the EXAM study (RET-mutation positive subgroup treated with cabozantinib), with all matched-on baseline characteristics included as independent variables in the model.

Since only summary statistics for baseline characteristics were available from the EXAM study, the logistic regression model was estimated using the method of moments. Based on the method of moments estimate, the baseline means were exactly matched after weighting. The distribution of weights was inspected for potential extreme values, which are indicative of poor overlap between the study populations in the distributions of patient characteristics.

Results of the MAIC

The comparison of baseline characteristics before and after matching for the any-line data set from LIBRETTO-001 (N=212) and the *RET*-mutation positive EXAM subgroup treated with cabozantinib (N=107) is presented in Table 14. The MAIC adjusted for age, weight, ECOG performance status, sex, smoking status, and *RET* M918T mutation status. After applying weights to the patients in LIBRETTO-001, baseline characteristics were exactly balanced between the two study populations (Table 14). The effective sample size for LIBRETTO-001 after weighting the effective sample size (Neff) was 166.8 and the distribution of weights is presented in Figure 3. Distribution of weights in the MAIC indicating no evidence of extreme weights. Weights were rescaled so that they were relative to the original unit weights of each individual, in line with the methodology proposed in NICE TSD.[35] Rescaling had a very limited impact on the results.

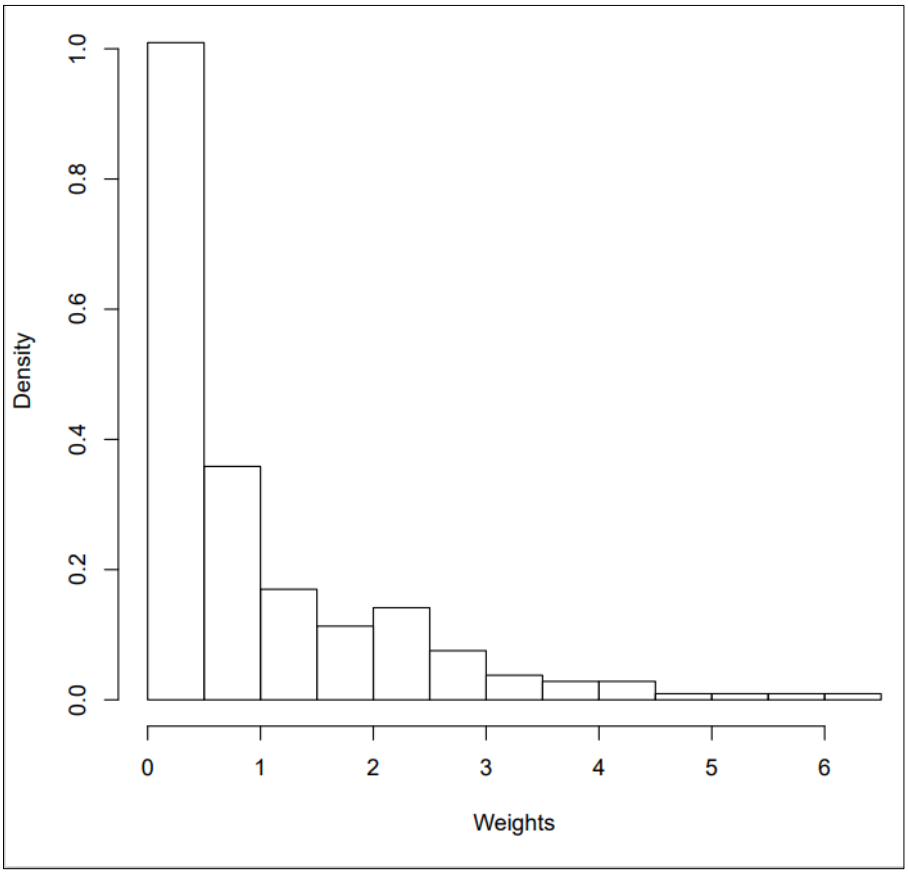
Table 14: Matching baseline characteristics between LIBRETTO-001 and EXAM before and after matching

Characteristic	Before matching		After matching and weighting
	LIBRETTO-001 any-line Selpercatinib (N=212)	EXAM *RET*-mutation positive Cabozantinib (N=107)	LIBRETTO-001 any-line Selpercatinib (N_{eff}= [redacted] 89)
Age, mean (SD)	[redacted]	55.00 (14.64)	[redacted]
Weight (kg), mean (SD)	[redacted]	74.00 (20.19)	[redacted]
ECOG-0, mean	[redacted]	0.62	[redacted]
Sex, mean	[redacted]	0.68	[redacted]
Smoking, mean(never)	[redacted]	0.51	[redacted]
***RET* M918T mutation status, mean**	[redacted]	0.75	[redacted]
Prior TKI, mean	[redacted]	0.21	[redacted]

[a] Median (min, max)

Abbreviations: ECOG PS: Eastern Cooperative Oncology Group Performance Status; SD: standard deviation; *RET*: rearranged during transfection.

Figure 3: Distribution of weights in the MAIC



Abbreviations: MAIC: matching-adjusted indirect comparison.

The weighted comparisons of efficacy outcomes between selpercatinib in the LIBRETTO-001 trial and cabozantinib and placebo in EXAM are presented in Table 15. Comparison of PFS for

selpercatinib (LIBRETTO-001, any-line dataset) versus cabozantinib and placebo (EXAM, *RET*-mutation positive subgroup and comparison of OS for selpercatinib (LIBRETTO-001, any-line dataset) versus cabozantinib and placebo (EXAM, *RET* M918T positive subgroup) for both arms before and after matching are presented in Table 15. For PFS, the hazard ratios (HRs) and corresponding 95% CIs were estimated from a weighted Cox proportional hazards (PH) model (with treatment indicator as to the only covariate). For OS, the HRs and corresponding 95% CIs were estimated from a weighted Cox PH model (with treatment indicator and *RET* M918T status as covariates). After weighting, there was a statistically significant improvement in PFS for selpercatinib versus cabozantinib ([redacted]) and versus placebo ([redacted]). There was a statistically significant improvement in OS for selpercatinib versus cabozantinib ([redacted]) and versus placebo ([redacted]).

Table 15: Comparison of PFS and OS for selpercatinib (LIBRETTO-001, any-line data set) versus cabozantinib and versus placebo (EXAM) before and after propensity score matching

	[a]PFS		[b]OS	
	HR (95% CI)	**p-value**	**HR (95% CI)**	**p-value**
Selpercatinib versus cabozantinib				
Unweighted	[redacted]	[redacted]	[redacted]	[redacted]
Weighted	[redacted]	[redacted]	[redacted]	[redacted]
Selpercatinib versus BSC (placebo)				
Unweighted	[redacted]	[redacted]	[redacted]	[redacted]
Weighted	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BSC: best supportive care; CI: confidence interval; HR: hazard ratio; OS: overall survival; PFS: progression-free survival.
[a]*RET*-mutation positive; [b]*RET*-M918 subgroup

Figure 4: PFS (IRC assessment) for selpercatinib (LIBRETTO-001, any-line dataset) versus cabozantinib and versus placebo (EXAM RET-mutation positive subgroup) before and after propensity score matching

Abbreviations: PFS: progression-free survival; IRC: independent review committee
Test for proportional hazards assumption in PFS was not rejected before and after matching (p>0.05)

Figure 5: Overall survival for selpercatinib (LIBRETTO-001, any-line dataset) versus cabozantinib and versus placebo (EXAM RET M918T positive subgroup) before and after propensity score matching

Abbreviations: OS: overall survival
Kaplan-Meier OS data for the RET-mutant group in EXAM is not available.
Test for proportional hazards assumption in OS was not rejected before and after matching (p>0.05)

Uncertainties in the indirect treatment comparison

***RET*-mutant MTC: Limitations of the MAIC for LIBRETTO-001 versus EXAM**

The limitations of these analyses must be considered in the interpretation of findings for MTC. The key limitation was that no randomised clinical trial evidence was available for selpercatinib versus any comparator, due to the trial being single-arm design.

No head-to-head randomised clinical trial evidence was available for selpercatinib comparing efficacy to relevant comparators due to fact that LIBRETTO-001 is a single-arm trial. Only known baseline prognostic factors (age, weight, ECOG performance status, sex, smoking status, prior TKI therapy, and *RET* M918T mutation status). that were consistently reported in both LIBRETTO-001 and EXAM were matched in the MAIC, and consequently, other potential prognostic factors and effect modifiers were not accounted for in the MAICs. As with any comparison of non-randomised treatment groups, the MAICs are also subject to potential bias due to unobserved or unmeasurable confounding.

No OS Kaplan–Meier data were available from the EXAM trial for the *RET*-mutation positive subgroup to allow for digitization of the data. As such, the KM curves for patients with *RET* M918T positive MTC receiving cabozantinib or placebo in the EXAM trial were used. These data were compared using a propensity score weighted approach to the any-line LIBRETTO-001 population.[11] In addition, baseline characteristics were not reported for the *RET* M918T positive subgroup, so despite comparing to the outcomes of this subgroup, the LIBRETTO-001 trial data was matched and weighted to the broader *RET*-mutation positive cabozantinib arm (although M918T status was included as a covariate in the Cox model). The assumption was made that the baseline characteristics of these groups were equivalent, but this is unknown.
PFS and OS were not reported separately for treatment-naïve and pre-treated patients in the *RET*-mutation positive subgroup of the EXAM trial. As such, subgroup analyses by the line of therapy could not be conducted to estimate the relative efficacy of selpercatinib in the treatment-naïve and pre-treated setting separately.

Narrative comparison of efficacy

Progression-free survival

In LIBRETTO-001 in the selpercatinib-treated PAS and IAS population, the median PFS were NE (24.4-NE) and NE (20.0-NE) with a follow-up time of 20.3 months and 13.9 months at the 30th of March 2020 data cut-off, respectively.

The 12-month PFS Kaplan-Meier estimates were: 12 months 82.3 % (95% CI: 68.7- 90.4) and 76.9 (95% CI: 67.9-83.7) in the PAS and IAS populations, respectively.

In the EXAM trial the median PFS for the RET mutation–positive population was approximate 14 months with cabozantinib[32], meaning ≤ 50 % of patients were alive after 14 months. Comparing this to the approximate 67.4 % of patients alive without documented disease progression in the PAS population treated with selpercatinib after approximately 17 months is a clear documentation of the improved efficacy of targeted therapy with selpercatinib compared to cabozantinib. As noted above, the patients in the LIBERETTO-001 trial had a worse prognosis, than for patients in the EXAM-trial.

Objective response rate (ORR)

In line with PFS estimates ORR strongly indicates improved efficacy of selpercatinib compared to cabozantinib in RET-mutation positive MTC.
For cabozantinib the ORR was 32 % in the RET mutation–positive patients treated with cabozantinib and 34% for the RET M918T–positive subgroup[11, 32].
This should be compared with the ORR of selpercatinib, which was 69.1% (95% CI: 55.2 - 80.9) and 69.2 % (95% CI: 61.0 – 76.7) in the PAS and IAS population, respectively, indicating a 2-fold increase in ORR compared to cabozantinib.

Adverse events (narrative comparison)

79% of those receiving cabozantinib had dose reductions and permanently discontinuation of therapy occurred in 16% of the patients[9]. This is a clear indication, that cabozantinib has a very high-toxicity and is poorly tolerated by patients.

By comparison, consistent with the selectivity of selpercatinib for RET, most related adverse events were of grade 1 or 2 and dose reductions and discontinuations were much less pronounced (Table 12).

Of the 531 patients who received selpercatinib, 160 (30%) had a dose reduction because of treatment-related adverse events were uncommon, and treatment discontinuation due to treatment-related adverse events occurred in only 2% of the patients[4]. The 531 patients refer to the safety cohort treated with selpercatinib, which include populations of patients with RET -altered medullary thyroid cancer and of those with non-medullary thyroid cancer[4]. The adverse-event profile of selpercatinib in patients with RET-altered thyroid cancer was broadly similar to non-medullary thyroid cancer.[4]

Notably comparing the safety reporting MTC-patients in the EXAM (Table 13) to the patients MTC-patients in LIBRETTO (Table 11 and Table 12) several grade 3-4 adverse events are much more common with cabozantinib including; hand foot syndrome, haemorrhages, several gastrointestinal related events such as diarrhoea, decreased weight, abdominal pain, decreased appetite, vomiting. Patient on cabozantinib also experienced much higher rates of grade 3-4 adverse events related to general function such as fatigue and asthenia.

As evidenced by the much higher discontinuation rate in EXAM compared to LIBERETTO-001 and a much higher rate of several grade 3-4 adverse events in EXAM, selpercatinib provides a far less toxic treatment modality. This is important, as patients who have progressed previously on a MKI are often frail patients, who would benefit from less toxic treatments.

5.3 Clinical question 3: What value does selpercatinib have compared to platinum-based chemotherapy for adults with advanced RET-altered NSCLC that is progressed after treatment with checkpoint inhibitor immunotherapy?

The DMC protocol requests the available evidence for adults with incurable RET-altered non-squamous, non-small cell lung cancer with PD-L1 expression ≥ 50% previously progressed after treatment with checkpoint inhibitor immunotherapy compared to platinum-based chemotherapy. As also stated in the protocol, limited data is available for second line chemotherapy within NSCLC as the treatment landscape has changed during the last 5 years with the introduction of immunotherapy. Hence, chemotherapy has shifted to second line treatment although very limited clinical evidence exists for use of chemotherapy after treatment with checkpoint inhibitor immunotherapy.
The search strings defined in the protocol includes searching for observational studies and for studies investigating platinum-based chemotherapy used as a first line treatment option in non-RET NSCLC populations.

5.3.1 Presentation of relevant studies

The systematic literature search conducted based on the search strings defined by the DMC protocol did not provide any clinical trials or studies for platinum-based chemotherapy in second line, as could be expected. The search for observational studies identified 3 publications reporting on salvage chemotherapy after checkpoint inhibitor immunotherapy. All of the studies report data on a subset of patients treated with platinum-based chemotherapy. None of the studies reported results for RET-specific populations or subsets.
The search for first line platinum-based chemotherapy yielded several hits of numerous combinations of platinum-based chemotherapy, some of very limited relevance to Danish clinical practice. Based on dialogue with the DMC secretariate and the clinical expert committee the relevant platinum-based chemotherapy regimens where limited to carboplatin in combination with vinorelbine and potentially with pemetrexed maintenance, as the most relevant treatment options and secondary platinum combined with pemetrexed.

5.3.1.1 LIBRETTO-001

LIBRETTO-001 is an ongoing multi-centre, open-label, single-arm, Phase I/II study in patients with advanced solid tumours, including RET fusion-positive solid tumours (including NSCLC). The primary and secondary outcomes have previously been described in section 5.1.1.

There were 5 analysis sets for patients with NSCLC. Only clinical effectiveness data from second line (pre-treated) patients, with measurable disease, are considered in this submission. These patients comprised the Primary Analysis Set (PAS - second line) and Integrated Analysis Set (IAS - second line) populations. The PAS analysis set is comprised of the first 105 RET fusion-positive NSCLC patients enrolled in Phase I and Phase II who met the following criteria:

1. Evidence of a protocol-defined qualifying and definitive RET fusion. Patients with a RET fusion co-occurring with another putative oncogenic driver, as determined at the time of study enrolment by local testing, were included
2. Measurable disease by RECIST v1.1 by investigator assessment
3. Received 1 or more lines of prior platinum-based chemotherapy
4. Received 1 or more doses of selpercatinib

The IAS analysis set is comprised by all RET fusion-positive NSCLC patients treated in LIBRETTO-001 (n=184) by the data cut-off date who met PAS criteria 1–4. Included all PAS patients and those enrolled after the 105th patient but on or before the data cut-off.

The overall safety analysis set is comprised of patients treated with selpercatinib as of a data cut-off of 16th December, and the subset safety analysis for NSCLC is comprised by RET fusion-positive NSCLC (n= 329).

Overall, patient demographics were similar across the populations of interest. The median age of all patients with *RET* fusion-positive NSCLC was 61 (range: 23–86) years.[36] Across the three population of interest, the most common age range was 45–64 years; 49.5% of patients in the PAS and 48.4% in the IAS fell into this age category, respectively. All populations of interest had a higher proportion of females than males (59.0% and 57.1% patients were female in the PAS and IAS, respectively). Overall, the majority (51%) of *RET* fusion-positive NSCLC patients were white, with a high proportion of patients identified as Asian (41%). Overall, most participants (70%) reported never smoking, with 71% and 70% of patients reporting never smoking in the PAS and IAS, respectively.[36] The younger age, as well as the higher proportion of females, Asian patients and never smokers is consistent with the patient profile of *RET* fusion-positive NSCLC reported in the literature.[1, 37, 38].

The median time from diagnosis was 18.4 months for the total population (PAS: 30.1 and IAS: 24.2). Most patients in the PAS (98%) and IAS (97%) had metastatic disease at enrolment, with 36% and 33% exhibiting CNS metastases at baseline in the PAS and IAS, respectively. In addition, most patients in the PAS were diagnosed with Stage IV disease (80%).

In accordance with the eligibility criteria for this population, all patients in the PAS population had received at least 1 prior line of platinum-based chemotherapy and 55.2% had also received prior immunotherapy. All patients in the IAS had received at least 1 prior line of platinum-based chemotherapy and 54.3% had also received prior immunotherapy.

More than half of patients in the PAS and IAS underwent prior radiotherapy (59.0% and 56.0%, respectively) and roughly half had undergone cancer related surgery (49.5% and 47.3%, respectively). For the PAS population, 43.8% (46/105) of patients had received 1–2 prior systemic therapies, with a similar value also reported for the IAS population (54.3% [100/184]). Notably, only 14.3% of patients in the PAS and 13.0% of IAS patients achieved a partial response with the last systemic therapy received.

5.3.1.2 Park et al. 2018

Park et al. 2018 was retrospective study which included (1) patients treated with anti–PD-1/PD-L1 inhibitors for advanced NSCLC, (2) patients who exhibited disease progression after treatment

with anti–PD-1/PD-L1 inhibitors and who received salvage chemotherapy administered after immunotherapy (SCAI), and (3) patients for whom SCAI efficacy data were available. Patients were excluded if small molecule inhibitors or targeted therapies were used in the period between PD-1/PD-L1 inhibitor treatment and SCAI.
The primary end point was the objective response rate (ORR), which was reassessed by the investigators according to RECIST. The secondary end point was PFS, which was defined as time from the start of SCAI to disease progression or death due to any cause. ORR and PFS between the SCAI and LCBI treatments were compared by using the chi-square test and logrank test, respectively. Given that platinum-based chemotherapy and non-platinum–based chemotherapy have different efficacies for treating NSCLC, we additionally compared SCAI and LCBI efficacy data by stratifying into platinum doublet chemotherapy and nonplatinum monotherapy groups. The study did not report on RET-specific alterations.

From October 2013 to March 2017, 309 patients received anti–PD-1/PD-L1 inhibitors for advanced NSCLC at the Samsung Medical Centre in South Korea. 212 patients had not received SCAI, nine had received tyrosine kinase inhibitors as the first therapy after immunotherapy, four were enrolled in the blind randomized study, and 11 had no available SCAI efficacy data. Thus, 73 patients met the inclusion criteria and were included in the analyses. 34 patients received nivolumab, 30 received pembrolizumab, 4 received durvalumab, 3 received avelumab, 1 received durvalumab plus tremelimumab, and 1 received atezolizumab. SCAI was administered as a second-line therapy (n = 10 [13.7%]), third-line therapy (n = 38 [52.1%]), fourth-line therapy (n = 10 [13.7%]), fifth-line therapy (n = 8 [11.0%]), and sixth-line therapy (n = 7 [9.5%]), counting immunotherapy into the line of therapy.
Of the 73 patients, 10 received anti–PD-1/PD-L1 inhibitors as the first-line therapy; LCBI data were not available for these patients. Thus, 73 had SCAI data, of which 24 received a platinum-based doublet as salvage chemotherapy after immunotherapy.

Patients enrolled were 60 years of age (median) and 68,5% male. The majority of patients had an ECOG performance status of 1 (79,5%) and 57,5% were former or current smokers. The histology in approximately two thirds of the patients were adenocarcinoma (60.3%) and on third squamous cell carcinoma (34.7%).

5.3.1.3 Metro et al. 2019

Metro et al. 2019 was a retrospective study of subsequent anticancer treatments received after progression on first-line pembrolizumab in non-oncogene addicted advanced NSCLC patients with PD-L1 ≥50% based on medical chart review of patients from 14 oncologic centres in four European countries. There were no clinical or pathological restrictions for patient enrolment, provided that eligible patients had been treated with first-line pembrolizumab, and had an EGFR wild type, ALK negative, and PD-L1 ≥50% biological profile of the tumour. Disease progression on pembrolizumab was defined as progressive disease (PD) as per RECIST 1.1 that occurred during treatment or within 6 months of the last dose of pembrolizumab. Following data were collected in the study: types of post-progression anticancer treatment, response to first-line pembrolizumab and to salvage chemotherapy as per RECIST 1.1 [complete response (CR), partial response (PR), stable disease (SD) and PD, with overall response rate (ORR) being the sum of CR and PR, and disease control rate being the sum of CR, PR and SD], progression-free survival (PFS) of salvage chemotherapy (calculated from the time of initiation of treatment to the radiographic evidence of disease progression or death of the patient in the absence of disease progression, with alive patients without documented radiographic progression being censored at the time of last follow-up).
Descriptive statistics were performed using frequencies, percentages, frequency tables for categorical variables, median and range for quantitative variables. Non-parametric Mann-Whitney test was performed to compare continuous variable with no normal distribution.

Categorical variables were evaluated by chi-square analysis or Fisher's exact test where appropriate. PFS was analysed according to the Kaplan-Meier method and survival curves were compared using the log-rank test. Cox model was used to estimate hazard ratio and related 95% confidence interval.

Out of 173 patients treated with first-line pembrolizumab from January 2017 to March 2019 60 patients received a post-progression treatment of subsequent anticancer treatments, consisting of salvage chemotherapy in 42 patients and pembrolizumab beyond progression in 18 cases. Platinum-based chemotherapy was delivered in approximately three quarters (31 of 42) of patients who received salvage chemotherapy, with platinum/pemetrexed being the most commonly administered chemotherapeutic regimen. The distribution of the platinum-based chemotherapies were: n=12 carboplatin/pemetrexed; n=5 carboplatin/gemcitabine; n=4 cisplatin/pemetrexed; n=3 carboplatin/paclitaxel; n=3 carboplatin/nab-paclitaxel; n=2 carboplatin/paclitaxel/ bevacizumab; n=1 cisplatin/gemcitabine.

Median age was 64 years (range 19−84); most of patients were male (64.3 %), 33.3 % had Eastern Cooperative Oncology Group performance status (ECOG PS) of 2, and histology was adenocarcinoma in 44.5% of patients. Brain metastases were present in 38.9% of patients at baseline.

At the time of analysis (June 2019), the median follow-up time calculated from the date of progression to first-line pembrolizumab was 5.7 months (range, 0.7–16.0 months) in the salvage chemotherapy group. Among the 42 patients who received salvage chemotherapy, 31 had at least one follow-up radiographic assessment, and were therefore evaluable for activity.

5.3.1.4 CLARITY

CLARITY was a retrospective, multicentre study, involving 20 Italian centres of advanced NSCLC patients treated with SCAI that previously received treatment with anti-PD-1/anti-PD-L1 at any treatment line.

The primary endpoint of the study was represented by overall survival (OS), defined as the time from CT initiation to death. PFS and ORR (according to RECIST 1.1 criteria) and toxicity of treatment (defined according to CTCAE version 5) have been investigated as secondary endpoints.
Data from clinical records of patients were anonymized, collected, and then analysed for the study purpose. All data about the clinical history of patients, including demographics and comorbidities, diagnosis and treatment of NSCLC, outcome of immunotherapy treatment and to the subsequent chemotherapy were collected.

Demographic variables and outcome measures have been reported using descriptive statistics. Survival curves were estimated with the Kaplan–Meier method and compared using log-rank test. Median survival times were reported along with their 95 % confidence intervals (95 % CI). Median follow-up times were estimated with the reverse method. Cox regression model was used to estimate hazard ratios (HR) and their 95 % CI.

The overall study population included 342 patients who received SCAI, from November 2013 to July 2019. Median age was 66 years (range 34−86); most of patients were male (61.4 %), 22.5 % had Eastern Cooperative Oncology Group performance status (ECOG PS) of 2, and histology was adenocarcinoma in the majority of patients (71 %). SCAI was administered in second line in 86 cases (25.1 %), in third line in 197 cases (57.6 %) and as fourth or further lines in 59 cases (17.3 %). Median follow-up time from chemotherapy initiation was 10.7 months (95 % CI 7.5–13.9). The majority of patients (38.9 %) received a taxane-based chemotherapy across different lines.

Among 86 patients who were treated with SCAI in second-line, 67 (78 %) received a platinum-based doublet.

5.3.1.5 First-line platinum-based chemotherapy

In Table 16 and Table 17 the study characteristics for the identified relevant studies for first-line platinum-based chemotherapy. Only one of the studies reported data for RET-specific populations or subpopulations (Gautschi et al. 2017).

Table 16 Overview of the 1L studies identified for pemetrexed in combination with platinum

Study	Study design	Histology	RET	Stage	ECOG PS	Intervention	Comparator	Smokers	Median age
Gautschi 2017[15]	Retrospective register study	Adenocarcinoma: 158/162	Yes	I-IV	NR	Platinum+pemetrexed (n=66)	NA	Total population: Former 27% Current 10%	61
Keynote-189[19, 20, 39]	double-blind, randomized, phase 3 trial	Adenocarcinoma: 198/206 NSCLC not otherwise specified: 4/206	No	IIIB or IV NSCLC	0-1	Pembrolizumab + pemetrexed + carboplatin (n=410)	Pemetrexed + cis/carboplatin (n=206)	87.9%	63.5
Keynote-21[16-18]	randomised, open-label, phase 2	Adenocarcinoma: 55/63 NSCLC not otherwise specified: 7/63 Large cell carcinoma: 1/63	No	IIIB or IV NSCLC	0-1	Pembrolizumab + pemetrexed + carboplatin	Pemetrexed + carboplatin	86%	63.2
Kim 2012[22]	single-arm phase II in Japanese patients	Adenocarcinoma: 48/49	No	IIIB or IV NSCLC	0-1	carboplatin + pemetrexed (n=862)	-	51%	63
Manegold 2000[23]	multicentre phase II trial	Squamous cell carcinoma:17/36 Adenocarcinoma: 17/36 NSCLC: 2/36	No	IIIB or IV NSCLC	Performance status ≤ 1 on the WHO scale	cisplatin + pemetrexed (n=36)	-	-	58
Scagliotti 2008[25]	noninferiority, phase III, randomized study	Adenocarcinoma: 436/862 Large-cell carcinoma: 76/862 Squamous cell carcinoma: 244/862	No	IIIB or IV NSCLC	0-1	cisplatin + gemcitabine (n=863)	cisplatin + pemetrexed (n=862)	73%	61.0

Table 17 Result overview of the 1L studies identified for vinorelbine in combination with platinum

Study	Study design	Histology	RET	Stage	ECOG PS	Intervention	Comparator	Smokers	Median age
NAVotrial 01[21]	Randomized Phase II Study	Adenocarcinoma: 88%	No	IIIB or IV NSCLC	NA	cisplatin + pemetrexed (n=51)	cisplatin + vinorelbine (n=100)	40%	61

		Large cell carcinoma: 10%							
Ohe 2017[24]	Randomized phase III study	Adenocarcinoma: 104-121 Squamous cell carcinoma: 16-29	No	IIIB or IV NSCLC	0-1	cisplatin + irinotecan (n=145)	carboplatin + paclitaxel (n=145) cisplatin + gemcitabine (n=146) cisplatin + vinorelbine (n=145)	NA	61-63

5.3.2 Results per study

5.3.2.1 LIBRETTO-001

For LIBRETTO-001 the following data cut-offs (DCO) are presented: 16th December 2019, which is used in the indirect comparisons and the health economic models, and a later DCO at 30th March 2020. In the following section data from the 30th March 2020 DCO will be presented in order to provide data with the longest follow-up, except for quality of life and safety estimates as only 16th December 2019 analyses are available at the time of submission.

Outcome	Data cut-off	Population(s)
Median OS	30th March 2020	RET fusion-positive NSCLC: IAS (n=218) and PAS (n=105)
	16th December 2019	IAS (n=184) and PAS (n=105)
OS rate at 24 months	16th December 2019	RET fusion-positive NSCLC: IAS (n=184) and PAS (n=105)
Quality of life	16th December 2019	RET fusion-positive NSCLC: IAS (n=184)
Objective response rate	30th March 2020	RET fusion-positive NSCLC: IAS (n=218) and PAS (n=105)
Median PFS	30th March 2020	RET fusion-positive NSCLC: IAS (n=218) and PAS (n=105)
	16th December 2019	IAS (n=184) and PAS (n=105)
Adverse events	16th December 2019	RET fusion-positive NSCLC safety population (n=329) Overall safety population (n [redacted])

Measures of mortality

Median OS

At the 30th March 2020 data cut-off the median OS was not reached for either the PAS (95% CI: 25.7–NE) nor the IAS (95% CI: 25.7 - NE) populations with a median follow-up of 19.9 months for the PAS population and a median follow-up of 14.3 months for the IAS[29].

Table 18 OS for second line (PAS) RET fusion-positive NSCLC patients - Patients Enrolled by 30 March 2020[29]

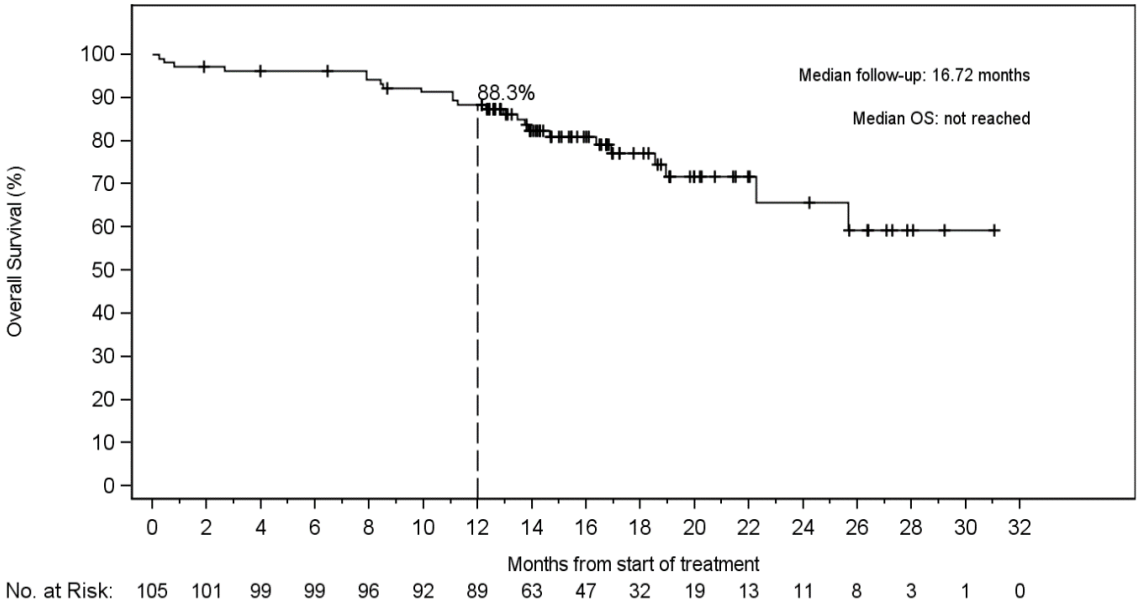
	Second line (PAS) N = 105	Second line (IAS) N = 218
Duration of OS (months)		
Median	NE	NE

95% CI	25.7-NE	25.7-NE
Duration of follow-up (months)		
Median	19.9	14.3

Abbreviations: CI: confidence interval; NE: not estimable; OS: overall survival; PAS: Primary Analysis Set.

Similar results were seen at 16th December 2019 data cut-off with median OS not reached for either the PAS (95% CI: 22.3–NE) nor the IAS (95% CI: 22.3 - NE) populations.[36]

Figure 6. Kaplan-Meier plot of OS for second line (PAS) *RET* fusion-positive NSCLC patients -16th December 2019 cut-off[29]



Note: Censored patients denoted by "+".
Abbreviations: OS: overall survival.

Figure 7. Kaplan-Meier plot of OS for second line (IAS) *RET* fusion-positive NSCLC patients - 16th December 2019 cut-off

Note: Censored patients denoted by "l".
Abbreviations: OS: overall survival.
Source: Eli Lilly and Company Ltd. Data on File (16th December 2019 cut-off).[36]

OS rate at 24 months

At 24 months, the Kaplan-Meier predicted OS rate was 68.0% (95% CI: 55.3–77.8) and 67.3% (95% CI: 55.4 – 76.7) for the PAS and IAS, respectively.[29] The Kaplan-Meier plot of OS for the PAS and IAS is shown in Figure 6 and Figure 7, respectively. Although OS data remains immature, preliminary results suggest that selpercatinib treatment may offer survival benefits to second line patients with advanced *RET* fusion-positive NSCLC.

Quality of life

Mean change from baseline in EORTC-QLQ-C30

As of the 16th December 2019 data cut-off, [redacted] patients (IAS population) with *RET* fusion-positive NSCLC had completed a baseline assessment as part of a "QLQ-C30 Analysis Set". EORTC QLQ-C30 questionnaires were administered at baseline and completed approximately every 8 weeks until the end of treatment visit.[36] Mean change from baseline was not available.

The mean baseline score for global health status/QoL subscale was [redacted] (standard deviation [SD]: [redacted]). Of the [redacted] patients, [redacted] experienced definite improvement in the global health status/QoL subscale. Of those with definite improvement, there was a median time to definite improvement of [redacted] months. The average scores for the physical, emotional, role, cognitive and social functioning subscales were each [redacted] points at baseline.[36]

NSCLC patients [redacted] reported mean (SD) baseline scores for QLQ-C30 subscales of [redacted] for physical functioning; [redacted] for emotional functioning; [redacted] for role functioning; [redacted] for cognitive functioning and [redacted]) for social functioning. Of these [redacted] patients, the proportion who experienced definite improvements in each of the QLQ-C30 subscales as of the data cut-off was [redacted] for physical functioning [redacted] for emotional functioning; [redacted] for role functioning; [redacted] for cognitive functioning and [redacted] for social functioning. The proportion of patients experiencing definite worsening in QLQ-C30 subscales was [redacted] for physical functioning; [redacted] emotional functioning; [redacted] for role functioning; [redacted] for cognitive functioning and [redacted] for social functioning. There were no consistent clinically meaningful differences in mean patient scores over time. The proportion of

patients with any clinically meaningful improvement or worsening is reported in Table 19 by cycle.[36]

Across the majority of the QLQ-C30 subscales, a numerically higher proportion of NSCLC patients reported improved scores versus worsening QLQ-C30 subscale scores. Overall, at the data cut-off the majority of advanced *RET* fusion-positive NSCLC patients had stable or improved quality of life as determined by QLQ-C30 subscales following treatment with selpercatinib.[36]

Table 19. EORTC-QLQ-C30: Proportion of patients with *RET* fusion-positive NSCLC who improved or worsened from baseline at scheduled follow-up visits

QLQ-C30 Subscale, n (%)		Cycle 3	Cycle 5	Cycle 7	Cycle 9
Global health status/QoL	N	[redacted]	[redacted]	[redacted]	[redacted]
	Improved	[redacted]	[redacted]	[redacted]	[redacted]
	Worsened	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: EORTC QLQ: European Platform of Cancer Research Quality of Life Questionnaire.
Source: Eli Lilly and Company Ltd. Data on File (16th December 2019 cut-off).[36]

Objective response rate

Proportion of patients with complete and partial response

The ORR, defined as the proportion of patients with BOR of confirmed CR or PR based on RECIST v1.1, was 64% (67/105; 95% CI: 53.9–73.0) by IRC assessment for the PAS and 57% (124/218 [95% CI: 50.0-63.6]) for the IAS population at the 30th March 2020 data cut-off. In the PAS population, the majority (64; 61.0%) of patients achieved a PR, whilst three (2.9%) patients achieved a CR.[29] A similar response to selpercatinib was observed in IAS patients, with the majority (115; 52.8%) achieving a PR and 9 (4.1%) achieving a CR.

Table 20. BOR and ORR for second line (PAS and IAS) *RET* fusion-positive NSCLC patients - Patients Enrolled by 30 March 2020[29]

	Second line (PAS) N = 105	Second line (IAS) N = 218
Best overall response, n (%)		
Complete response	3 (2.9)	9 (4.1)
Partial response	64 (61.0)	115 (52.8)
Stable disease	30 (28.6)	81 (37.2)
Progressive disease	4 (3.8)	5 (2.3)
Not evaluable	4 (3.8)	8 (3.7)
Objective response rate (CR+PR)		
n (%)	67 (63.8)	124 (56.9)
95% CI	(53.9–73.0)	(50.0-63.6)

Abbreviations: CI: confidence intervals; CR: complete response; IAS: Integrated Analysis Set; PAS: Primary Analysis Set; PR: partial response.

The robustness and consistency of the primary analysis was confirmed by pre-specified subgroup analyses. Response rate and duration of response were analysed by several demographic variables using IRC assessment for PAS patients. Subgroup analyses were not performed in the IAS population at the 16th December 2019 cut-off.[36] The ORR and DOR by other baseline disease characteristics are presented in Table 21.

In patients with ECOG of 0, the ORR was [redacted] and the DOR was [redacted] months, whilst patients with an ECOG of 1–2 reported an ORR and DOR of [redacted] and [redacted] months, respectively.[36] In patients who never

smoked, the ORR was [redacted] and the DOR was not reached.[36] In patients who had smoked, the ORR was [redacted] and the DOR was [redacted] months. Women had a higher ORR than men ([redacted] versus [redacted]), although the underpinning cause of this minor efficacy differential was unclear.[36]

Table 21. ORR and DOR by demographics for *RET* fusion-positive NSCLC patients (PAS) based on IRC assessment - 16th December 2019 cut-off

	N	Responders	ORR% (95% CI)	DOR (Range)
Overall	105	67	[redacted]	[redacted]
Age				
<65 years	[redacted]	[redacted]	[redacted]	[redacted]
≥65 years	[redacted]	[redacted]	[redacted]	[redacted]
Sex				
Male	[redacted]	[redacted]	[redacted]	[redacted]
Female	[redacted]	[redacted]	[redacted]	[redacted]
ECOG				
0	[redacted]	[redacted]	[redacted]	[redacted]
1-2	[redacted]	[redacted]	[redacted]	[redacted]
Smoking status				
Never smoked	[redacted]	[redacted]	[redacted]	[redacted]
Smoker	[redacted]	[redacted]	[redacted]	[redacted]
CNS metastasis at baseline by investigator				
Yes	[redacted]	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]	[redacted]

Notes: Censored observations denoted by "+".
Abbreviations: CNS: central nervous system; DOR: duration of response; ECOG: Eastern Cooperative Oncology Group; NR: not reached; ORR: objective response rate; PR: partial response.
Source: Eli Lilly and Company Ltd. Data on File (16th December 2019 cut-off).[36]

In patients that had prior anti-PD-1/PD-L1 therapy, the ORR was [redacted] and the DOR was not reached. In patients that did not receive prior anti-PD-1/PD-L1 therapy, the ORR was [redacted] and the DOR was [redacted] months.

Table 22. ORR and DOR by number and type of prior therapy for *RET* fusion-positive NSCLC patients (PAS) based on IRC assessment - 16th December 2019 cut-off

	N	Responders	ORR% (95% CI)	DOR (Range)
Overall	105	67	[redacted]	[redacted]
Number of prior therapies				
1–2	[redacted]	[redacted]	[redacted]	[redacted]
3 or more	[redacted]	[redacted]	[redacted]	[redacted]

Prior anti-PD-1/PD-L1 therapy				
Yes	58	38	65.5 (51.9–77.5)	[redacted]
No	47	29	61.7 (46.4–75.5)	[redacted]

Notes: Censored observations denoted by "+".
Abbreviations: DOR: duration of response; NR: not reached; PD-L1: programmed death ligand 1; ORR: objective response rate.
Source: Eli Lilly and Company Ltd. Data on File (16th December 2019 cut-off).[36] Drilon et al. 2020, Supplementary Appendix.[40]

Progression-free survival

Median PFS

As of the 30th March 2020 data cut-off the median PFS was 19.3 months (95% CI: 13.9–NE) in the PAS, with a median follow-up of 13.9 months. The median PFS for the IAS was slightly longer at 19.3 months (95% CI: 16.5, NE), with a median follow-up of 13.6 months.

By Kaplan-Meier estimate, the probability of being progression-free at 24 months was 42[redacted] and 43.7[redacted] respectively for the PAS and IAS populations.[29]. The Kaplan-Meier plots of PFS for the PAS and IAS populations are presented in **Figure 8** and **Figure 9**, respectively.[36]

Table 23. PFS for second line (PAS and IAS) *RET* fusion-positive NSCLC patients - Patients Enrolled by 30 March 2020[29]

	Second line (PAS) N = 105	Second line (IAS) N = 218
Duration of PFS (months)		
Median	19.3	19.3
95% CI	13.9–NE	16.5-NE
Duration of follow-up (months)		
Median	13.9	13.6

Notes: Censored observations denoted by "+".
Abbreviations: CI: confidence intervals; NE: not evaluable; IAS: Integrated Analysis Set; PAS: Primary Analysis Set; PFS: progression free survival.

Figure 8. Kaplan-Meier plot of PFS based on IRC assessment for second line (PAS) *RET* fusion-positive NSCLC patients

Note: Censored patients denoted by "+".
Abbreviations: PFS: progression free survival.
Source: Eli Lilly and Company Ltd. Data on File (16th December 2019 cut-off).[36]

Figure 9. Kaplan-Meier plot of PFS based on IRC assessment for second line (IAS) *RET* fusion-positive NSCLC patients

Note: Censored patients denoted by "+".
Abbreviations: PFS: progression free survival.
Source: Drilon et al. 2020, Supplementary Appendix.[40]

Adverse events

Proportion of patients with a grade 3-4 adverse events

In the OSAS, Grade 3 or 4 TEAEs were reported in [redacted] patients, irrespective of relatedness to study drug (**Table 24**). The most common Grade 3–4 events were hypertension ([redacted], ALT increase ([redacted] AST increase ([redacted] and hyponatraemia ([redacted] Despite the relatively high level of Grade 3–4 TEAEs observed in the OSAS, only a small proportion ([redacted] were considered by the Investigator to be related to selpercatinib. In the NSCLC SAS, [redacted]) patients experienced Grade 3–4 TEAS, irrespective of relatedness to selpercatinib (Table 24). A smaller proportion ([redacted]) were considered by the Investigator to be related to selpercatinib. Common TEAES mirrored the OSAS analysis set.[36]

Table 24. Grade 3–4 adverse events in 2% or more of patients (Safety Analysis Sets)

Preferred term	*RET* fusion-positive NSCLC (N = 329)	Related to selpercatinib (*RET* fusion-positive NSCLC) (N = 329)	Overall population (N [redacted])	Related to selpercatinib (overall population) (N [redacted])
1 or more Grade 3–4 AEs	[redacted]	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]	[redacted]
ALT increased	[redacted]	[redacted]	[redacted]	[redacted]
AST increased	[redacted]	[redacted]	[redacted]	[redacted]
Hyponatraemia	[redacted]	[redacted]	[redacted]	[redacted]
Lymphopenia	[redacted]	[redacted]	[redacted]	[redacted]
ECG QT prolonged	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]	[redacted]	[redacted]
Thrombocytopaenia	[redacted]	[redacted]	[redacted]	[redacted]
Dyspnoea	[redacted]	[redacted]	[redacted]	[redacted]
Neutropoenia	[redacted]	[redacted]	[redacted]	[redacted]
Hypocalcaemia	[redacted]	[redacted]	[redacted]	[redacted]
Hypophosphatemia	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AE: adverse event; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; ECG: electrocardiogram; NSCLC: non-small cell lung cancer; NR: not reported; *RET* rearranged during transfection.
Source: Eli Lilly and Company Ltd. Data on File (16th December 2019 cut-off).[36]

Narrative assessment of adverse events

The two safety analysis sets utilised in LIBRETTO-001 that were pertinent to this submission are as follows:

- The Overall Safety Analysis Set (OSAS, N = [redacted]) includes all patients, regardless of tumour type or treatment history, who were enrolled in LIBRETTO-001 and received one or more doses of selpercatinib as of the 16th December 2019 data cut-off date
- The *RET* fusion-positive NSCLC Safety Analysis Set (SAS) (N = 329) includes all patients with documented *RET* fusion-positive NSCLC who were enrolled in LIBRETTO-001 and received one or more doses of selpercatinib as of the 16th December 2019 data cut-off date

In the OSAS, [redacted] of AEs were considered to be related to selpercatinib but the majority were deemed to be of low severity, with [redacted] classed as Grade 3 or Grade 4 (**Table 25**).[36] A similar

pattern was observable in the NSCLC SAS. Permanent discontinuation of selpercatinib due to AEs were infrequent ([redacted] in the OSAS, with no predominant pattern among the individual AEs reported. No deaths within 28 days of last dose were attributed to selpercatinib. All were attributed to either disease progression ([redacted]), to an AE unrelated to the drug or to unknown reasons.[36]

Selpercatinib was therefore well tolerated across all tumour types studied in LIBRETTO-001, with a safety profile characterised by recognisable toxicities that were easily monitored, reversed with dose interruption or addressed through dose reduction or concomitant medication.

Table 25. Summary of safety trends (Safety Analysis Sets)

	RET fusion-positive NSCLC (N = 329)	Overall population (N = [redacted])
Any AE, n (%)		
All	[redacted]	[redacted]
Related to selpercatinib	[redacted]	[redacted]
Grade 3 or 4 AE, n (%)		
All	[redacted]	[redacted]
Related to selpercatinib	[redacted]	[redacted]
AE leading to treatment discontinuation, n (%)		
All	[redacted]	[redacted]
Related to selpercatinib	[redacted]	[redacted]
SAE, n (%)		
All	[redacted]	[redacted]
Related to selpercatinib	[redacted]	[redacted]
Fatal AE (none related to selpercatinib)	[redacted]	[redacted]

Abbreviations: AE: adverse event; NSCLC: non-small cell lung cancer; *RET* rearranged during transfection; SAE: serious adverse event.
Source: Eli Lilly and Company Ltd. Data on File (16th December 2019 cut-off).[36]

Treatment-emergent adverse events

A high proportion of patients in the OSAS ([redacted]) experienced at least 1 TEAE during treatment. The most common TEAEs in the OSAS were: dry mouth ([redacted] diarrhoea ([redacted] hypertension ([redacted] aspartate aminotransferase (AST) increase ([redacted]%), alanine transaminase (ALT) increase ([redacted]%), fatigue ([redacted]%), constipation ([redacted] peripheral oedema ([redacted] headache ([redacted]%) and nausea ([redacted]%).[36] The vast majority of adverse events were classified as Grades 1–2 and deemed to be clinically manageable in clinical practice. Rates of different TAEs were broadly similar between the OSAS and NSCLC SAS analysis sets, as presented in **Table 25**.[36]

Adverse events of special interest

Based on predictions from the *RET*-related literature, the preclinical toxicology programme and clinical experience with selpercatinib, AEs of special interest were identified for focussed analysis: ALT/AST increase, drug hypersensitivity reaction, hypertension and notable event QT prolongation. These special interest AEs are monitorable and reversible with successful dose modification strategies, which allow the majority of patients who experience these events to continue safely on therapy.[36]

ALT/AST increase

In the OSAS, the TEAE of AST increase was reported in [redacted] patients ([redacted] related to selpercatinib; [redacted] Grade 3–4; [redacted] Grade 3–4 and related to selpercatinib). The TEAE of ALT increase was reported in [redacted] of OSAS patients ([redacted] related to selpercatinib; [redacted]% Grade 3–4; [redacted]% Grade 3-4 and related to selpercatinib). The majority of ALT and AST TEAEs were Grade 1 or 2.[36] Although ALT and AST TEAEs were the most common reasons for dose interruptions (ALT = [redacted]%; AST= [redacted]%) and reductions (ALT= [redacted]%; AST= [redacted]%), they led to permanent discontinuation in only [redacted] OSAS patients. In addition, no patients met Hy's Law criteria of drug induced liver injury.[36]

Hypersensitivity

Selpercatinib-related hypersensitivity was defined as patients who, early in their treatment course, experienced a constellation of symptoms or findings inclusive of maculopapular rash that was often preceded by fever and associated with arthralgias or myalgias. These were often followed by platelet decrease and/or transaminase increases or, less commonly, by a blood pressure decrease, tachycardia and/or creatinine increase.[36]

In the OSAS, drug hypersensitivity was observed in a [redacted] of patients who had one or more AE of hypersensitivity. [redacted] patients had a single event; [redacted] had multiple events (range [redacted]). The median time to first onset was [redacted] weeks (range: [redacted]). Eleven patients ([redacted] experienced Grade 3 as the worst severity and there were no Grade 4 hypersensitivity events. Hypersensitivity was deemed serious (all related to selpercatinib) in [redacted] OSAS patients.[36] Overall, interventions through dose interruption and dose reduction were successful and, in most cases, patients were able to continue study drug treatment after dose reduction and/or interruption. Of the [redacted] OSAS patients with hypersensitivity reactions, [redacted] patients underwent dose reduction, dose interruption or both. Only 3 of the [redacted] patients were reported to permanently discontinue selpercatinib due to a hypersensitivity reaction.[36]

Hypertension

In the OSAS, the AE of hypertension was reported in [redacted] of patients ([redacted] considered related to selpercatinib), with [redacted] of patients having experienced Grade 3–4 AEs of hypertension ([redacted] Grade 3–4 and related to selpercatinib). A similar proportion of NSCLC SAS patients experienced hypertension ([redacted] with [redacted] classified as Grade 3–4.[36]

Of the [redacted] OSAS patients, [redacted] of patients had a reported chronic history of hypertension and [redacted] did not. The frequency of reported hypertension AEs was similar between these patients despite the difference in medical history. A minority of OSAS patients required dose interruption ([redacted] considered related to selpercatinib) and/or reduction ([redacted] considered related to selpercatinib). No patients discontinued therapy due to an AE of hypertension.[36]

Notable Event-QT Prolongation

Any grade ECG QT prolongation was reported for [redacted] patients ([redacted] with [redacted] considered related to selpercatinib in the OSAS. The majority of events were Grade 1 or Grade 2. One patient had an AE of QTcF prolongation that was deemed serious. QTcF prolongation was manageable by selpercatinib dose interruptions ([redacted] patients) or reductions ([redacted] patients), while no action with drug was taken in [redacted] patients. No patients discontinued treatment due to QT prolongation in the OSAS.[36]

To date, no clinically significant TEAE related to QT prolongation such as treatment emergent arrhythmias, ventricular tachycardia, ventricular fibrillation, sudden death or Torsades de Pointes have been observed. QT prolongation events can be managed and reversed with successful dose modification strategies, allowing patients to continue safely on therapy.[36]

Safety conclusions

In LIBRETTO-001, selpercatinib was well tolerated across all tumour types studied. The safety profile was characterised by recognisable toxicities across both the NSCLC SAS and OSAS. These toxicities were easily reversable through dose interruption or addressed through dose reduction or concomitant medication. As a result, permanent discontinuation of selpercatinib due to TEAEs were infrequent ([redacted]), meaning patients could consistently benefit from the highly efficacious anti-tumour activity of selpercatinib. This favourable safety profile is as anticipated given the high specificity of selpercatinib for *RET*.

CNS progression

Median time to CNS progression

In patients who had CNS metastasis at baseline by Investigator assessment, the ORR was [redacted] and the DOR was [redacted] months.[36] In patients who did not have CNS metastasis, the ORR was [redacted] and the DOR was not reached. The ORR and DOR for patients with no metastasis at baseline were difficult to characterise due to the low number of patients.[36] Subgroup analysis confirmed that the beneficial results of selpercatinib treatment, in terms of a reduction in tumour size, were broadly consistent across age, gender, race and smoking status.

The CNS data have been based on the PAS (n=105), [redacted] patients had CNS metastasis and [redacted] of these were measurable. CNS ORR was seen among [redacted] among these [redacted] had CR, [redacted] had PR, and [redacted]) stable disease. Median DOR was [redacted], and median duration of response follow-up was [redacted] months.[Data on file]

Table 26 CNS Response Rate by IRC at 16th December data cut-off

Status	RET fusion-positive NSCLC patients with measurable CNS metastases (n=[redacted])*
CNS objective response rate, % (n)	[redacted]
95% CI	[redacted]
CNS best overall response, % (n)	
Complete response	[redacted]
Partial response	[redacted]
Stable disease	[redacted]
CNS duration of response (mo)	
Median (95% CI)	[redacted]
CNS duration of response follow-up (mo)	
Median (25th-75th percentile)	[redacted]

*Patients had CNS measurable lesions per RECIST v1.1

5.3.2.2 Park et al. 2018

Measures of mortality

Median OS

In the subset analysis of patients receiving platinum-based therapy as salvage chemotherapy after immunotherapy (n=24) the median overall survival times was 10.9 months.

OS rate at 24 months

The study did not report on OS rate at 24 months.

Quality of life

Mean change from baseline in EORTC-QLQ-C30

The study did not report on EORTC-QLQ-C30.

Objective response rate

Proportion of patients with complete and partial response

The ORR for platinum doublet SCAI therapy was 66.7% (16 of 24).

Progression-free survival

Median PFS

In the subset analysis of patients receiving platinum-based therapy as salvage chemotherapy after immunotherapy (n=24) the median PFS was 4.5 months.

Adverse events

Proportion of patients with a grade 3-4 adverse events

The study did not report on adverse events.

Narrative assessment of adverse events

The study did not report on adverse events.

CNS progression

Median time to CNS progression

The study did not report on median time to CNS progression.

5.3.2.3 Metro et al. 2019

Measures of mortality

Median OS

Not reported

OS rate at 24 months

Not reported

Quality of life

Mean change from baseline in EORTC-QLQ-C30

Not reported

Objective response rate

Proportion of patients with complete and partial response

Of the 31 evaluable patients 21 were treated with platinum-based chemotherapy, and of these 9 (42.9% CI: 25.5 – 67.0) obtained an objective response. The ORR was similar in the single-agent chemotherapy group (40.0%).

Progression-free survival

Median PFS

The median PFS reported among the 42 patients who received salvage chemotherapy was 4.5 months (95% CI: 3.1–6.5 months).

Adverse events

Proportion of patients with a grade 3-4 adverse events

Not reported

Narrative assessment of adverse events
Not reported

CNS progression
Median time to CNS progression
Not reported

5.3.2.4 CLARITY

Measures of mortality
Median OS
Median OS from initiation of chemotherapy was 6.8 (95% CI: 5.5–8.1) months in the overall population. The median OS for the subset of patients receiving chemotherapy as second line treatment were 8.4 (95% CI: 5.6−11.2) months.

OS rate at 24 months
Not reported

Quality of life
Mean change from baseline in EORTC-QLQ-C30
Not reported

Objective response rate
Proportion of patients with complete and partial response
The ORR for the patients treated with chemotherapy was 22.8 % (77 partial responses and 1 complete response).

Progression-free survival
Median PFS
Median PFS for the subset of patients receiving chemotherapy was 4.1 months (95 % CI: 3.4−4.8).

Adverse events
Proportion of patients with a grade 3-4 adverse events
Not reported

Narrative assessment of adverse events
Not reported

CNS progression
Median time to CNS progression
Not reported

5.3.3 Comparative analyses

In the following section narrative comparisons are presented individually for the observational studies identified and for the first-line platinum-based chemotherapy studies.

5.3.3.1 Narrative comparison of efficacy in LIBRETTO-001 and observational studies

The results from LIBRETTO-001 indicates a better efficacy, across all outcomes, compared to the estimates for platinum-based chemotherapy reported in the observational studies in patients previously treated with immunotherapy (Table 27). Park et al. 2008 reported an ORR of 66.7%, a result that is higher than the reported ORR for selpercatinib. Although the ORR reported by Park

et al. 2008 the effect cannot be seen in the estimates for PFS and OS, which both are significantly lower than the PFS and OS reported for selpercatinib treatment.

Table 27 Results overview of LIBRETTO-001 and observational studies

	LIBRETTO-001	Park et al. 2018	Metro et al. 2019	CLARITY
Median OS	NE (25.7–NE)	10.9	NA	8.4 (5.6–11.2)
OS rate at 24 months	68.0%	NA	NA	NA
Mean CFB in EORTC-QLQ-C30	NA	NA	NA	NA
ORR; % (95% CI)	64% (53.9–73.0)	66.7%	42.9% (25.5 – 67.0)	22.8%
Median PFS	19.3 (13.9–NE)	4.5	4.5 (3.1–6.5)	4.1 (3.4–4.8)
Grade 3-4 adverse events	[redacted]%*	NA	NA	NA

*Based on the *RET* fusion-positive NSCLC Safety Analysis Set (SAS) (N = 329).
NA: not available, NR: not reached; NE: not estimated

5.3.3.2 Narrative comparison of efficacy in LIBRETTO-001 and first-line platinum-based chemotherapy studies

As previously described, it is not feasible to conduct any formal comparative statistical analyses between the results for 2L selpercatinib treatment in a RET-specific population and 1L platinum-based chemotherapy in non-RET-specific populations. As illustrated in the data for clinical question 2 the difference on efficacy between first and second line is significant, hence comparing estimates for 1L platinum-based chemotherapy with 2L RET-targeted therapy should be interpretated with great caution given the obvious limitations in the underlying data. Additionally, there is considerable differences between the studies in terms of inclusion and exclusions criteria and baseline characteristics. Hence, the following section will present the reported results for the identified studies for 1L platinum-based chemotherapy in a table format without any comparative analysis.

Table 28 Result overview of the 1L studies identified for pemetrexed in combination with platinum

Study	Median OS	OS at 24 months	EORTC-QLQ-C30	ORR	Median PFS	Grade 3-4 AEs	CNS progression
LIBRETTO-001[1]	NE (25.7–NE)	68.0%	NA	64% (53.9–73.0)	19.3 (13.9–NE)	[redacted]%*	NA
Gautschi 2017[15]	24.8 (13.6-32.3)	NA	NA	51% (38.1-63.4)	7.8 (5.3-10.2)	NA	NA
Keynote-189[19, 20]	10.7 (8.7-13.6)	29.9%	-2.6 (-5.8 – 0.5)	ORR: 40/206 (19.4%) CR: 1 PR: 39	4.9 (4.7-5.5) PFS-2**: 9.0 (7.6-10.4)	135/202 (66.8%)	NA
Keynote-21[16, 17]	21.1 (14.9-NR)	48%	NA	ORR: 21/63 (33%; 22-46) CR: 2 PR: 19	9.9 (6.2-15.2)	19/62 (31%)	NA
Kim 2012[22]	24.3 (18.7-29.9)	NA	NA	ORR: 51% CR: 0	6.3 (4.0-8.6)	NA	NA

				PR: 25/49			
Manegold 2000[23]	10.9 (6.8-16.9)	NA	NA	ORR: 39% CR: 0 PR: 14/36	TTP***: 6.3 (2.9-14.1)	24%	NA
Scagliotti 2008[25]	10.3 Smokers: 10.0 (9.4-11.1) Non-smokers: 15.9 (13.8-20.2)	18.9%	NA	30.6%	4.8	556/839 (66.3%)	NA

*Based on the *RET* fusion-positive NSCLC Safety Analysis Set (SAS) (N = 329) ***time to progression; **PFS-2: was defined as the time from randomization to objective tumour progression on next-line treatment (including subsequent anti–PD-[L]1 therapy) or death from any cause, whichever occurs first.
NA: not available, NR: not reached; NE: not estimated

Table 29 Result overview of the 1L studies identified for vinorelbine in combination with platinum

Study	Median OS	OS at 24 months	EORTC-QLQ-C30	ORR	PFS	Grade 3-4 AEs	CNS progression
LIBRETTO-001[1]	NE (25.7–NE)	68.0%	NA	64% (53.9–73.0)	19.3 (13.9–NE)	[redacted]%*	NA
NAVotrial 01[21]	10.2	NA	NA	24%	4.2	NA	NA
Ohe 2017[24]	11.4	21.4	NA	31.1%	4.1**	NA	NA

*Based on the *RET* fusion-positive NSCLC Safety Analysis Set (SAS) (N = 329) **TTP, time to progressive disease
NA: not available, NR: not reached; NE: not estimated

5.4 Clinical question 4: What value does selpercatinib have compared to docetaxel or pemetrexed in adults with advanced RET-altered non-small non-squamous cell lung cancer that has progressed after treatment with checkpoint inhibitor immunotherapy and platinum-based chemotherapy?

The DMC protocol requests the available evidence for adults with incurable RET-altered non-squamous, non-small cell lung cancer with PD-L1 expression <50% previously progressed following treatment with checkpoint inhibitor immunotherapy and platinum-based chemotherapy compared to docetaxel or pemetrexed monotherapy. As also stated in the protocol limited data is available for second line docetaxel or pemetrexed within NSCLC as the treatment landscape has changed during the last 5 years with the introduction of immunotherapy. Hence, the clinical evidence for docetaxel or pemetrexed after treatment with checkpoint inhibitor immunotherapy and platinum-based chemotherapy are very limited.
The search strings defined in the protocol resulted in a very limited number of relevant hits: 2 for pemetrexed and one for docetaxel, in RET-specific populations. Both studies identified for pemetrexed were observational studies in NSCLC patients with RET rearrangements. The study identified for docetaxel was the REVEL trial, which investigated ramucirumab + docetaxel versus placebo + docetaxel and included patients with advanced, squamous or non-squamous NSCLC who had progressed after a first-line platinum-based chemotherapy regimen irrespective of RET status. Although, the population included in REVEL differ from LIBRETTO-001 (not RET specific) and the clinical question (patients had not progressed after treatment with checkpoint inhibitor immunotherapy and platinum-based chemotherapy) the control arm is included in the

comparison, as the best available estimates for docetaxel treatment in adults with advanced RET-altered NSCLC.

5.4.1 Presentation of relevant studies

5.4.1.1 LIBRETTO-001

The description of LIBRETTO-001 and the subset relevant for clinical question 4 has previously been in section 5.3.1.1.

5.4.1.2 Shen et al. 2020

Shen et al. 2020 was a multicentre, retrospective study involving 10 hospitals in China from 2011 to 2018. Data was collected from all patients during disease progression, including the chemotherapy regimen and targeted drugs used. The response to systemic therapies was assessed locally by each investigator and 1 radiologist using the RECIST, version 1.1, including the complete response (CR), partial response (PR), stable disease, and progressive disease. The ORR was defined as the sum of CR and PR. The disease control rate (DCR) was defined as the sum of the objective response and stabilization rates (CR plus PR plus stable disease).

PFS was defined as the period from the initial date of drug treatment to the date of confirmation of disease progression, as evaluated by RECIST, version 1.1, or death. OS was measured from the date of confirmed stage IIIB/IV NSCLC to death or the last follow-up evaluation. The last follow-up date was April 12, 2019. Kaplan-Meier estimates and the log-rank test were applied to evaluate PFS and OS.

A total of 62 patients with NSCLC and RET rearrangements were enrolled in the present study. Of the 62 patients, 33 were men and 29 were women, with a median age of 59 years (range, 25-78 years). The smoking history was divided into former or current (n = 25) and never (n = 37). Of the 62 patients, 18 had undergone surgery and 12 had not developed a relapse. Also, 6 patients had stage IIIB and 44 had stage IV lung adenocarcinoma.

Of the 62 patients, 28 patients received second line treatment, including pemetrexed-based chemotherapy for 10 and other treatment regimens for 18. 40 had received first-line chemotherapy regimen, including pemetrexed/platinum (n = 19), pemetrexed monotherapy (n = 3), paclitaxel/platinum (n = 14), and gemcitabine/platinum (n = 4)

5.4.1.3 Tan et al. 2020

Tan et al. 2020 retrospective cohort study of patients with RET-rearranged NSCLC treated at the National Cancer Centre Singapore between April 2014 and March 2020. The study aimed to conduct a comparative analysis of FISH and next-generation sequencing (NGS) methods of molecular testing for RET rearrangements, to correlate their clinical and treatment outcomes to the different classes of systemic therapies.
Descriptive statistics, including median and range for continuous variables, and percentages for categorical variables were used. Kaplan-Meier survival analysis was performed to determine progression-free survival and overall survival (OS). Survival was tested using Cox proportional hazard model. Hazard ratio (HR) with its 95% confidence intervals (CIs) is displayed with the associated log-rank p value.

There were a total of 64 patients with RET-rearranged NSCLC included during the study period. The median age of the patients at diagnosis was 62 years (range 25–85), with 36 patients (56%) who were women, 49 (77%) were of Chinese ethnicity, 61 (95%) had histologic diagnosis of

adenocarcinoma, 50 (78%) had stage IV disease at diagnosis, 44 (69%) were never smokers, and the median number of lines of systemic therapies received were 2 (range: 0-7).

5.4.1.4 REVEL

REVEL was a randomised, double-blind, placebo-controlled phase 3 study enrolling adults at in 26 countries on six continents. Eligible patients had pathologically confirmed, squamous or non-squamous stage IV NSCLC that had progressed during or after a single platinum-based chemotherapy regimen, with or without bevacizumab or maintenance therapy.
Patients were randomly assigned (1:1) to receive intravenous docetaxel 75 mg/m² plus intravenous ramucirumab 10 mg/kg (ramucirumab group; n=628) or intravenous docetaxel 75 mg/m² plus placebo (control group; n=625) on day 1 of a 21 day cycle. Randomisation was done via a centralised, interactive voice-response system and was stratified by performance status, sex, previous maintenance therapy (yes vs no), and geographical region. Patients, study staff, and the sponsor were masked to treatment assignment.
The REVEL trial enrolled 328 patients with squamous NSCLC, of which 171 patients were allocated to placebo+docetaxel. This subgroup matches the study population of LIBRETTO-001, hence results for this subgroup will be presented where data is available.

The primary endpoint was overall survival (time from randomisation until death). Secondary endpoints included PFS (time from randomisation until disease progression or death) and ORR as assessed by investigators according to RECIST 1.1 at baseline, and every 6 weeks thereafter. Adverse events were reported according to NCI-CTCAE.

Primary efficacy analysis was conducted through a stratified logrank comparison of overall survival in the intention-to-treat population. Safety analyses included all patients who received at least one dose of study drug. Overall survival and PFS survival curves were created with the Kaplan-Meier method, and HRs were estimated with stratified Cox proportional hazards models. Multivariable analysis with a stepwise Cox regression model of predefined baseline characteristics were used to examine the effect of treatment after adjustment for other significant prognostic factors. Comparison of ORRs (percentage of patients in the intention-to-treat population with a complete response or partial response) in each treatment group with the Cochran-Mantel-Haenszel test.

5.4.2 Results per study

5.4.2.1 LIBRETTO-001

Results for LIBRETTO-001 and the subset relevant for clinical question 4 have already been shown in section 5.3.2.1.

5.4.2.2 Tan et al. 2020

Median OS

Median OS in patients with late stage or recurrent disease was 37.7 months. OS was prolonged in patients treated with selective RET TKI versus untreated patients (median 49.3 versus 15.3 months; HR: 0.16 (95% CI: 0.06–0.40, p < 0.001))

OS rate at 24 months

Not reported in the study.

Quality of life

Mean change from baseline in EORTC-QLQ-C30

Not reported in the study

Objective response rate

Proportion of patients with complete and partial response

Objective response rate on platinum-pemetrexed chemotherapy was 54%.

Progression-free survival

Median PFS

The median progression-free survival on platinum-pemetrexed chemotherapy was 7.7 months.

Adverse events

Proportion of patients with a grade 3-4 adverse events

Not reported in the study

Narrative assessment of adverse events

Not reported in the study

CNS progression

Median time to CNS progression

Not reported in the study

5.4.2.3 Shen et al. 2020

Measures of mortality

Median OS

Of 40 patients with stage IIIB/IV NSCLC with RET rearrangements who had received treatment, 38 had survival follow-up data available. The median OS for the 38 patients was 26.4 months OS rate at 24 months.

OS rate at 24 months

Not reported in the study.

Quality of life

Mean change from baseline in EORTC-QLQ-C30

Not reported in the study

Objective response rate

Proportion of patients with complete and partial response

ORR and DCR after pemetrexed-based chemotherapy was 50% (11 of 22) and 90.9% (20 of 22).

Progression-free survival

Median PFS

The median PFS for the 10 patients receiving pemetrexed-based chemotherapy in the second line was 4.9 months compare to 9.2 months for the 22 patients who had received pemetrexed-based chemotherapy as first line treatment.

Adverse events

Proportion of patients with a grade 3-4 adverse events

Not reported in the study

Narrative assessment of adverse events

Not reported in the study

CNS progression

Median time to CNS progression

Not reported in the study

5.4.2.1 REVEL

Measures of mortality

Median OS

The median OS for the subgroup of patients with non-squamous histology was [redacted]n = 447][redacted] and the estimate for the overall population allocated to placebo and docetaxel was 9.1 (4.2-18.0) months.[28]

OS rate at 24 months

The OS rate at 24 months was not reported in the study but can be roughly estimated to approx. 18% from the Kaplan-Meier curve.[28]

Quality of life

Mean change from baseline in EORTC-QLQ-C30

Not reported in the study

Objective response rate

Proportion of patients with complete and partial response

ORR was reported as 14% (85 of 625) for the patients receiving placebo and docetaxel.[28]

Progression-free survival

Median PFS

The median PFS for the subgroup of patients with non-squamous histology was [redacted] and the estimate for the overall population allocated to placebo and docetaxel was 3.0 (1.4-6.9) months.[28]

Adverse events

Proportion of patients with a grade 3-4 adverse events

A total of 71% (444 of 618) of patients receiving placebo and docetaxel reported a treatment-emergent adverse event of grade 3-4. [28]

Narrative assessment of adverse events

204 (33%) of 627 patients treated with ramucirumab-docetaxel had an adverse event resulting in at least one dose adjustment (ie, reduction, delay, or omission of any study drug during a cycle). 139 (23%) of 618 patients in the placebo-docetaxel group had at least one dose adjustment. The most common adverse events leading to dose adjustments for ramucirumab compared with placebo were neutropenia (77 [12%] patients in the ramucirumab group vs 55 [9%] controls), fatigue (54 [9%] patients vs 34 [6%] controls), and febrile neutropenia (44 [7%] patients vs 28 [5%] controls). Grade 3 or worse haematological adverse events occurring in at least 10% of patients in the ramucirumab group included neutropenia, febrile neutropenia, and leucopenia. 75 patients in each group had grade 3 neutropenia. 231 (37%) of patients in the ramucirumab group and 171 (28%) controls had grade 4 neutropenia. Incidence of febrile neutropenia was higher in patients treated with ramucirumab than controls (grade 3: 61 [10%] patients vs 40 [6%] controls; grade 4: 39 [6%] patients vs 22 [4%] controls). Use of granulocyte colonystimulating factors and granulocyte macrophage colonystimulating factors did not diff er between groups (262 [42%] patients vs 226 [37%] controls). 82 (13%) patients in the ramucirumab group and 50 (8%) controls were admitted to hospital for febrile neutropenia. Rates of sepsis did not diff er

between groups, with three deaths in each group. Incidence of anaemia was higher in the control group than the ramucirumab group, with 62 (10%) patients in the ramucirumab group and 76 (12%) controls receiving a transfusion. Patients in the ramucirumab group had more bleeding or haemorrhage events of any grade (181 [29%] vs 94 [15%] controls), although rates of grade 3 or worse events were much the same (six grade 3 events in each group and one grade 4 event in the ramucirumab group [intracranial tumour haemorrhage]). Incidence of epistaxis of any grade was significantly higher in the ramucirumab group than in the control group, but few grade 3 or worse events occurred. Gastrointestinal and respiratory tract bleeding events, including haemoptysis and pulmonary haemorrhage, did not diff er between groups or according to histological disease type. Hypertension occurred more frequently in the ramucirumab group than the control group, with one grade 4 hypertension event occurring in the ramucirumab group. The number of patients who had infusion-related reactions, venous or arterial thromboembolic events, or renal failure was low and much the same between groups. Most adverse events were manageable with dose adjustments or supportive care treatments. Occurrence of serious adverse events was much the same in both treatment groups (269 [43%] in the ramucirumab group [263 hospital admissions] vs 262 [42%] in the control group [263 hospital admissions]). Increased incidence of neutropenia and febrile neutropenia in east Asia (Taiwan and South Korea) led to a docetaxel dosage change in this region: 65 (73%) patients received docetaxel 75 mg and 24 (27%) patients received docetaxel 60 mg. The lowered dose decreased the incidence of febrile neutropenia from 14 (44%) of 32 patients to none of 11 patients in the ramucirumab group and from four (12%) of 33 patients to one (8%) of 13 patients in the control group, and lowered the incidence of neutropenia to that reported in other regions. The mean duration of docetaxel treatment was much the same in the east Asian population and the rest of the world. In the treated safety population, 53 patients in the ramucirumab group and 58 controls died on study or within 30 days of final study drug dose. The number of deaths due to adverse events was much the same between groups.[28]

CNS progression

Median time to CNS progression

Not reported in the study

5.4.3 Comparative analyses

5.4.3.1 Narrative comparison of efficacy in LIBRETTO-001 and pemetrexed studies

Although, the evidence for pemetrexed in patients previously treated with immunotherapy and platinum-based chemotherapy is limited and the obvious differences in study designs between the identified studies makes it unfeasible to directly compare the results of the studies, the literature supports that treatment with selpercatinib has a superior efficacy to pemetrexed in the above defined patient population, as illustrated in Table 30.

Table 30 Result overview of the studies identified for pemetrexed

Study	Median OS	OS at 24 months	EORTC-QLQ-C30	ORR	PFS	Grade 3-4 AEs	CNS progression
LIBRETTO-001[1]	NE (25.7–NE)	68.0%	NA	64% (53.9–73.0)	19.3 (13.9–NE)	[redacted]%	NA
Shen 2020**	26.4	NR	NR	50%	4.9	NR	NR
Tan 2020	37.7	NR	NR	54%	7.7	NR	NR

REVEL[28]	9.7 (8.5-10.6)***	18%*	NR	14%	[redacted]	71%	NR

NA: not available, NR: not reached; NE: not estimated; *Estimated from KM curve **First line treatment population which does not fully match the population of LIBRETTO-001 ***Only non-squamous population

6. Other considerations

Patients with *RET* fusion-positive NSCLC and TC currently do not have access to a selective targeted therapy in Denmark.

The transition to next generation sequencing panel tests for common oncogenic drivers (ALK translocation, EGFR mutation, ROS-1 rearrangements and *RET*) are currently being performed at most of the treating university hospitals in Denmark, and is expected to be standard practice in most hospitals within the near future. This should allow clinicians to prescribe targeted therapies, like selpercatinib, when an oncogenic driver has been identified. Statements from Danish KOLs within NSCLC[41, 42] suggests that targeted treatment of the underlying oncogenic driver should be considered as early as possible in the treatment algorithm to address the underlying cause of the disease.

For patients with advanced, non-squamous NSCLC who have progressed from first line therapy, several therapeutic options are indicated depending on the first line treatment received, of which most are platinum-based chemotherapies and associated with prominent adverse events and tolerability concerns. There are currently no targeted therapeutic options available for *RET* fusion-positive NSCLC patients in the second line setting, hence it is assumed that the majority of patients will be treated with selpercatinib.
There is currently no data available to inform how the introduction of selpercatinib will impact the type, effect and duration of subsequent treatment after selpercatinib. As seen with the introduction of targeted therapy (EGFR) and ALK inhibitors and immunotherapy in Denmark, the use of chemotherapy shifted from first-line to second-line, which is a likely scenario with the introduction of selpercatinib that chemotherapy will be shifted to subsequent lines.
[redacted]

For patients with advanced TC who have progressed from first line therapy, several therapeutic options are indicated. There are second line options but these are not selective RET inhibitors but MKIs with several targets and many AEs.
Hence, it is assumed that the majority of patients will be treated with selpercatinib.
There is currently no data available to inform how the introduction of selpercatinib will impact the type, effect and duration of subsequent treatment after selpercatinib. Treatment with TKIs can be tried depending on patient performance status, hence it is expected that currently used TKIs will be shifted from second line to third line treatment options in select patients.

X

7. References

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8. Appendices

8.1 Literature search

Table A1 Inclusion and exclusion criteria	
Inclusion criteria	Population: NSCLC and thyroid cancer Intervention(s): selpercatinib Comparator(s): sorafenib, vandetanib, cabozantinib, platinum-based chemotherapy, pemetrexed or docetaxel Outcomes: as specified in the DMC protocol Settings (if applicable): Study design: RCT or observational Language restrictions: English and danish Other search limits or restrictions applied: For NSLC first line chemotherapy only carboplatin in combination with vinorelbine and potentially with pemetrexed maintenance, and secondary platinum combined with pemetrexed
Exclusion criteria	Population: other than defined in the protocol Intervention(s): other than defined in the protocol Comparator(s): other than defined in the protocol Outcomes: other than defined in the protocol Settings (if applicable): NA Study design: other than defined in the protocol Language restrictions: NA Other search limits or restrictions applied: NA

8.2 Search strategy with results

The search strings carried out in PubMed and CENTRAL via Cochrane are presented in the following tables:

Table 31 Clinical question 1 and 2 (thyroid) - PubMed

Search number	Query	Results
19	#16 OR #18	107
18	#13 AND #17	56

17	("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])	1,286,250
16	#13 AND (#14 OR #15)	67
15	(RET[tiab] OR "rearranged during transfection"[tiab]) AND (alteration*[tiab] OR altered[tiab] OR aberration*[tiab] OR aberrant[tiab] OR rearrange*[tiab] OR re-arrange*[tiab] OR fusion*[tiab] OR fused[tiab] OR mutant*[tiab] OR mutat*[tiab])	4,93
14	Proto-Oncogene Proteins c-ret[mh]	3,551
13	#11 NOT #12	238
12	Case Reports[pt] OR Comment[pt] OR Editorial[pt] OR Guideline[pt] OR Letter[pt] OR News[pt] OR Review[pt] OR Systematic Review[pt] OR case report[ti] OR review[ti]	6,888,267
11	#5 AND #10	517
10	#6 OR #7 OR #8 OR #9	10,661
9	cabozantinib[nm] OR cabozantinib[tiab] OR Cometriq*[tiab]	997
8	N-(4-bromo-2-fluorophenyl)-6-methoxy-7-((1-methylpiperidin-4-yl)methoxy)quinazolin-4-amine[nm] OR vandetanib[tiab] OR Caprelsa*[tiab] OR Zactima*[tiab]	749
7	Sorafenib[mh] OR sorafenib[tiab] OR Nexavar*[tiab]	9,38
6	selpercatinib[nm] OR selpercatinib[tiab] OR LOXO-292[tiab] OR Retevmo*[tiab]	50
5	#1 OR #4	31,045
4	#2 AND #3	31,008
3	papillary[tw] OR differentiated[tiab] OR nonmedullary[tiab] OR "non medullary"[tiab] OR medullary[tw] OR Carcinoma, Neuroendocrine[mh:noexp] OR Carcinoma, Medullary[mh]	281,611
2	(thyroid[ti] AND (cancer[ti] OR cancers[tiab] OR adenocarcinoma[ti] OR carcinoma[ti])) OR Thyroid Neoplasms[mh:noexp]	57,071
1	Thyroid Cancer, Papillary[mh] OR Thyroid cancer, medullary[nm]	5,412

Table 32 Clinical question 1 and 2 (thyroid) - CENTRAL

ID	Search	Hits
#1	[mh "Thyroid Cancer Papillary"] or "thyroid papillary carcinoma":kw	128
#2	("thyroid medullary carcinoma"):kw	70
#3	(thyroid near/4 (cancer or adenocarcinoma or carcinoma)):tiab OR [mh ^"Thyroid Neoplasms"]	1314
#4	(papillary or differentiated or nonmedullary or "non medullary" or medullary):tiab	4725
#5	[mh ^"Carcinoma Neuroendocrine"] or [mh "Carcinoma Medullary"]	63
#6	#3 AND (#4 OR #5)	796
#7	#1 or #2 or #6	832
#8	(selpercatinib or LOXO-292 or Retevmo*):tiab kw	7
#9	(sorafenib OR Nexavar*):tiab kw	1845
#10	(vandetanib or Caprelsa* or Zactima*):tiab kw	196
#11	(cabozantinib or Cometriq*):tiab kw	331
#12	#8 or #9 or #10 or #11	2281
#13	#7 and #12	135
#14	[mh "Proto-Oncogene Proteins c-ret"]	9

#15	protein next Ret:kw	13
#16	((RET OR "rearranged during transfection") near/5 (alteration* or altered or aberration* or aberrant or rearrange* or re-arrange* or fusion* or fused or mutant* or mutat*)):tiab	82
#17	#14 or #15 or #16	91
#18	#13 and #17	22
#19	("conference abstract" or review):pt	186576
#20	(abstract or review):ti	14929
#21	NCT*:au	201959
#22	(clinicaltrials.gov or trialsearch):so	353754
#23	(abstract or conference or meeting or proceeding*):so	44786
#24	annual meeting:ab	13377
#25	18-#24	587859
#26	#18 not #25	8
#27	(#13 not #18) not #25	31

Table 33 Clinical question 3 and 4 (NSCLC) - PubMed

Search number	Query	Results
29	#18 OR #28	120
28	#7 AND #17 AND #27	108
27	#19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26	5,833,404
26	Registries[mh] OR registry[tiab] OR nation-wide[tiab] OR nationwide[tiab] OR real-worl[tiab] OR real-life[tiab]	241,177
25	(observational[tiab] OR cohort[tiab] OR prospective[tiab] OR retrospective*[tiab]) AND (study[tiab] OR analy*[tiab])	1,511,864
24	(comparative[tiab] OR multicent*[tiab] OR multi-cent* OR single-cent*[tiab] OR single-arm[tiab]) AND (trial*[tiab] OR study[tiab])	429,945
23	(phase 1[tiab] OR phase I[tiab] OR phase 2[tiab] OR phase II[tiab] OR phase 3[tiab] OR phase III[tiab]) AND (trial*[tiab] OR study[tiab])	129,351
22	randomized[tiab] OR randomised[tiab] OR randomly[tiab] OR controlled[tiab] OR placebo[tiab]	1,465,987
21	clinical trial[tiab] OR controlled trial[tiab]	283,191
20	Cohort Studies[mh] OR Prospective Studies[mh] OR Retrospective Studies[mh]	2,087,571
19	Clinical Trial[pt] OR Comparative Study[pt] OR Multicenter Study[pt] OR Observational Study[pt]	2,761,299
18	#7 AND #12 AND #17	28
17	#15 NOT #16	5,426
16	Case Reports[pt] OR Comment[pt] OR Editorial[pt] OR Letter[pt] OR News[pt] OR case report[ti]	4,092,536
15	#13 OR #14	6,207
14	(RET[tiab] OR "rearranged during transfection"[tiab]) AND (alteration*[tiab] OR altered[tiab] OR aberration*[tiab] OR aberrant[tiab] OR rearrange*[tiab] OR re-arrange*[tiab] OR fusion*[tiab] OR fused[tiab] OR mutant*[tiab] OR mutat*[tiab])	4,93
13	Proto-Oncogene Proteins c-ret[mh]	3,551
12	#8 OR #9 OR #10 OR #11	161,639

11	Pemetrexed[mh] OR pemetrexed[tiab]	3,601
10	Docetaxel[mh] OR docetaxel[tiab]	17,242
9	Platinum[mh] OR Platinum Compounds[mh] OR Cisplatin[mh] OR Organoplatinum Compounds[mh] OR Carboplatin[mh] OR platin*[tiab] OR cisplatin[tiab] OR cis-platin[tiab] OR carboplatin[tiab]	148,052
8	selpercatinib[nm] OR selpercatinib[tiab] OR LOXO-292[tiab] OR Retevmo*[tiab]	50
7	#1 OR #2 OR #3 OR #4 OR #5 OR #6	63,005
6	Adenocarcinoma of Lung[mh] AND drug therapy[sh]	2,002
5	lung[ti] AND adenocarcinoma[ti]	10,074
4	(nonsquamous[ti] OR non-squamous[ti]) AND lung[ti] AND (cancer[ti] OR carcinoma[ti])	511
3	Carcinoma, Non-Small-Cell Lung[mh] AND drug therapy[sh]	21,824
2	(non-small-cell-lung[ti] OR nonsmall-cell-lung[ti]) AND (cancer[ti] OR cancers[ti] OR carcinoma[ti] OR adenocarcinoma[ti])	42,029
1	nsclc[ti]	5,469

Table 34 Clinical question 3 and 4 (NSCLC) – CENTRAL

ID	Search	Hits
#1	nsclc:ti	3912
#2	((non-small-cell-lung or nonsmall-cell-lung) and (cancer or carcinoma or adenocarcinoma)):ti	8840
#3	[mh "Carcinoma Non-Small-Cell Lung"] or "non small cell lung cancer":kw	8596
#4	[mh "Adenocarcinoma of Lung"] or (lung next adenocarcinoma):ti kw	550
#5	#1 or #2 or #3 or #4	13071
#6	(selpercatinib or LOXO-292 or Retevmo*):tiab kw	7
#7	(organoplatinum or carboplatin or platin* or cisplatin or cis-platin):ti kw	18125
#8	(docetaxel or pemetrexed):tiab kw	8963
#9	#6 or #7 or #8	24293
#10	[mh "Proto-Oncogene Proteins c-ret"]	9
#11	protein next Ret:kw	13
#12	((RET OR "rearranged during transfection") near/5 (alteration* or altered or aberration* or aberrant or rearrange* or re-arrange* or fusion* or fused or mutant* or mutat*)):tiab	82
#13	#10 or #11 or #12	91
#14	NCT*:au	201959
#15	(clinicaltrials.gov or trialsearch):so	353754
#16	(abstract or conference or meeting or proceeding*):so	44786
#17	#14 or #15 or #16	398713
#18	(#5 and #9 and #13) not #17	5
#19	((#5 and #13) not #17) not #18	7

Table 35 NSCLC observational studies - PubMed

Search number	Query	Results
23	#18 AND #22	14

22	#19 OR #20 OR #21	3,098,534
21	Registries[mh] OR registry[tiab] OR database[tiab] OR nation-wide[tiab] OR nationwide[tiab] OR real-world[tiab]	558,737
20	(observational[tiab] OR cohort[tiab] OR prospective[tiab] OR retrospective[tiab]) AND (study[tiab] OR analysis[tiab])	1,317,544
19	Observational Study[pt] OR Multicenter Study[pt] OR Cohort Studies[mh] OR Prospective Studies[mh] OR Retrospective Studies[mh]	2,265,467
18	#12 AND #17	46
17	#13 OR #14 OR #15 OR #16	46,42
16	programmed cell death[ti] OR programmed death ligand[ti]	4,892
15	PD-L1[ti] OR PDL1[ti] OR PD-1[ti] OR PD1[ti]	8,804
14	checkpoint[ti] AND inhibit*[ti]	4,625
13	immunotherapy[ti] OR prior immunotherapy[tiab]	29,557
12	#10 AND #11	1,427
11	Platinum[mh] OR Platinum Compounds[mh] OR Cisplatin[mh] OR Organoplatinum Compounds[mh] OR Carboplatin[mh] OR platin*[tiab] OR cisplatin[tiab] OR cis-platin[tiab] OR carboplatin[tiab] OR chemotherapy[ti]	231,211
10	#7 AND #8 AND #9	3,361
9	2L[tiab] OR second-line[tiab] OR late* line[tiab] OR salvage[tiab] OR palliative[tiab] OR progressed[tiab] OR relapsed[tiab] OR Salvage Therapy[mh]	263,95
8	advanced[tiab] OR metasta*[tw] OR stage III*[tiab] OR stage IV[tiab]	1,007,789
7	#1 OR #2 OR #3 OR #4 OR #5 OR #6	63,006
6	Adenocarcinoma of Lung[mh] AND drug therapy[sh]	2,002
5	lung[ti] AND adenocarcinoma[ti]	10,074
4	(nonsquamous[ti] OR non-squamous[ti]) AND lung[ti] AND (cancer[ti] OR carcinoma[ti] OR adenocarcinoma[ti])	511
3	Carcinoma, Non-Small-Cell Lung[mh] AND drug therapy[sh]	21,824
2	(non-small-cell-lung[ti] OR nonsmall-cell-lung[ti]) AND (cancer*[ti] OR carcinoma[ti] OR adenocarcinoma[ti])	42,031
1	NSCLC[ti]	5,469

Table 36 NSCLC 1L platinum-based chemotherapy - PubMed

Search number	Query	Results
26	#22 AND #25	192
25	#23 OR #24	776,119
24	naive[tiab] OR untreated[tiab] OR non-treated[tiab] OR nontreated[tiab]	275,905
23	1st[ti] OR 1L[tiab] OR first-line[tiab] OR firstline[tiab] frontline[tiab] OR front-line[tiab] OR induction[tiab]	516,554
22	#17 NOT #21	448
21	#18 OR #19 OR #20	198,601
20	pre-treated[tiab] OR pretreated[tiab] OR previously treated[tiab] OR heavily treated[tiab]	87,897
19	2L[ti] OR second-line[ti] OR late* line[ti] OR salvage[ti] OR palliative[ti] OR Salvage Therapy[mh]	56,094
18	resectable[ti] OR resected[ti] OR neoadjuvant[ti] OR adjuvant[ti]	56,957

17	#15 NOT #16	496
16	Case Reports[pt] OR Comment[pt] OR Editorial[pt] OR Guideline[pt] OR Letter[pt] OR News[pt] OR Review[pt] OR case report[ti]	6,718,876
15	#13 AND #14	522
14	("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])	1,286,250
13	#11 AND #12	1,35
12	Platinum[mh] OR Platinum Compounds[mh] OR Cisplatin[mh] OR Organoplatinum Compounds[mh] OR Carboplatin[mh] OR platin*[ti] OR cisplatin[ti] OR cis-platin[ti] OR carboplatin[ti]	93,697
11	#9 AND #10	9,993
10	advanced[tiab] OR metasta*[tw] OR stage* III*[tiab] OR stage* IV[tiab] OR unresectable[tiab] OR inoperable[tiab] OR aNSCLC[tiab] OR mNSCLC[tiab]	1,040,299
9	#5 OR #6 OR #7 OR #8	20,149
8	Adenocarcinoma of Lung[mh] AND drug therapy[sh]	2,002
7	lung[ti] AND adenocarcinoma[ti]	10,074
6	(nonsquamous[ti] OR non-squamous[ti]) AND lung[ti] AND (cancer[ti] OR carcinoma[ti] OR adenocarcinoma[ti])	511
5	(#1 OR #2 OR #3) AND #4	9,675
4	nonsquamous[tiab] OR non-squamous[tiab] OR adenocarcinoma*[tw]	249,894
3	Carcinoma, Non-Small-Cell Lung[mh] AND drug therapy[sh]	21,824
2	(non-small-cell-lung[ti] OR nonsmall-cell-lung[ti]) AND (cancer*[ti] OR carcinoma[ti] OR adenocarcinoma[ti])	42,031
1	NSCLC[ti]	5,469

Table 37 NSCLC 1L platinum-based chemotherapy - CENTRAL

ID	Search	Hits
#1	nsclc:ti	3912
#2	((non-small-cell-lung or nonsmall-cell-lung) and (cancer or carcinoma or adenocarcinoma)):ti	8840
#3	[mh "Carcinoma	8596
#4	(nonsquamous or "non squamous" or adenocarcinoma):ti	9270
#5	(#1 or #2 or #3) and #4	2092
#6	[mh "Adenocarcinoma of Lung"] or (lung next adenocarcinoma):ti	550
#7	#5 or #6	2526
#8	(advanced or metasta* or stage* next III* or stage* next IV or unresectable or inoperable or aNSCLC or mNSCLC):tiab kw	93525
#9	#7 and #8	2110
#10	(organoplatinum or carboplatin or platin* or cisplatin or cis-platin):ti kw	18125
#11	#9 and #10	1003
#12	(resectable or resected or neoadjuvant or adjuvant or 2L or second-line or late* next line or salvage or palliative):ti	22493
#13	(pre-treated or pretreated or previously next treated or heavily next treated):tiab	9610
#14	#12 or #13	31768
#15	#11 not #14	888

#16	(1st or 1L or first-line or firstline or frontline or front-line or induction or naive or untreated or non-treated or nontreated):tiab	104597
#17	#15 and #16	608
#18	("conference abstract" or review):pt	186576
#19	(abstract or review):ti	14929
#20	NCT*:au	201959
#21	(clinicaltrials.gov or trialsearch):so	353754
#22	(abstract or conference or meeting or proceeding*):so	44786
#23	annual meeting:ab	13377
#24	6-#23	587859
#25	#17 not #24	232
#26	#25 not pubmed:an	58

Table 38 NSCLC docetaxel or pemetrexed - PubMed

Search number	Query	Results
25	#21 AND #24	102
24	#22 OR #23	227,001
23	pre-treated[tiab] OR pretreated[tiab] OR previously treated[tiab]	87,581
22	2L[tiab] OR second-line[tiab] OR salvage[tiab] OR palliative[tiab] OR Salvage Therapy[mh]	142,645
21	#17 NOT #20	301
20	#18 OR #19	256,828
19	resectable[ti] OR resected[ti] OR neoadjuvant[ti] OR adjuvant[ti]	56,957
18	treatment-naive[tiab] OR untreated[tiab] OR non-treated[tiab] OR nontreated[tiab]	200,672
17	#15 NOT #16	366
16	Case Reports[pt] OR Comment[pt] OR Editorial[pt] OR Guideline[pt] OR Letter[pt] OR News[pt] OR Review[pt] OR case report[ti]	6,718,876
15	#13 AND #14	424
14	("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])	1,286,250
13	#11 AND #12	1,189
12	Docetaxel[mh] OR docetaxel[tiab] OR Pemetrexed[mh] OR pemetrexed[tiab]	20,374
11	#9 AND #10	9,993
10	advanced[tiab] OR metasta*[tw] OR stage* III*[tiab] OR stage* IV[tiab] OR unresectable[tiab] OR inoperable[tiab] OR aNSCLC[tiab] OR mNSCLC[tiab]	1,040,299
9	#5 OR #6 OR #7 OR #8	20,149
8	Adenocarcinoma of Lung[mh] AND drug therapy[sh]	2,002
7	lung[ti] AND adenocarcinoma[ti]	10,074
6	(nonsquamous[ti] OR non-squamous[ti]) AND lung[ti] AND (cancer[ti] OR carcinoma[ti] OR adenocarcinoma[ti])	511

5	(#1 OR #2 OR #3) AND #4	9,675
4	nonsquamous[tiab] OR non-squamous[tiab] OR adenocarcinoma*[tw]	249,894
3	Carcinoma, Non-Small-Cell Lung[mh] AND drug therapy[sh]	21,824
2	(non-small-cell-lung[ti] OR nonsmall-cell-lung[ti]) AND (cancer*[ti] OR carcinoma[ti] OR adenocarcinoma[ti])	42,031
1	NSCLC[ti]	5,469

Table 39 NSCLC docetaxel or pemetrexed - CENTRAL

ID	Search	Hits
#1	nsclc:ti	3912
#2	((non-small-cell-lung or nonsmall-cell-lung) and (cancer or carcinoma or adenocarcinoma)):ti	8840
#3	[mh "Carcinoma	8596
#4	(nonsquamous or "non squamous" or adenocarcinoma):ti	9270
#5	(#1 or #2 or #3) and #4	2092
#6	[mh "Adenocarcinoma of Lung"] or (lung next adenocarcinoma):ti	550
#7	#5 or #6	2526
#8	(advanced or metasta* or stage* next III* or stage* next IV or unresectable or inoperable or aNSCLC or mNSCLC):tiab kw	93525
#9	#7 and #8	2110
#10	(docetaxel or pemetrexed):tiab kw	8963
#11	#9 and #10	1083
#12	(treatment-naive or untreated or non-treated or nontreated):tiab	23917
#13	(resectable or resected or neoadjuvant or adjuvant):tiab kw	39958
#14	#11 not (#12 or #13)	838
#15	(2L or second-line or salvage or palliative):tiab kw	16994
#16	(pre-treated or pretreated or previously next treated):tiab	9588
#17	#14 and (#15 or #16)	262
#18	("conference abstract" or review):pt	186576
#19	(abstract or review):ti	14929
#20	NCT*:au	201959
#21	(clinicaltrials.gov or trialsearch):so	353754
#22	(abstract or conference or meeting or proceeding*):so	44786
#23	annual meeting:ab	13377
#24	6-#23	587859
#25	#17 not #24	72
#26	#25 not pubmed:an	20

8.3 Studies excluded based on full-text screening

Table 40 Studies excluded based on full-text screening - thyroid

Full reference	Reason for exclusion

Endocrine effects of the tyrosine kinase inhibitor vandetanib in patients treated for thyroid cancer, Brassard et al., J Clin Endocrinol Metab, 2011	The publication do not report any of the outcomes defined in the protocol
Analysis of Biomarkers and Association With Clinical Outcomes in Patients With Differentiated Thyroid Cancer: Subanalysis of the Sorafenib Phase III DECISION Trial, Brose et al., Clin Cancer Res, 2019	The publication do not report any additional results for the population in scope compared to the original publication by Brose et al. 2014
Identification of Expression Profiles Defining Distinct Prognostic Subsets of Radioactive-Iodine Refractory Differentiated Thyroid Cancer from the DECISION Trial, Capdevila et al., Mol Cancer Ther, 2020	The publication do not report any additional results for the population in scope compared to the original publication by Brose et al. 2014
Multikinase inhibitors for the treatment of radioiodine refractory thyroid cancer: what have we learned from the 'real-world' experience?, Costante et al., Curr Opin Oncol, 2021	The publication do not report any of the outcomes defined in the protocol
Real-World Efficacy and Safety of Cabozantinib and Vandetanib in Advanced Medullary Thyroid Cancer, Koehler et al., Thyroid, 2020	Patients are treated in 1L with either cabozantinib or vandetanib
Long-term analysis of the efficacy and tolerability of sorafenib in advanced radio-iodine refractory differentiated thyroid carcinoma: final results of a phase II trial, Schneider et al., Eur J Endocrinol, 2021	Only patients that have not received any systemic treatment (1L)

Table 41 Studies excluded based on full-text screening - NSCLC

Full reference	Reason for exclusion
Vandetanib plus docetaxel versus docetaxel as second-line treatment for patients with advanced non-small-cell lung cancer (ZODIAC): a double-blind, randomised, phase 3 trial, Herbst et al., The Lancet Oncology, 2010	2L after chemotherapy which does not match the population defined in the protocol (post immunotherapy + chemotherapy. No PD-L1 status reported.
Clinical outcomes with pemetrexed-based systemic therapies in RET-rearranged lung cancers, Drilon et al., Annals of oncology, 2016	The study only reports on four patients with RET-arranged lung cancer in 2L
Immune checkpoint inhibitors for patients with advanced lung cancer and oncogenic driver alterations: Results from the IMMUNOTARGET registry, Mazieres et al., Annals of Oncology, 2019	No relevant comparators reported
Cisplatin in combination with metronomic vinorelbine as front-line treatment in advanced non-small cell lung cancer: a multicenter phase II study of the Hellenic Oncology Research Group (HORG), Katsaounis et al., Cancer chemotherapy and pharmacology, 2015	Only squamous NSCLC

8.4 Main characteristics of included studies

Table 42 DECISION

DECISION	
Trial name	DECISION
NCT number	NCT00984282

Objective	1. Evaluation of efficacy and safety of sorafenib versus placebo in patients with locally advanced or metastatic progressive RAI-refractory DTC[5]. 2. To elucidate the patterns and management of effective adverse events (AEs) in sorafenib-treated patients in the DECISION trial, by detailed describing by-treatment-cycle analyses of the incidence, prevalence, and severity of hand–foot skin reaction (HFSR), rash/desquamation, hypertension, diarrhoea, fatigue, weight loss, increased serum thyroid stimulating hormone, and hypocalcaemia [6].
Publications – title, author, journal, year	1. Sorafenib in locally advanced or metastatic, radioactive iodinerefractory, differentiated thyroid cancer: a randomized, double-blind, phase 3 trial, Brose et al. (2014), Lancet, 2014. 2. Safety and tolerability of sorafenib in patients with radioiodine-refractory thyroid cancer, Worden et al., Endocrine-Related Cancer, 2015
Study type and design	Phase 3, double-blinded , parallel-group RCT. Double-blinded randomized placebo-controlled phase 3 study. Patients were randomized 1:1 via an interactive voice response system (IVRS) to either sorafenib 400 mg (2x200 mg tablets) or matching placebo. Patients receiving placebo could crossover to open-label sorafenib upon progression. The study is completed.
Follow-up time	Median time from randomization until last known follow-up was 16.2 months (range, 0.03–33.2).
Population (inclusion and exclusion criteria)	<u>Inclusion criteria:</u> • Age ≥ 18 year • Locally advanced or metastatic differentiated thyroid cancer (papillary, follicular and Hurthle cell) • Poorly differentiated and other thyroid variants (e.g. insular, tall cell, etc.) are eligible provided that the histology has no medullary differentiation nor anaplastic features • Progression within 14 months (RECIST [Response Evaluation Criteria in Solid Tumours] should be used as a basis for the assessment of disease progression) • RAI (radioactive iodine) refractory <u>Exclusion Criteria:</u> • Histologic subtypes of thyroid cancer other than differentiated (i.e. like anaplastic and medullary carcinoma, lymphoma or sarcoma) • Prior anti-cancer treatment with tyrosine kinase inhibitors, monoclonal antibodies (licensed or investigational) that target VEGF (vascular endothelial growth factor) or VEGF Receptors or other targeted agents • Prior anti-cancer treatment for thyroid cancer with use of chemotherapy (low dose chemotherapy for radiosensitization is allowed) or Thalidomide or any of its derivatives
Intervention	Patients were randomized 1:1 to either sorafenib 400 mg or matching placebo, both given orally twice-daily (taken 12 hours apart without food, ≥1 hour before or 2 hours after a meal) for a 28 days cycle.

- Intervention (sorafenib): 207 patients
- Placebo: 210 patients

Baseline characteristics

Baseline demographic characteristics were well balanced. In total, 96.4% (n=402/417) of patients had distant metastases, most commonly in lung (86.1%; n=359/417), lymph nodes (51.3%; n=214/417), and bone (27.1%; n=113/417). Over 75% of patients were positive for fluorodeoxyglucose (FDG) uptake on positron emission tomography scintigraphy. The median age of the patient population was 63 for both groups (range 24-82 for sorafenib and range 30-87 for placebo). In the intervention group 103 (49.8) were women, and there were women 115 (54.8%) in the placebo group.

	Sorafenib (n=207)	Placebo (n=210)
Female, n (%)	103 (49·8)	115 (54·8)
Age (years)		
Median (range)	63 (24–82)	63 (30–87)
≥60 years, n (%)	127 (61·4)	129 (61·4)
Ethnicity, n (%)		
White	123 (59·4)	128 (61·0)
Asian	47 (22·7)	52 (24·8)
Black	6 (2·9)	5 (2·4)
Hispanic	2 (1·0)	2 (1·0)
Not reported	29 (14·0)	23 (11·0)
Region, n (%)		
Europe	124 (59·9)	125 (59·5)
North America	36 (17·4)	36 (17·1)
Asia	47 (22·7)	49 (23·3)
Metastases, n (%)		
Locally advanced	7 (3·4)	8 (3·8)
Distant	200 (96·6)	202 (96·2)
Time from diagnosis, months		
Median (range)	66·2 (3·9–362·4)	66·9 (6·6–401·8)
ECOG performance status, n (%)		
0	130 (62·8)	129 (61·4)
1	69 (33·3)	74 (35·2)
2	7 (3·4)	6 (2·9)
Histology by central review,[a] n (%)		
Papillary	118 (57·0)	119 (56·7)
Follicular	50 (24·2)	56 (26·7)
Poorly differentiated	24 (11·6)	16 (7·6)
Well differentiated	2 (1·0)	1 (0·5)
Nonthyroid	0	1 (0·5)
Medullary	0	1 (0·5)
Oncocytic carcinoma	2 (1·0)	0
Carcinoma, not otherwise specified	0	3 (1·4)
Missing/nondiagnostic	13 (6·3)	14 (6·7)
Most common metastatic lesion sites, n (%)		
Lung	178 (86·0)	181 (86·2)
Lymph nodes	113 (54·6)	101 (48·1)
Bone	57 (27·5)	56 (26·7)
Pleura	40 (19·3)	24 (11·4)

	Sorafenib (n=207)	Placebo (n=210)
Head and neck	33 (15·9)	34 (16·2)
Liver	28 (13·5)	30 (14·3)
Baseline FDG uptake		
Positive	161 (77·8)	159 (75·7)
Negative	14 (6·8)	15 (7·1)
Missing	32 (15·5)	36 (17·1)
Prior therapy		
Median cumulative radioiodine activity, mCi	400	376
Any prior systemic anticancer therapy, n (%)	7 (3·4)	6 (2·9)
Any prior radiotherapy, n (%)	83 (40·1)	91 (43·3)

FDG, 2-[^{18}F] fluoro-2-deoxy-D-glucose; ECOG, Eastern Cooperative Oncology Group

[a]All patients had differentiated thyroid cancer as per investigator assessment.

Primary and secondary endpoints	The primary endpoint was progression-free survival assessed every 8 weeks by central independent blinded review using modified RECIST criteria, version 1.0, modified for bone lesion. PFS for participants without disease progression or death at the time of analysis or unblinding were censored at the last date of tumour assessment before unblinding. Participants with no tumour evaluation after baseline were censored at Day 1. PD (Progression Disease)=At least a 20% increase in sum of longest diameters (LD) of measured lesions taking as reference the smallest sum LD on study since the treatment started or the appearance of 1 or more new lesions. New lesions also constituted PD. In exceptional circumstances, unequivocal progression of a nonmeasured lesion may have been accepted as evidence of disease progression in participants with measurable disease. Secondary endpoints included overall survival (OS), time to progression (TTP), objective response rate (ORR; complete or partial response [PR]), disease control rate (DCR; complete or PR and stable disease [SD] ≥4 weeks [or ≥6 months via post-hoc analysis]), and duration of response. Progression and objective response were confirmed by a repeat CT or MRI scan performed ≥4 weeks later. Safety was assessed according to National Cancer Institute Common Terminology Criteria for Adverse Events v 3.0. Patients were followed up for safety for 30 days following the last study treatment, and then every 3 months for OS. Histologic diagnoses were assessed retrospectively by an independent pathology panel.
Method of analysis	Intention-to-treat analysis were performed for PFS, OS and TTP. Assuming a one-sided alpha of 0.01, 90% power, and a 55.5% increase in median PFS, 267 PFS events were required from 420 randomized patients. PFS, TTP, and OS were assessed in all randomized patients by log-rank test using one-sided significance levels of 0.01 (PFS) and 0.025 (TTP and OS). Hazard ratios (HR) and confidence intervals (CI) were derived from a Cox proportional hazards model. ORR and DCR were assessed by Cochran–Mantel–Haenszel test (one-sided significance level: 0.025) in patients who received study medication and had a baseline and a post-baseline tumour evaluation.
Subgroup analyses	A subgroup analysis was performed for progression-free survival (PFS) stratified after population, age group, histology, lung metastases only, bone metastases, FDG-uptake, number of target or non-target lesions, target lesion size, sex and cumulative RAI ≥ 600 mCi.[5]

Table 43 Kloos et al. 2009

Kloos et al. 2009[7]	
Trial name	NA
NCT number	NA
Objective	Based on the pivotal role of Ras-Raf-MAP-ERK signalling and vascular endothelial growth factor (VEGF) in papillary thyroid cancer (PTC), a phase II clinical trial of sorafenib targeting RAF and VEGF receptor kinases in PTC were conducted.
Publications – title, author, journal, year	Phase II Trial of Sorafenib in Metastatic Thyroid Cancer, Kloos et al., Journal of Clinical Oncology, 2009.
Study type and design	Phase 2, Simon minimax two-stage design. Using a Simon minimax two-stage design, 16 or 25 chemotherapy naïve metastatic PTC patients were to be enrolled in arm A (accessible tumour for biopsy). Arm B patients had other subtypes of thyroid carcinoma or prior chemotherapy and did not require tumour biopsies.
Follow-up time	Sorafenib was continued until one of the following: progressive disease (PD), patient off of sorafenib for any reason for longer than 21 consecutive days, intercurrent illness that prevented further therapy, unacceptable adverse events (AEs), or patient withdrawal. The median follow-up is not reported.
Population (inclusion and exclusion criteria)	Inclusion and exclusion criteria were not available from www.clinicaltrials.gov. Therefore, criteria's available from the study are reported. Inclusion criteria: Patients were required to be ≥ 18 years of age with adequate performance status and measurable disease. Chemotherapy or radiation therapy was not allowed within 4 weeks before entry. Iodine-131 (131I) therapy was not allowed within 24 weeks before entry (4 weeks if negative post-treatment scan). Leukocytes 3,000/L, absolute neutrophil count 1,500/L, platelets 100,000/ L, serum bilirubin, AST/ALT, and creatinine 1.5 upper limit of normal were required. Exclusion criteria: NA.
Intervention	16 or 25 chemotherapy naive metastatic PTC patients were to be enrolled in arm A (accessible tumour for biopsy). Arm B patients had other subtypes of thyroid carcinoma or prior chemotherapy, and did not require tumour biopsies. Sorafenib was administered at 400 mg orally twice a day (with or without food). Blood pressure was monitored at least weekly until stable or at least the first 4 weeks. Patients were observed every 4 weeks for 1 year and every 12 weeks thereafter if stable. In the event of grade ≥ 3 or recurrent grade ≥2 drug-related nonhematologic toxicity or grade ≥ 2 hand-foot skin reaction (HFSR), therapy was held until the toxicity had

resolved to grade 1. Dose reduction to 600 mg/d or 400 mg/d was allowed and subsequent dose re-escalation up to 800 mg/d was allowed.

Baseline characteristics

Table 1. Patient Demographics and Clinical Characteristics

Characteristic	Arm A: PTC No.	Arm A: PTC %	Arm PTC No.	Arm PTC %
Total no. of patients	19	100	22	100
Median age, years	67		56	
Range	33-90		27-76	
Sex				
Male	11	58	10	45
Female	8	42	12	55
Race				
White	16	84	20	90
Hispanic, African American, or Asian	3	16	2	10
Pathologic type of thyroid carcinoma				
Classic PTC	15	79	15	68
Follicular variant of PTC	2	10	3	14
Tall cell variant of PTC	1	5	3	14
Poorly differentiated PTC	1	5	1	4
Follicular	—	—	—	—
Hürthle cell	—	—	—	—
Anaplastic	—	—	—	—
Site of metastasis				
Lymph node	19	100	19	86
Lung	18	95	22	100
Bone	2	10	3	14
Liver, kidney, or adrenal	4	20	2	9
Prior therapy				
I^{131}	19	100	22	100
External beam radiation	7	37	8	36
Cytotoxic chemotherapy	0	0	8	36
Celecoxib or thalidomide	5	26	8	36
Other	0	0	3	14
Study entry Tg				
Interpretable Tg	11	59	11	50
Presence of Tg antibodies	5	26	6	27
Undetectable Tg	0		2	9
Low Tg < 15 ng/mL	1	5	3	14
Unsuppressed TSH	2	10	0	
Disease status at study entry				
Symptomatic progression in preceding 6 months	1	5	4	18
RECIST progression in preceding 12 months	7	37	11	50
Stable disease	8	42	6	27
Unknown	3	16	1	5
Tumor genotype				
No. of positive *BRAF* mutation/No. tested	10/12		7/10	
Median sum of target measurable lesions at baseline, cm	6		13	
Average	9		13	
Range	3-29		3-32	
Median serum Tg at baseline, ng/mL	159		113	
Average	714		19,340	
Range	28-6,162		18-188,000	

Abbreviations: PTC, papillary thyroid cancer; I^{131}, iodine-131; Tg, serum thyroglobulin; TSH, thyroid-stimulating hormone; RECIST, Res
Solid Tumors.

Primary and secondary endpoints

The primary end point of this study was to assess the objective response rate of sorafenib in chemotherapy-naïve patients with metastatic PTC enrolled in arm A. The number of patients to be enrolled in arm B was not specified, as this arm was to explore activity of sorafenib in patients with diverse histologic types of thyroid cancers. Accrual to arm B was designed to stop as soon as arm A was fully accrued.

Secondary end points included response correlation with serum thyroglobulin (Tg); functional imaging; tumour genotype; and signalling inhibition in tumour biopsies.

Response was assessed every 2 months using RECIST (Response Evaluation Criteria in Solid Tumours).

Method of analysis

A minimax two-stage Simon design was chosen, which resulted in a trial with decision to continue after 16 response-assessable patients were accrued on arm A. Sorafenib would be ineffective or uninteresting if the true response (PR complete response [CR]) probability was lower than 10% and the regimen would be worthy of further study if the true response probability were ≥ 30%.

If two or more patients responded in the first 16, an additional nine patients would be treated for a total of 25. If five or more patients responded of the 25, it would warrant further study.

	The objective response rate for Arm A and Arm B were analysed using a Kaplan-Meier Analysis of progression-free survival (PFS), and overall survival data (OS). Response data in PTC patients were analysed in two groups: chemotherapy-naïve PTC patients on arm A and B; PTC patients with prior chemotherapy on arm B. Of note, among four response-assessable patients with follicular variant of PTC, two patients had PRs of 23- and 26-months duration, and two patients had SD of 10- or 21-months duration.
Subgroup analyses	Tumour Marker Response Serum thyroglobulin (Tg) response in differentiated thyroid cancers (DTC) were classified as ≥ 25% reduction in serum Tg compared to baseline Tg when noted on two consecutive tests obtained 8 weeks apart.

Table 44 LIBRETTO-001

LIBRETTO-001[4]	
Trial name	LIBRETTO-001
NCT number	NCT03157128
Objective	To evaluate the safety, tolerability, pharmacokinetics (PK) and preliminary anti-tumour activity of selpercatinib (also known as LOXO-292) administered orally to patients with advanced solid tumours, including RET-fusion-positive solid tumours, medullary thyroid cancer (MTC) and other tumours with RET activation
Publications – title, author, journal, year	Efficacy of Selpercatinib in RET-Altered Thyroid Cancers, Wirth et al., NEJM, 2020
Study type and design	Open-label, multi-centre Phase 1/2 study conduction in 2 parts: Phase 1 (dose escalation) and phase 2 (dose expansion) were conducted in 65 centres in 12 countries. The study is ongoing, and the expected primary completion is in March 2022.
Follow-up time	Responses were observed across all RET mutations. At a median follow-up of 7.8 months, 60 of 64 responses were ongoing.
Population (inclusion and exclusion criteria)	Inclusion Criteria: *For Phase 1:* • Patients with a locally advanced or metastatic solid tumour who: ○ patients were 12 years of age or older (where allowed by regulatory authorities otherwise, they were ≥18 years of age) and ○ have progressed on or are intolerant to standard therapy, or ○ no standard therapy exists, or in the opinion of the Investigator, are not candidates for or would be unlikely to tolerate or derive significant clinical benefit from standard therapy, or ○ decline standard therapy

- Prior MKIs with anti-RET activity are allowed.
- A RET gene alteration is not required initially. Once adequate PK exposure is achieved, evidence of RET gene alteration in tumour and/or blood is required as identified through molecular assays, as performed for clinical evaluation.
- Measurable or non-measurable disease as determined by RECIST 1.1 or RANO as appropriate to tumour type.
- Eastern Cooperative Oncology Group (ECOG) score of 0, 1, or 2 or Lansky Performance Score (LPS) ≥ 40% (age < 16 years) with no sudden deterioration 2 weeks prior to the first dose of study treatment.
- Adequate hematologic, hepatic and renal function.
- Life expectancy of at least 3 months.

For Phase 2

As for phase 1 with the following modifications:

- For Cohort 1 (up to 250 patients): Subjects must have received prior standard therapy appropriate for their tumour type and stage of disease, or in the opinion of the Investigator, would be unlikely to tolerate or derive clinical benefit from appropriate standard of care therapy.

- Cohorts 1 and 2: enrolment will be restricted to patients with evidence of a RET gene alteration in tumour.
- Cohorts 1 and 2: at least one measurable lesion as defined by RECIST 1.1 or RANO, as appropriate to tumour type and not previously irradiated.
- Cohorts 3 and 4: Enrolment closed.
- Cohort 5: (up to 200 patients):
    - Cohorts 1 and 2 without measurable disease;
    - MTC syndrome spectrum cancers (e.g., MTC, pheochromocytoma), cancers with neuroendocrine features/differentiation, or poorly differentiated thyroid cancers with other RET alteration/activation may be allowed with prior Sponsor approval;
    - cfDNA positive for a RET gene alteration not known to be present in a tumour sample.
- Cohort 6 (up to 50 patients):
    - Patients who otherwise are eligible for Cohorts 1, 2 or 5 who discontinued another RET inhibitor due to intolerance may be eligible with prior Sponsor approval.

<u>Exclusion Criteria (Phase 1 and Phase 2):</u>

- Phase 2 Cohorts 1 and 2: an additional known oncogenic driver.
- Cohorts 3 and 4: Enrolment closed.
- Cohorts 1, 2 and 5: prior treatment with a selective RET inhibitor

Notes:

	• Patients otherwise eligible for Cohorts 1, 2, and 5 who discontinued another selective RET inhibitor may be eligible for Phase 2 Cohort 6 with prior Sponsor approval. • Investigational agent or anticancer therapy (including chemotherapy, biologic therapy, immunotherapy, anticancer Chinese medicine or other anticancer herbal remedy) within 5 half-lives or 2 weeks (whichever is shorter) prior to planned start of LOXO-292 (selpercatinib). In addition, no concurrent investigational anti-cancer therapy is permitted. *Note:* Potential exception for this exclusion criterion will require a valid scientific justification and approval from the Sponsor. • Major surgery (excluding placement of vascular access) within 4 weeks prior to planned start of LOXO-292 (selpercatinib). • Radiotherapy with a limited field of radiation for palliation within 1 week of planned start of LOXO-292 (selpercatinib), with the exception of patients receiving radiation to more than 30% of the bone marrow or with a wide field of radiation, which must be completed at least 4 weeks prior to the first dose of study treatment. • Any unresolved toxicities from prior therapy greater than CTCAE Grade 1 at the time of starting study treatment with the exception of alopecia and Grade 2, prior platinum-therapy related neuropathy. • Symptomatic primary CNS tumour, metastases, leptomeningeal carcinomatosis, or untreated spinal cord compression. Patients are eligible if neurological symptoms and CNS imaging are stable and steroid dose is stable for 14 days prior to the first dose of LOXO-292 (selpercatinib) and no CNS surgery or radiation has been performed for 28 days, 14 days if stereotactic radiosurgery [SRS]. • Clinically significant active cardiovascular disease or history of myocardial infarction within 6 months prior to planned start of LOXO-292 (selpercatinib) or prolongation of the QT interval corrected (QTcF) > 470 msec. • Required treatment with certain strong CYP3A4 inhibitors or inducers and certain prohibited concomitant medications.
Intervention	A total number of 162 patients were enrolled in phase 1: • 55 patients with RET-mutant medullary thyroid cancer who had previously received vandetanib, cabozantinib, or both. • 88 patients with RET-mutant medullary thyroid cancer who had not previously received vandetanib or cabozantinib. • 19 patients with previously treated RET fusion–positive thyroid cancer. Selpercatinib was administered orally (capsule or liquid), continuously, in 28-day cycles, until disease progression, death, unacceptable toxic effects, or withdrawal of consent. *Phase 1:*

Patients who were enrolled in the phase 1 dose-escalation portion of the trial received selpercatinib at doses ranging from 20 mg once daily to 240 mg twice daily. Intrapatient dose escalation to higher doses that were determined to be safe was permitted after a minimum of one cycle of treatment.

Phase 2:

All the patients who were further enrolled in the phase 2 portion received the recommended dose of 160 mg twice daily. Patients with documented disease progression could continue selpercatinib if they were deriving clinical benefit.

Baseline characteristics

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	*RET*-Mutant MTC Previously Treated (N = 55)	*RET*-Mutant MTC Not Previously Treated (N = 88)
Median age (range) — yr	57 (17–84)	58 (15–82)
Sex — no. (%)		
Male	36 (65)	58 (66)
Female	19 (35)	30 (34)
Race — no. (%)†		
White	49 (89)	75 (85)
Asian	0	4 (5)
Black	1 (2)	1 (1)
Other	5 (9)	8 (9)
ECOG performance-status score — no. (%)§		
0	11 (20)	43 (49)
1	41 (75)	42 (48)
2	3 (5)	3 (3)
Histologic type of thyroid cancer		
Medullary	55 (100)	88 (100)
Papillary	—	—
Poorly differentiated	—	—
Hürthle cell	—	—
Anaplastic	—	—
Median no. of previous systemic regimens (range)	2 (1–8)	0 (0–2)
Previous regimen — no. (%)		
Cabozantinib, vandetanib, or both	55 (100)	0
Vandetanib only	18 (33)	0
Cabozantinib only	13 (24)	0
Cabozantinib and vandetanib	24 (44)	0
Radioiodine	—	—
Sorafenib, lenvatinib, or both	—	—
Multitargeted kinase inhibitor therapy	55 (100)	7 (8)
1	26 (47)	6 (7)
≥2	29 (53)	1 (1)
Therapy other than multitargeted kinase inhibitor therapy	17 (31)	9 (10)
Brain metastases — no. (%)	4 (7)	2 (2)
RET alteration — no. (%)		
RET M918T mutation	33 (60)	49 (56)
RET V804 M/L mutation	5 (9)	6 (7)
RET extracellular cysteine mutation¶	7 (13)	20 (23)
Other mutations‖	10 (18)	13 (15)
CCDC6-RET fusion	—	—
NCOA4-RET fusion	—	—
Other *RET* fusion**	—	—

* Percentages may not total 100 because of rounding. For *RET*-mutant medullary thyroid cancer (MTC), "previously tre
treated with vandetanib, cabozantinib, or both, and "not previously treated" indicates not previously treated with van
† Race was reported by the patient.
‡ One patient with missing data on race is included.
§ Eastern Cooperative Oncology Group (ECOG) performance-status scores range from 0 to 5, with higher scores inc
¶ Extracellular cysteine mutation was defined as a mutation that included at least one of the following cysteine re
630, or 634.
‖ Other mutations included D631-liter633delinsE, E632-liter633del, A883F, D631-liter633delinsV, L790F, D898-E901c
_S904delinsEP, K666 N, T636-V637insCRT, and D378-G385delinsE.
** Fusions that were identified in single tumors included *CCDC186-RET*, *ERC1-RET*, *KTN1-RET*, and *RUFY3-RET*.

Primary and secondary endpoints

<u>Primary end point</u>

- **Phase 1:** Identification of the MTD, and the recommended phase 2 dose (RP2D) of selpercatinib for further clinical investigation.
- **Phase 2:** The primary endpoint was overall response rate (ORR) based on the Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1 or Response assessment in neuro-oncology criteria (RANO), as appropriate to the tumour type as assessed by an independent review committee (IRC).

	Secondary end points Included progression-free survival, the duration of response, and safety. All responses required confirmation by a second consecutive scan obtained at least 4 weeks after the first scan showing a response. • **Phase 1**: Determination of the safety and tolerability of selpercatinib, characterization of the pharmacokinetics properties, and assessment of the anti-tumour activity of selpercatinib by determining ORR using RECIST 1.1 or RANO. • **Phase 2:** best overall response (BOR), duration of response (DOR), clinical benefit rate (CBR), central nervous system (CNS), overall response rate (ORR), CNS DOR, progression free survival (PFS), overall survival (OS), adverse events (AEs), and changes from baseline in clinical safety laboratory values and vital signs, characterisation of pharmacokinetic properties. Exploratory end point • Determination of the relationship between pharmacokinetics and drug effects (including efficacy and safety). • Evaluations of serum tumour markers. • CEA and calcitonin (MTC), thyroglobulin (for patients with non-MTC thyroid cancer), and ACTH/cortisol (for patients with Cushing's disease related to their cancer), before, during, and at the end of treatment with selpercatinib. • Characterisation of RET gene fusions and mutations. • Concurrently activated oncogenic pathways by molecular assays, including NGS from tumour biopsies and cfDNA. • Collection of PROs data to explore disease-related symptoms and health related quality of life HRQoL.
Method of analysis	Phase 1 Incidence rate and category of dose limiting toxicities (DLTs) were measured during the first 28-day cycle of selpercatinib treatment. Phase 2 Objective Response Rate were assessed by RECIST v1.1 or RANO, as appropriate to tumour type, as assessed by independent review committee (IRC). Kaplan–Meier Plots were used to estimate duration of response and progression-free survival among patients with RET-mutant MTC previously treated with vandetanib, cabozantinib, or both
Subgroup analyses	

Table 45 Leboulleux et al. 2012

Leboulleux et al. 2012[8]

Trial name	NA
NCT number	NCT00537095
Objective	Assess efficacy of vandetanib in patients with locally advanced or metastatic differentiated thyroid carcinoma in a randomised phase 2 setting.
Publications – title, author, journal, year	Vandetanib in locally advanced or metastatic differentiated thyroid cancer: a randomised, double-blind, phase 2 trial, Leboulleux et al., Lancet Oncol, 2012.
Study type and design	Phase 2, double-blinded, parallel-group RCT. Patients were randomized 1:1 to once-daily oral vandetanib 300 mg or matched placebo. Eligible patients were allocated sequentially with a standard computerised randomisation scheme, with randomisation balanced by study centre. Active and placebo tablets were identical and presented in identical packaging. Individual treatment codes, indicating the treatment to which a patient was randomised, were available to the local investigators. The treatment code was broken only in medical emergencies; otherwise, codes remained unbroken for the planned analyses until decisions on the assessment of individual patient data had been documented. The randomised phase of study treatment ended after patients had objective disease progression or 12 months of stable disease; patients were then given the option to either discontinue study treatment or begin open-label treatment with vandetanib 300 mg. Patients treated with vandetanib were allowed to remain on therapy at the end of the randomised phase if the investigator believed that they were obtaining a clinical benefit t or until they received another anticancer treatment. For patients entering the open-label phase, treatment codes were broken after 12 months of masked treatment, or at progression according to RECIST assessment; treatment codes were not broken for patients entering follow-up for survival
Follow-up time	The median duration of follow-up was 18.9 months (IQR 14.8–21.5) for patients randomly allocated vandetanib and 19.5 months (15.1–21.8) for patients in the placebo group.
Population (inclusion and exclusion criteria)	<u>Inclusion Criteria:</u> • Aged ≥18 years • Previously confirmed histological diagnosis of locally advanced or metastatic papillary or follicular thyroid carcinoma, without anaplastic component. Tumour sample available for centralized exploratory analysis. • Presence of one or more measurable lesions at least 1 cm in the longest diameter by spiral CT scan or 2 cm with conventional techniques. • Progressive disease following RAI131 or patient unsuitable for RAI131 after surgery. • Serum TSH<0.5mU/L. • Normal cardiac, haematological, hepatic, and renal function.

	• Patients with brain metastases were eligible if their treatment had stopped ≥ 4 weeks before the date of randomisation. • <u>Exclusion Criteria:</u> • Major surgery within 4 weeks before randomization. • Prior chemotherapy within the last 4 weeks prior to randomization. • RAI131 therapy within 3 months in patients with radioiodine uptake. • Radiation therapy within the last 4 weeks prior to randomization (with the exception of palliative radiotherapy). • Serum bilirubin >1.5 x the upper limit of reference range (ULRR). • Creatinine clearance < 30 ml/min (calculated by Cockcroft-Gault formula). • Alanine aminotransferase (ALT), aspartate aminotransferase (AST), or alkaline phosphatase (ALP) greater than 2.5 × ULRR, or greater than 5.0 × ULRR if judged by the investigator to be related to liver metastases. • Clinically significant cardiovascular event (e.g. myocardial infarction), superior vena cava [SVC] syndrome, New York Heart Association [NYHA] classification of heart failure >II within 3 months before entry, or presence of cardiac disease that in the opinion of the Investigator increases the risk of ventricular arrhythmia. • History of arrhythmia (multifocal premature ventricular contractions [PVCs], bigeminy, trigeminy, ventricular tachycardia or uncontrolled atrial fibrillation), which is symptomatic or requires treatment (CTCAE grade 3), , or asymptomatic sustained ventricular tachycardia. Subjects with atrial fibrillation controlled by medication are permitted. • Congenital long QT syndrome or 1st degree relative with unexplained sudden death under 40 years of age.
Intervention	• **Intervention:** vandetanib 300 mg oral once daily oral dose for 12 months (N=72). • **Placebo:** matched placebo presented in identical packaging as vandetanib for 12 months (N=73).

Baseline characteristics

	Vandetanib group (n=72)	Placebo group (n=73)
Median age, years (range)	63 (29–81)	64 (23–87)
Age group		
18–44 years	3 (4%)	3 (4%)
45–64 years	37 (51%)	34 (47%)
≥65 years	32 (44%)	36 (49%)
Sex		
Male	39 (54%)	39 (53%)
Female	33 (46%)	34 (47%)
WHO performance status		
0	50 (69%)	44 (60%)
1	20 (28%)	23 (32%)
2	2 (3%)	6 (8%)
Histological status*		
Papillary carcinoma	25 (40%)	24 (38%)
Follicular carcinoma†	8 (13%)	12 (19%)
Poorly differentiated carcinoma	29 (47%)	28 (44%)
Lesions at screening		
No distant metastases (M0)‡	1 (1%)	2 (3%)
Distant metastases (M1)	71 (99%)	71 (97%)
Median sum of tumour longest diameters at screening, cm (IQR)§	7·3 (3·8–11·2)	8·1 (4·1–14·3)
Previous therapy		
Radioiodine	70 (97%)	67 (92%)
Radiotherapy	36 (50%)	30 (41%)
Cytotoxic chemotherapy	8 (11%)	12 (16%)
Targeted therapy	3 (4%)	3 (4%)
Other	8 (11%)	6 (8%)
Median time from initial diagnosis to screening, years (IQR)	6·1 (2·3–9·0)	5·7 (2·3–9·7)

Data are n (%) unless otherwise stated. Additional baseline characteristics are listed in the appendix. *Histological status was confirmed by independent central review for 126 patients (62 patients in the vandetanib group and 64 patients in the placebo group) because archived tissue samples were not available for 19 patients. †Two patients with follicular carcinoma had oncocytic lesions; both patients were randomly allocated to the placebo group. ‡All three patients had locally advanced disease. §Estimated from target lesions only.

Table 1: **Demographics and baseline characteristics of the intention-to-treat population**

Primary and secondary endpoints

Primary endpoint

Was PFS, which was done following data cut-off; for those patients who crossed over, PFS was censored at the date of last evaluable RECIST assessment before the first dose of open-label treatment.

Secondary endpoints

Were the proportion of patients who achieved disease control (complete response, partial response, or stable disease at 6 months), the proportion of patients who achieved an objective response (complete response or partial response), overall survival, and safety and tolerability. Secondary endpoints were analysed at the time of the PFS analysis.

Exploratory endpoints

Were biochemical response, measured by changes in the

	concentrations of serum thyroglobulin, and early tumour response assessed by change in F-FDG tumour uptake on PET scans.
Method of analysis	The study was designed to have 80% power to detect an improvement in PFS with vandetanib treatment, corresponding to a hazard ratio (HR) of less than 0.71 (one-sided p<0.20). The corresponding two-sided p-value is also presented. Assuming a recruitment period of 12 months, a follow-up of 12 months, and a dropout rate of 10%, the study aimed to enrol at least 135 patients to provide 100 events. PFS were analysed with the log-rank test (unadjusted model with treatment factor only) in the intention-to-treat population.
Subgroup analyses	Subgroup analysis of progression-free survival (investigator assessed) were performed according to baseline assessment of clinical factors; age, metastasis size, metastasis lung site, metastasis bone site, previous radioiodine uptake, and metastatic lymph nodes, papillary carcinoma, follicular and poorly differentiated carcinoma using a hazard ratio (HR) 95% CI.

Table 46 EXAM

EXAM	
Trial name	EXAM
NCT number	NCT00704730
Objective	To evaluate the progression-free survival (PFS) with XL184 (cabozantinib) as compared with placebo (an inactive substance) in subjects with unresectable, locally advanced, or metastatic medullary thyroid cancer (MTC)
Publications – title, author, journal, year	Cabozantinib in Progressive Medullary Thyroid Cancer, Elisei et al., J Clin Oncol, 2013 [9]. Correlative analyses of RET and RAS mutations in a phase 3 trial of cabozantinib in patients with progressive, metastatic medullary thyroid cancer, Sherman et al., Cancer, 2016 [10]. Overall survival analysis of EXAM, a phase III trial of cabozantinib in patients with radiographically progressive medullary thyroid carcinoma, Schlumberger et al., Ann Oncol, 2017 [11].
Study type and design	An International, Randomized, Double-Blinded, Phase 3 Efficacy Study of XL184 Versus Placebo in Subjects With Unresectable, Locally Advanced, or Metastatic Medullary Thyroid Cancer.
Follow-up time	Exact follow-up time NA, though minimum follow-up was 42 months. Patients received treatment or placebo in 4-week cycles with radiologic tumour assessment every 12 weeks until date of first documented PD or date of death from any cause, assessed up to 34 months.
Population (inclusion and exclusion criteria)	Inclusion Criteria: • The subject has a histologically confirmed diagnosis of MTC that cannot be removed by surgery, is locally advanced, or has spread in the body.

- The subject is at least 18 years old.
- The subject has an ECOG (Eastern Cooperative Oncology Group) performance status ≤ 2.
- The subject has documented worsening of disease (progressive disease) at screening compared with a previous CT scan or MRI image done within 14 months of screening.
- The subject has recovered from clinically significant adverse events (side effects) due to any other medications that were administered prior to randomization.
- The subject has adequate organ and bone marrow function.
- Subjects who are sexually active (male and female) must agree to use medically accepted methods of contraception during the course of the study and for 3 months following discontinuation of study treatments.
- The subject has no other diagnosis of cancer (unless non-melanoma skin cancer, an early form of cervical cancer, or another cancer diagnosed ≥ 2 years previously) and currently has no evidence of malignancy (unless non-melanoma skin cancer or an early form of cervical cancer).
- Female subjects of childbearing potential must have a negative pregnancy test at screening.

Exclusion Criteria:

- The subject has received prior treatment for their cancer within 4 weeks of randomization (6 weeks for nitrosoureas or mitomycin C).
- The subject has received radiation to ≥ 25 % of bone marrow.
- The subject has received treatment with other investigational agents (unapproved therapies) within 4 weeks of randomization.
- The subject has received treatment with XL184.
- The subject has brain metastases or spinal cord compression, unless completed radiation therapy ≥ 4 weeks prior to randomization and stable without steroid and without anti-convulsant treatment for ≥ 10 days.
- The subject has a history of clinically significant episodes of vomiting blood or a recent history of vomiting > 2.5 mL (about 1/2 teaspoon) of red blood.
- The subject has serious illness other than cancer.
- The subject is pregnant or breastfeeding.
- The subject has an active infection requiring ongoing treatment.
- The subject is incapable of understanding and complying with the protocol or unable to provide informed consent.

Intervention	330 patients were randomized 2:1 in a double-blind fashion to receive either:

- Single oral daily dose of 140 mg (freebase equivalent weight) XL184 (cabozantinib) in 4-week cycles (N=219) or
- Gelatin capsules colour and size-matched to XL184 capsules administered orally daily in 4-week cycles (N=111).

Furthermore, radiographic tumour assessments were performed every 12 weeks using modified Response Evaluation Criteria in Solid Tumours (mRECIST) guidelines.

Baseline characteristics

Table 1. Baseline Demographic and Disease Characteristics

Characteristic	Cabozantinib (n = 219) No.	Cabozantinib (n = 219) %	Placebo (n = 111) No.	Placebo (n = 111) %
Male sex	151	68.9	70	63.1
Age, years				
Median	55.0		55.0	
Range	20-86		21-79	
≤ 65	172	78.5	86	77.5
> 65	47	21.5	25	22.5
ECOG PS				
0	123	56.2	56	50.5
1-2	95	43.4	55	49.5
RET mutation status				
Positive	101	46.1	58	52.3
Negative	31	14.2	10	9.0
Unknown	87	39.7	43	38.7
MTC disease type				
Hereditary	12	5.5	8	7.2
Sporadic	191	87.2	94	84.7
Unknown	16	7.3	9	8.1
RET M918T mutation status				
Positive	75	34.2	43	38.7
Negative	67	30.6	30	27.0
Unknown*	77	35.2	38	34.2
Patients with prior anticancer therapy	85	38.8	48	43.2
Patients with prior systemic therapy for MTC	81	37.0	47	42.3
Patients with two or more prior systemic therapies	52	23.7	31	27.9
Patients with prior thyroidectomy	201	91.8	104	93.7
Prior TKI status				
Yes†	44	20.1	24	21.6
Vandetanib	25	11.4	9	8.1
Sorafenib	11	5.0	8	7.2
Motesanib	7	3.2	2	1.8
Sunitinib	6	2.7	3	2.7
No	171	78.1	86	77.5
Unknown	4	1.8	1	0.9
No. of organs and anatomic locations involved at enrollment				
0-1	28	12.8	15	13.5
≥ 2	191	87.2	96	86.5
Main sites of metastatic disease				
Lymph nodes	175	79.9	86	77.5
Liver	152	69.4	67	60.4
Lung	116	53.0	64	57.7
Bone	112	51.1	56	50.5

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; MTC, medullary thyroid cancer; *RET*, rearranged during transfection; TKI, tyrosine kinase inhibitor.

*In the M918T unknown category, five of 77 patients in the cabozantinib group and four of 38 in the placebo group exhibited mutations in other exons and are therefore less likely to harbor an M918T mutation.

†Other prior TKI treatments not shown in the table: axitinib (three patients), pazopanib (three patients), and imatinib (two patients).

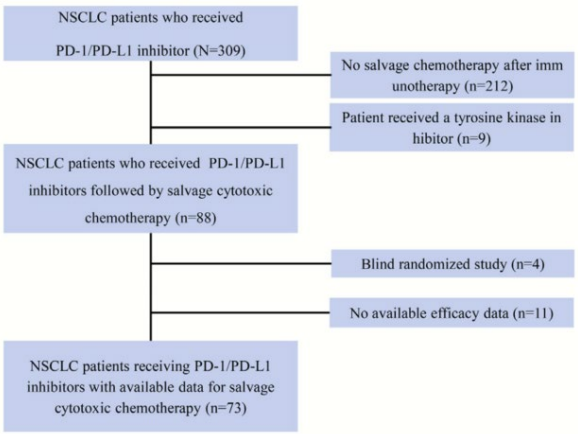
Primary and secondary endpoints

Primary outcome measures

- Progression-Free Survival (PFS) measured after treatment periods of 4-week cycles with radiologic tumour assessment every 12 weeks.

	• The duration of Progression-Free Survival (PFS) using progression events as determined by Independent Review Committee (IRC) per mRECIST, or death due to any cause. **Secondary outcome measures** • Overall Survival (OS) was assessed at 44% of required events. Duration of OS from the time of randomization to death due to any cause. A Kaplan-Meier analysis was performed to estimate the median. • Objective Response Rate (ORR) assessed at baseline and every 12 weeks until Progressive Disease (PD) up to 34 months using best overall response (BOR) of confirmed complete response (CR) or partial response (PR) as determined mRECIST v1.0 by the Independent Review Committee (IRC). • Duration of Objective Response (OR) measured from time of first documentation of Objective Response (OR), confirmed at a later visit ≥28 days later as Progressive Disease (PD) as defined by mRECIST or death due to any cause, assessed up to 34 months determined by Independent Radiology Committee (IRC). • Biochemical Response Calcitonin (CTN) % measured every 12 weeks (±5 days from randomization) until date of first documented progression or date of death from any cause, whichever came first, assessed for up to 34 months. • Biochemical Response Carcinoembryonic Antigen (CEA) % measured every 12 weeks (±5 days from randomization) until date of first documented progression or date of death from any cause, whichever came first, assessed for up to 34 months. **Exploratory measures** 1. RET mutational status was assessed using a blood sample collected predose (cycle 1, day 1) from all patients, and formalin-fixed paraffin embedded (FFPE) archival tissue collected from the primary lesion, a metastatic site, or both, unless a RET mutation could be verified from a previous analysis [32].
Method of analysis	Efficacy analyses for PFS and OS used the Kaplan-Meier method and the stratified log-rank test for inference testing. The stratified Cox proportional hazards model was used to estimate hazard ratios (HRs). The primary analysis of PFS was event driven, included radiographic progression events per the IRC and deaths, and included all randomly assigned patients (i.e., the intention-to-treat population). Patients who received subsequent anticancer treatment were censored.
Subgroup analyses	Unstratified hazard ratios (HRs) and 95% CIs for subgroup analyses of estimated PFS by prespecified baseline characteristics and by ad hoc RET mutational characteristics (sporadic, hereditary, and M918T status) [9]. The potential relationship between RET DNA sequence alterations and the efficacy of cabozantinib, which included the evaluation of PFS and ORR in patient subgroups defined by RET and RAS mutational status, and AEs by RET mutational status [11].

Table 47 Park et al 2018

Park et al. 2018[12]	
Trial name	NA
NCT number	NA
Objective	Evaluation of whether PD-1/PD-L1 inhibitors affect the antitumor effects of salvage chemotherapy administered after immunotherapy (SCAI) in patients with NSCLC.
Publications – title, author, journal, year	Increased Response Rates to Salvage Chemotherapy Administered after PD-1/PD-L1 Inhibitors in Patients with Non–Small Cell Lung Cancer, Park et al., Journal of oncology, 2018.
Study type and design	An observational retrospective, phase 2 study. From October 2013 to March 2017, 309 patients received anti–PD-1/PD-L1 inhibitors for advanced NSCLC. The study is completed.
Follow-up time	NA
Population (inclusion and exclusion criteria)	Inclusion Criteria: The study included: 1. Patients treated with anti-PD-1/PD-L1 inhibitors for advanced NSCLC. 2. Patients who exhibited disease progression after treatment with anti-PD-1/PD-L1 inhibitors and who received SCAI. 3. Patients for whom SCAI efficacy data were available.  **Figure 1.** Study flowchart. PD-1, programmed cell death 1; PD-L1, programmed death ligand 1. Exclusion Criteria: Patients were excluded if small molecule inhibitors or targeted therapies were used in the period between PD-1/PD-L1 inhibitor treatment and SCAI.
Intervention	Salvage chemotherapy administered after immunotherapy (SCAI) in patients with NSCLC.

Baseline characteristics

From October 2013 to March 2017, 309 patients received anti–PD-1/PD-L1 inhibitors for advanced NSCLC. As of data lockdown (May 2017), 212 patients had not received SCAI, nine had received tyrosine kinase inhibitors as the first therapy after immunotherapy, four were enrolled in the blind randomized study, and 11 had no available SCAI efficacy data. Thus, 73 patients met the inclusion criteria and were included in the analyses. Of these;

- 34 patients received nivolumab
- 30 received pembrolizumab
- 4 received durvalumab
- 3 received avelumab
- 1 received durvalumab plus tremelimumab
- 1 received atezolizumab.

Table 1. Patient Baseline Characteristics

Characteristics	Total (N = 73)
Median age (range), y	60 (35-83)
Sex, n (%)	
Male	50 (68.5%)
Female	23 (31.5%)
ECOG performance status, n (%)	
0	1 (1.4%)
1	58 (79.5%)
2	14 (19.2%)
Smoking status, n (%)	
Former or current	42 (57.5.9%)
Never	31 (42.5%)
Histologic subtype, n (%)	
Squamous cell carcinoma	25 (34.7%)
Adenocarcinoma	44 (60.3%)
Other	4 (5.5%)
EGFR mutation, n (%)	
Wild type	49 (67.1%)
Mutant	8 (11.0%)
Unknown	16 (21.9%)
ALK, n (%)	
Wild type	55 (75.3%)
Mutant	3 (4.1%)
Unknown	15 (20.5%)
Immunotherapy, n (%)	
Nivolumab	34 (46.5%)
Pembrolizumab	30 (41.1%)
Durvalumab	4 (5.5%)
Avelumab	3 (4.1%)
Durvalumab plus tremelimumab	1 (1.4%)
Atezolizumab	1 (1.4%)
Salvage chemotherapy after immunotherapy, n (%)	
Second-line	10 (13.7%)
Third-line	38 (52.1%)
Fourth-line	10 (13.7%)
Fifth-line	8 (11.0%)
Sixth-line or more	7 (9.5%)

ECOG, Eastern Cooperative Oncology Group; ALK, ALK receptor tyrosine kinase gene.

Primary and secondary endpoints

Primary outcome measures

- Objective response rate (ORR), which was reassessed by the investigators according to the guideline of the Response Evaluation Criteria in Solid Tumours.

Secondary outcome measures

- PFS, which was defined as time from the start of SCAI to disease progression or death due to any cause.

Method of analysis	To more objectively evaluate the clinical outcomes for SCAI, comparison of response rates and PFS with those for LCBI were performed. For example, if a patient was treated with pemetrexed plus cisplatin as a first-line therapy followed by second-line docetaxel, third-line nivolumab, and fourth-line gemcitabine therapy, gemcitabine chemotherapy would be defined as the SCAI and docetaxel therapy would be the LCBI. Comparison of ORR and PFS between the SCAI and LCBI treatments was performed by using the chi-square test and logrank test, respectively. Given that platinum-based chemotherapy and non-platinum–based chemotherapy have different efficacies for treating NSCLC, an additionally comparison of SCAI and LCBI efficacy data were performed by stratifying into platinum doublet chemotherapy and nonplatinum monotherapy groups.
Subgroup analyses	Not relevant.

Table 48 Metro et al 2019

Metro et al. 2019[13]	
Trial name	NA
NCT number	NA
Objective	Address the activity of post-progression anticancer treatments after first line pembrolizumab in advanced non-small cell lung cancer (NSCLC) patients with PD-L1 ≥50% in a real-world multicentre study.
Publications – title, author, journal, year	Outcomes from salvage chemotherapy or pembrolizumab beyond progression with or without local ablative therapies for advanced non-small cell lung cancers with PD-L1 ≥50% who progress on first-line immunotherapy: real-world data from a European cohort, Metro et al., Journal of thoracic disease, 2019.
Study type and design	An observational retrospective study.
Follow-up time	At the time of the analysis (June 2019), median follow-up time calculated from the date of progression to first line pembrolizumab (based on the objectives of this analysis) was 5.7 months (range, 0.7–16.0 months) in the salvage chemotherapy group and 5.5 months (range, 1.2–20.9 months) in the pembrolizumab beyond progression group.
Population (inclusion and exclusion criteria)	As it was a real-life study, there were no clinical or pathological restrictions for patient enrolment, provided that eligible patients had been treated with first line pembrolizumab, and had an EGFR wild type, ALK negative, and PD-L1 ≥50% biological profile of the tumour (as per local assessment).

Intervention	Salvage chemotherapy or pembrolizumab (for patients who progress on first line immunotherapy).
	• In total, 42 patients received salvage chemotherapy;
	  ○ 31 patients received platinum-based chemotherapy.
	  ○ 11 patients received mono-chemotherapy.

- 18 patients received pembrolizumab.

Baseline characteristics	Data were extracted from 14 Oncologic Centres operating in four different countries (Greece n=7; Italy n=5; Switzerland n=1; Spain n=1).

Table 2 Characteristics of patients

Characteristic	Total patients (n=60) (%)	Salvage chemotherapy (n=42) (%)	Pembrolizumab beyond progression (n=18) (%)
Median age, years [range]	66 [19–86]	64 [19–84]	71 [49–86]
Gender			
Male	38 (63.3)	27 (64.3)	11 (61.1)
Female	22 (36.7)	15 (35.7)	7 (38.9)
Performance status			
0–1	36 (60.0)	24 (57.1)	12 (66.7)
2	24 (40.0)	18 (42.9)	6 (33.3)
Smoking history			
Never smokers*	7 (11.7)	4 (9.5)	3 (16.7)
Ever smokers	53 (88.3)	38 (90.5)	15 (8.3)
Histology			
Adenocarcinoma	37 (61.7)	29 (69.0)	8 (44.5)
Squamous	14 (23.3)	8 (19.0)	6 (33.3)
Other	9 (15.0)	5 (11.9)**	4 (22.2)***
Brain metastases			
Yes	16 (26.7)	9 (21.4)	7 (38.9)
No	44 (73.3)[¨]	33 (78.6)	11 (61.1)
PD-L1 TPS[§]			
≥50–74%	41 (68.3)	30 (71.4)	11 (61.1)
≥75–100%	19 (31.7)	12 (28.6)	7 (38.9)
Response to prior pembrolizumab			
PR or SD	34 (56.7)	20 (47.6)	14 (77.8)
PD	26 (43.3)	22 (52.4)	4 (22.2)
Median duration of prior pembrolizumab, months (range)	3.7 (0.4–18.2)	3.6 (0.7–14.6)	5.9 (0.4–18.1)

*, less than 100 cigarettes in the lifetime; **, 3 non-small cell lung cancers not otherwise specified, 1 larg adenosquamous; ***, 2 non-small cell lung cancers not otherwise specified, 2 sarcomatoid carcinomas; [¨], includes for brain metastases, 3 in each group; [§], as assessed by immunohistochemistry (Dako 22C3 PharmDx). PD, prog partial response; SD, stable disease; TPS, tumor proportion score.

Primary and secondary endpoints	Following data were collected: clinicopathological characteristics, types of post-progression anticancer treatment, response to first-line pembrolizumab and to salvage chemotherapy as per RECIST 1.1 [complete response (CR), partial response (PR), stable disease (SD) and PD, with overall response rate (ORR) being the sum of CR and PR, and disease control rate being the sum of CR, PR and SD], progression-free survival (PFS) of salvage chemotherapy (calculated from the time of initiation of treatment to the radiographic evidence of disease progression or death of the patient in the absence of disease progression, with alive patients without documented radiographic progression being censored at the time of last follow-up).
Method of analysis	Descriptive statistics were performed using frequencies, percentages, frequency tables for categorical variables, median and range for quantitative variables. Non-parametric Mann-Whitney test was performed to compare continuous variable with no normal distribution. Categorical variables were evaluated by chi-square analysis or Fisher's exact test where appropriate. PFS and PPS were analysed according to Kaplan-Meier method and survival curves were compared using the log-rank test. Cox model was used to estimate hazard ratio and related 95% confidence interval (CI). Given the retrospective nature of the study, statistical

	significance should be used in an exploratory view and median time estimation with their 95% CI: reported to better interpret the data.
Subgroup analyses	

Table 49 Bersanelli et al 2020

Bersanelli et al. 2020[14]	
Trial name	NA
NCT number	NA
Objective	Exploring the efficacy of salvage chemotherapy after immunotherapy (SCAI) in advanced NSCLC patients.
Publications – title, author, journal, year	Chemotherapy in non-small cell lung cancer patients after prior immunotherapy: The multicentre retrospective CLARITY study, Bersanelli et al., Lung cancer, 2020.
Study type and design	An observational retrospective study.
Follow-up time	Median follow-up time from CT initiation was 10.7 months (95 % CI 7.5–13.9).
Population (inclusion and exclusion criteria)	Inclusion criteria: • Age ≥ 18 years. • Diagnosis of metastatic NSCLC. • Previous treatment with anti-PD-1/anti-PD-L1 CKI at any treatment line. • At least one administration of SCAI, from November 2013 to July 2019. Exclusion criteria: • Concomitant synchronous metastatic malignancies aside from NSCLC. • Further therapies received between CKI. • CT (e.g. targeted drugs or other non-immunotherapeutic agents).
Intervention	Salvage chemotherapy administered after immunotherapy (SCAI) in patients with advanced NSCLC (N=342).
Baseline characteristics	The overall study population included 342 patients who received SCAI, from November 2013 to July 2019. Patient characteristics at the time of CT initiation are reported in Table 1. Histology was adenocarcinoma in the majority of patients (71 %). SCAI was administered in second line in 86 cases (25.1 %), in third line in 197 cases (57.6 %) and as fourth or further lines in 59 cases (17.3 %). Among 86 patients who were treated

with SCAI in second-line, 67 (78 %) received a platinum-based doublet.

Table 1
Characteristics of patients from the CLARITY study.

	N° of patients (%) Overall population (N = 342)
Age (median, range)	66 (34–86)
Sex	
Male	210 (61.4 %)
Female	132 (38.6 %)
ECOG PS at CT start	
0	61 (17.8 %)
1	200 (58.5 %)
2	77 (22.5 %)
NA	4 (1.2 %)
Stage at diagnosis	
I	17 (5 %)
II	16 (4.7 %)
III	64 (18.8 %)
IV	243 (71.1 %)
Histotype	
Adenocarcinoma	243 (68.4 %)
Squamous cell carcinoma	84 (24.6 %)
NOS/other	15 (4.3 %)
Treatment line for CT	
II line	86 (25.1 %)
III line	197 (57.6 %)
≥ IV line	59 (17.3 %)
Type of CKI treatment prior to CT	
Nivolumab	219 (64.0 %)
Pembrolizumab	91 (26.6 %)
Atezolizumab	21 (6.1 %)
Other*	11 (3.3 %)
Best response to prior CKI	
Complete response	0
Partial response	72 (21.1 %)
Stable disease	109 (31.8 %)
Progressive disease	161 (47.1 %)
CT regimen	
Platinum combination	100 (29.2 %)
Gemcitabine alone	64 (18.7 %)
Taxane-based	133 (38.9 %)
Vinorelbine alone	46 (13.5 %)
Other	10 (2.9 %)

NA = not available; ECOG PS = Eastern European Oncology Group Performance Status; CT = chemotherapy; CKI = immune checkpoint inhibitor.
* Other CKI included: avelumab, durvalumab, ipilimumab plus nivolumab, tremelimumab plus durvalumab (clinical trials were allowed).

Primary and secondary endpoints

Primary outcome measures:

- Overall survival (OS), defined as the time from CT initiation to death.

Secondary outcome measures:

- PFS (according to RECIST 1.1 criteria)
- ORR (according to RECIST 1.1 criteria)
- Toxicity of treatment (defined according to CTCAE version 5)

Explorative co-endpoints:

As exploratory co-endpoints measurement of the levels of lactate dehydrogenase (LDH), calcium, albumin, leukocytes, haemoglobin, neutrophils, lymphocytes, NLR, platelets and their trend during immunotherapy, considering the basal values and at least a subsequent value, and correlated their trend to clinical outcomes.

Measures were collected from clinical records at two time-points: the basal time (at the immunotherapy initiation) and subsequently during immunotherapy, conventionally immediately before the second

	administration of CKI. Only for LDH values, they were also collected at the time of the disease progression to CKI, before initiating CT.
Method of analysis	Demographic variables and outcome measures have been reported using descriptive statistics. Survival curves have been estimated with the Kaplan–Meier method and compared using log-rank test. Median survival times were reported along with their 95 % confidence intervals (95 % CI). Median follow-up times were estimated with the reverse method. Cox regression model was used to estimate hazard ratios (HR) and their 95 % CI. Variables mostly associated with OS were selected using a stepwise forward method, based on Wald statistics. A prognostic score for OS was built considering each significant variable to which a weight proportional to its regression β coefficient was assigned. Coefficients were rounded up for an easier calculation. Harrell's C test was used to assess the goodness of calibration of the model.
Subgroup analyses	

Table 50 KEYNOTE-21

KEYNOTE-21	
Trial name	KEYNOTE-21
NCT number	NCT02039674
Objective	A Phase I/II Study of MK-3475 (SCH900475) in Combination With Chemotherapy or Immunotherapy in Patients With Locally Advanced or Metastatic Non-Small Cell Lung Carcinoma
Publications – title, author, journal, year	Long-Term Overall Survival From KEYNOTE-021 Cohort G: Pemetrexed and Carboplatin With or Without Pembrolizumab as First-Line Therapy for Advanced Nonsquamous NSCLC, Awad et al., Journal of thoracic oncology, 2021 [16]. 24-Month Overall Survival from KEYNOTE-021 Cohort G: Pemetrexed and Carboplatin with or without Pembrolizumab as First-Line Therapy for Advanced Nonsquamous Non-Small Cell Lung Cancer, Borghaei et al., Journal of thoracic oncology, 2019 [17]. Carboplatin and pemetrexed with or without pembrolizumab for advanced, non-squamous non-small-cell lung cancer: a randomised, phase 2 cohort of the open-label KEYNOTE-021 study, Langer et al., The Lancet Oncology, 2016 [18].
Study type and design	Phase 1/2 Study of Pembrolizumab (MK-3475) in Combination with Chemotherapy or Immunotherapy in Patients With Locally Advanced or Metastatic Non-Small Cell Lung Carcinoma.
Follow-up time	In the study of Borghaei et al. (2019) the median follow-up time was 10.6 months (at the primary analysis).
Population (inclusion and exclusion criteria)	Inclusion Criteria: • Stage IIIb/IV NSCLC • Disease progression >1 year after completing adjuvant therapy for Stage I-IIIA disease and no systemic therapy for the recurrent disease

- Resolution of any toxic effects (excepting alopecia) of the most recent therapy
- At least one radiographically measurable lesion
- Performance status of 0 or 1 on the Eastern Cooperative Oncology Group (ECOG) Performance Status scale
- Female participants of reproductive potential must not be pregnant (negative urine or serum human chorionic gonadotropin test within 72 hours of study start)
- Female and male participants of reproductive potential must agree to use adequate contraception throughout the study period and for up to 120 days after the last dose of study therapy and for up to 180 days after the last dose of chemotherapeutic agents or tyrosine kinase inhibitors

Exclusion Criteria:

- Currently participating or has participated in a study of an investigational agent or using an investigational device within 4 weeks of administration of pembrolizumab
- Expected to require any other form of antineoplastic therapy while on study
- Is on chronic systemic steroid therapy or on any other form of immunosuppressive medication
- Has received a live-virus vaccination within 30 days of planned treatment start
- Clinically active diverticulitis, intra-abdominal abscess, gastrointestinal (GI) obstruction, or abdominal carcinomatosis (known risks factors for bowel perforation)
- History of a hematologic malignancy, primary brain tumour or sarcoma, or of another primary solid tumour, unless the participant has undergone potentially curative therapy with no evidence of that disease for 5 years
- Active central nervous system (CNS) metastases and/or carcinomatous meningitis
- Severe hypersensitivity reaction to treatment with another monoclonal antibody (mAb)
- Active autoimmune disease that has required systemic treatment in the past 2 years (replacement therapies for hormone deficiencies are allowed)
- Prior treatment with any other anti-programmed cell death protein-1 (anti-PD-1), or PD Ligand-1 (PD-L1) or PD Ligand-2 (PD-L2) agent or an antibody targeting other immuno-regulatory receptors or mechanisms
- Systemic cytotoxic chemotherapy, antineoplastic biologic therapy, or major surgery within 3 weeks of the first dose of study medication
- Radiation therapy to lung >30 Gy within 6 months of first dose of study medication
- Prior tyrosine kinase inhibitor therapy or palliative radiation within 7 days of first dose of study medication
- Active infection requiring therapy
- History of Human Immunodeficiency Virus (HIV)

- Active Hepatitis B or C
- Symptomatic ascites or pleural effusion
- Interstitial lung disease or pneumonitis requiring oral or IV glucocorticoids
- Pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the study
- Psychiatric disorders and substance (drug/alcohol) abuse

Intervention

Patients (N=123) received pemetrexed 500 mg/m2 plus carboplatin at area under the concentration-time curve of 5 mg/mL/min (four cycles) with (N=60) or without (N=63) pembrolizumab 200 mg (up to 2 years), with optional pemetrexed maintenance, each administered every 3 weeks. Eligible patients could crossover from the chemotherapy arm to pembrolizumab monotherapy after progression [16].

Baseline characteristics

Table 1. Patient Baseline Characteristics

Characteristic	Pembro + PC, n = 60	PC Alone, n = 63
Age, y, median (range)	62.5 (40-77)	66.0 (37-80)
Female, n (%)	38 (63)	37 (59)
ECOG performance status, n (%)		
0	24 (40)	29 (46)
1	35 (58)	34 (54)
2	1 (2)	0
Tumor histology, n (%)		
Adenocarcinoma	58 (97)	55 (87)
NSCLC not otherwise specified	2 (3)	7 (11)
Large-cell carcinoma	0	1 (2)
Stable brain metastases[a]	12 (20)	7 (11)
Current or former smoker, n (%)	45 (75)	54 (86)
PD-L1 TPS, n (%)		
<1%	21 (35)	23 (37)
1%-49%	19 (32)	23 (37)
≥50%	20 (33)	17 (27)

[a]Patients with previously treated brain metastases were enrolled if clinically stable for at least 4 weeks, have no evidence of new or enlarging brain metastases, and had not received steroids during the 3 days before the start of study treatment.
ECOG, Eastern Cooperative Oncology Group; PC, pemetrexed plus carboplatin; PD-L1, programmed death ligand 1; pembro, pembrolizumab; TPS, tumor proportion score.

Primary and secondary endpoints

Awad et al. 2021:

Primary endpoint:

- ORR (by blinded independent central review per RECIST version 1.1), estimated using the Clopper-Pearson method, and the treatment difference and associated confidence interval (CI) were estimated using the stratified Miettinen and Nurminen's method with strata weighting by sample size.

Secondary end points:

- Progression-free-survival (PFS) defined as the time from randomization to the first documented disease progression, or death due to any cause, whichever occurred first. Per RECIST 1.1, progressive disease was defined as at least a 20% increase in the sum of diameters of target lesions. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. The

	appearance of one or more new lesions was also considered progression. PFS was assessed by BICR. • Duration of response (DOR) for participants who demonstrated a confirmed response (Complete Response [CR]: Disappearance of all target lesions or Partial Response [PR]: At least a 30% decrease in the sum of diameters of target lesions) per RECIST 1.1. Per RECIST 1.1, DOR was defined as the time from first documented evidence of CR or PR until disease progression or death. DOR was assessed by BICR. • Overall survival (OS) Exploratory end points: • PFS (by investigator assessment per RECIST version 1.1) OS in patients who crossed over from chemotherapy to pembrolizumab monotherapy, both calculated from time of first dose of crossover therapy.
Method of analysis	The primary end point was estimated using the Clopper-Pearson method, and the treatment difference and associated confidence interval (CI) were estimated using the stratified Miettinen and Nurminen's method with strata weighting by sample size [16].
Subgroup analyses	Patients with unknown best overall response were considered non-responders. The Kaplan-Meier method was used to estimate progression-free survival, overall survival, and duration of response. For progression-free survival, patients who were alive and without disease progression or who were lost to follow-up were censored at the time of last radiological imaging. For overall survival, patients who were alive or who were lost to follow-up were censored at the time of last known survival. For duration of response, patients with confirmed response who were without subsequent radiological disease progression were censored at the time of last radiological imaging. Treatment differences in progression-free and overall survival were assessed with a stratified log-rank test. Hazard ratios and associated 95% CIs were assessed with a stratified Cox proportional hazard model with Efron's method of tie handling. The same stratification factor used for randomisation was applied to all stratified statistical analyses [18].

Table 51 Gautschi et al. 2017

Gautschi et al. 2017	
Trial name	NA
NCT number	NA
Objective	The aims of this study were to describe the clinicopathologic characteristics of patients with RET-rearranged lung cancers and to document the outcomes of patients with advanced disease who were treated with systemic therapy, focusing on multikinase inhibitors that target the RET kinase.

Publications – title, author, journal, year	Targeting RET in Patients With RET-Rearranged Lung Cancers: Results From the Global, Multicenter RET Registry; Gautschi et al., Journal Of Clinical Oncology, 2017[15]
Study type and design	A retrospective global, multicenter register study based on data derived from a network of thoracic oncologists accrued patients with RET-rearranged lung cancers.
Follow-up time	At data cut-off (September 21, 2018), median (range) study follow-up (time from randomization to database cut-off) was 23.1 (18.6 to 30.9) months, and median (range) time from randomization to death or database cut-off, whichever occurred first, was 18.7 (0.2 to 30.9) months [19].
Population (inclusion and exclusion criteria)	Inclusion Criteria: Eligible patients had a pathologic diagnosis of NSCLC of any stage (I to IV) and RET-rearrangement by a validated test that was performed in an accredited local laboratory. Accepted test methods were fluorescence in situ hybridization, reverse transcriptase polymerase chain reaction, and next generation sequencing. Validation of test results by a second method was not mandatory.
Intervention	Investigators administered multikinase inhibitors cabozantinib, vandetanib, sunitinib, sorafenib, alectinib, lenvatinib, nintedanib, ponatinib, and regorafenib according to the approved initial starting dose of these drugs in their respective approved cancer indications—data on dose interruption and modification were not collected.
Baseline characteristics	**Table 1.** Clinicopathologic Features Characteristic / All Patients (N = 165) / Patients not Treated With a RET Inhibitor (n = 112) / Patients Treated With a RET Inhibitor (n = 53) / P* Age, years — .166 Median (range) — 61 (28-89) — 62 (29-89) — 57 (28-83) < 70 — 126 (76) — 82 (79) — 44 (83) ≥ 70 — 39 (24) — 30 (27) — 9 (17) Gender — .260 Male — 79 (48) — 57 (51) — 22 (42) Female — 86 (52) — 55 (49) — 31 (59) Smoking history — .110 Never — 103 (63) — 69 (62) — 34 (65) Former — 45 (27) — 35 (31) — 10 (19) Current — 16 (10) — 8 (7) — 8 (15) Unknown — 1 — 0 — 1 Tumor histology — .487 Adenocarcinoma — 158 (98) — 108 (98) — 50 (96) Squamous — 1 (1) — 0 — 1 (2) NSCLC NOS — 3 (2) — 2 (2) — 1 (2) Unknown — 3 — 2 — 1 *RET* fusion gene partner — .327 *KIF5B* — 58 (72) — 39 (68) — 19 (79) Other — 23 (28) — 18 (32) — 5 (21) Unknown — 84 — 55 — 29 Stage at diagnosis — .004 I and II — 14 (9) — 14 (13) — 0 III — 31 (19) — 24 (22) — 7 (14) IV — 117 (72) — 73 (66) — 44 (86) Unknown — 3 — 1 — 2 Region — .3103 United States — 68 (41.2) — 48 (42.9) — 20 (37.7) Europe and Israel — 71 (43.0) — 44 (39.3) — 27 (50.9) Asia — 26 (15.8) — 20 (17.9) — 6 (11.3) NOTE. Data are given as No. (%) unless otherwise noted. Clinicopathologic features of 165 patients with *RET*-rearranged lung cancers are summarized. In addition, the clinicopathologic features of 53 patients with advanced *RET*-rearranged lung cancers who received a RET inhibitor during the course of treatment are summarized and compared with 112 patients who did not receive a RET inhibitor. Abbreviations: NOS, not otherwise specified; NSCLC, non–small-cell lung cancer. *Fisher's exact and χ^2 tests
Primary and secondary endpoints	Endpoints: • Overall survival (OS) • Progression-free survival (PFS) • Objective response rate (ORR)
Method of analysis	Data were summarized according to frequency and percentage for qualitative variables as well as by medians and ranges for quantitative variables. Comparisons between groups were performed by using the X^2 test or Fisher's exact test for qualitative variable test, and by the Mann-Whitney test for quantitative variables. Progression-free survival was measured as the time from the first administration of RET inhibitor therapy to progression defined by RECIST v1.1 or death from any cause.

	Patients who were alive without having experienced progression at the time of analysis were censored at their last follow-up. Overall survival was measured as the time from the first administration of RET inhibitor therapy to death from any cause. Patients who were alive at the time of analysis were censored at their last follow-up. Survival rates were estimated by using the Kaplan-Meier method.
Subgroup analyses	NA

Table 52 KEYNOTE-189

KEYNOTE-189	
Trial name	KEYNOTE-189
NCT number	NCT02578680
Objective	Evaluate patient-reported outcomes (PROs) following pembrolizumab or placebo plus pemetrexed and platinum in patients with previously untreated, metastatic, non-squamous non-small-cell lung cancer.
Publications – title, author, journal, year	Updated Analysis From KEYNOTE-189: Pembrolizumab or Placebo Plus Pemetrexed and Platinum for Previously Untreated Metastatic Nonsquamous Non-Small-Cell Lung Cancer, Gadgeel et al., Journal of clinical oncology, 2020 [19]. Patient-reported outcomes following pembrolizumab or placebo plus pemetrexed and platinum in patients with previously untreated, metastatic, non-squamous non-small-cell lung cancer (KEYNOTE-189): a multicentre, double-blind, randomised, placebo-controlled, phase 3 trial, Garassino et al., The Lancet, 2020 [20].
Study type and design	A Randomized, Double-Blind, Phase 3 Study of Platinum + Pemetrexed Chemotherapy With or Without Pembrolizumab (MK-3475) in First Line Metastatic Non-squamous Non-small Cell Lung Cancer Subjects.
Follow-up time	At data cut-off (September 21, 2018), median (range) study follow-up (time from randomization to database cut-off) was 23.1 (18.6 to 30.9) months, and median (range) time from randomization to death or database cut-off, whichever occurred first, was 18.7 (0.2 to 30.9) months [19].
Population (inclusion and exclusion criteria)	<u>Inclusion Criteria:</u> • ≥ 18 years of age or older. • Has a histologically-confirmed or cytologically confirmed diagnosis of stage IV nonsquamous NSCLC. • Has confirmation that epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK)-directed therapy is not indicated. • Has measurable disease. • Has not received prior systemic treatment for their advanced/metastatic NSCLC. • Can provide tumour tissue. • Has a life expectancy of at least 3 months.

- Has a performance status of 0 or 1 on the Eastern Cooperative Oncology Group (ECOG) Performance Status.
- Has adequate organ function
- If female of childbearing potential, is willing to use adequate contraception for the course of the study through 120 days after the last dose of study medication or through 180 days after last dose of chemotherapeutic agents.
- If male with a female partner(s) of child-bearing potential, must agree to use adequate contraception starting with the first dose of study medication through 120 days after the last dose of study medication or through 180 days after last dose of chemotherapeutic agents.

Exclusion Criteria:

- Has predominantly squamous cell histology NSCLC.
- Is currently participating and receiving study therapy or has participated in a study of an investigational agent and received study therapy or used an investigational device within 4 weeks prior to administration of pembrolizumab.
- Before the first dose of study medication: a) Has received prior systemic cytotoxic chemotherapy for metastatic disease, b) Has received antineoplastic biological therapy (e.g., erlotinib, crizotinib, cetuximab), c) Had major surgery (<3 weeks prior to first dose)
- Received radiation therapy to the lung that is >30 Gray (Gy) within 6 months of the first dose of study medication.
- Completed palliative radiotherapy within 7 days of the first dose of study medication.
- Is expected to require any other form of antineoplastic therapy while on study.
- Received a live-virus vaccination within 30 days of planned start of study medication.
- Has clinically active diverticulitis, intra-abdominal abscess, gastrointestinal obstruction, peritoneal carcinomatosis.
- Known history of prior malignancy except if participant has undergone potentially curative therapy with no evidence of that disease recurrence for 5 years since initiation of that therapy, except for successful definitive resection of basal cell carcinoma of the skin, superficial bladder cancer, squamous cell carcinoma of the skin, in situ cervical cancer, or other in situ cancers.
- Has known active central nervous system (CNS) metastases and/or carcinomatous meningitis.
- Previously had a severe hypersensitivity reaction to treatment with another monoclonal antibody (mAb).
- Known sensitivity to any component of cisplatin, carboplatin or pemetrexed.
- Has active autoimmune disease that has required systemic treatment in past 2 years.
- Is on chronic systemic steroids.
- Is unable to interrupt aspirin or other nonsteroidal anti-inflammatory drugs (NSAIDs), other than an aspirin dose ≤1.3

	g per day, for a 5-day period (8-day period for long-acting agents, such as piroxicam). • Is unable or unwilling to take folic acid or vitamin B12 supplementation. • Had prior treatment with any other anti-programmed cell death-1 (PD-1), or PD-ligand 1 (PD-L1) or PD-L2 agent or an antibody targeting other immuno-regulatory receptors or mechanisms. Has participated in any other pembrolizumab study and has been treated with pembrolizumab. • Has an active infection requiring therapy. • Has known history of Human Immunodeficiency Virus (HIV). • Has known active Hepatitis B or C. • Has known psychiatric or substance abuse disorder that would interfere with cooperation with the requirements of the trial. • Is a regular user (including "recreational use") of any illicit drugs or had a recent history (within the last year) of substance abuse (including alcohol). • Has symptomatic ascites or pleural effusion. • Has interstitial lung disease or a history of pneumonitis that required oral of IV glucocorticoids to assist with management. • Is pregnant or breastfeeding, or expecting to conceive or father children prior to 120 days after the last dose of study medication or through 180 days after last dose of chemotherapeutic agents.
Intervention	Patients received intravenous pembrolizumab 200 mg every 3 weeks or saline placebo every 3 weeks for up to 2 years (35 cycles). All patients received four cycles of pemetrexed 500 mg/m² plus investigator's choice of cisplatin 75 mg/m² or carboplatin area under the concentration–time curve 5 mg/mL per min followed by pemetrexed 500 mg/m² maintenance therapy every 3 weeks. Study treatment was continued until disease progression, unacceptable toxicity, illness precluding further treatment, investigator decision, or withdrawal of consent. Pembrolizumab dose reductions were not permitted. Crossover to pembrolizumab mono therapy was permitted for patients in the placebo plus pemetrexed–platinum group who had disease progression verified by blinded, independent central radio logical review and met safety criteria [19].

Baseline characteristics

TABLE 1. Patient Demographics and Baseline Disease Characteristics

Characteristic	Pembrolizumab Combination (n = 410)	Placebo C
Age, median (range), years	65.0 (34-84)	
Male	254 (62.0)	
ECOG performance status		
0	186 (45.4)	
1	220 (53.7)	
2	1 (0.2)	
Smoking status		
Former or current	362 (88.3)	
Never	48 (11.7)	
Liver metastases	66 (16.1)	
Brain metastases	73 (17.8)	
Previously treated	43 (10)	
PD-L1 TPS		
< 1%	127 (31.0)	
1%-49%	128 (31.2)	
≥ 50%	132 (32.2)	
Could not be evaluated	23 (5.6)	
Previous therapy		
Thoracic radiotherapy	29 (7.1)	
Neoadjuvant therapy	5 (1.2)	
Adjuvant therapy	25 (6.1)	

NOTE. Data are No. (%) unless otherwise indicated.
Abbreviations: ECOG, Eastern Cooperative Oncology Group; PD-L1, programmed death-ligand 1; TPS, tumor propo

Primary and secondary endpoints

Primary endpoints:

The primary endpoints of the KEYNOTE-189 study were overall survival (OS) and progression-free survival (PFS) as per RECIST (version 1.1) assessed by blinded, independent central radiological review [20].

Secondary endpoints:

The secondary endpoints included the proportion of patients with an objective response per RECIST (version 1.1) by blinded, independent central radiological review and safety [20].

Exploratory endpoints:

Patient-reported-outcomes (PROs) were evaluated as prespecified exploratory endpoints. Key PRO endpoints were mean change from baseline to weeks 12 and 21 in the QLQ-C30 GHS/QOL scale, and time to deterioration (defined as the time to first onset of a ≥10-point increase from baseline score, confirmed by a second consecutive increase of ≥10 points from baseline) in the composite endpoint of cough (QLQ-LC13, question 1), chest pain (QLQ-LC13, question 10), or dyspnoea (QLQ-C30, question 8).

Method of analysis

Efficacy analyses were performed in the intention-to-treat (ITT) population, which included all randomly assigned patients; safety analyses were performed in the as-treated population, which included all randomly assigned patients who received ≥ 1 dose of therapy. The Kaplan-Meier method was used to estimate OS, PFS, and PFS-2. A stratified Cox proportional hazards model with Efron's method of tie handling was used to determine HRs and 95% CIs. Stratification factors used for randomization were applied. Analyses were not controlled for multiplicity; no alpha was assigned to this updated analysis [19].

PRO analyses included all randomly assigned patients who received at least one dose of study treatment and completed at least one PRO assessment, analysed according to allocated treatment. Patients were considered to have completed at least one PRO assessment if they completed at least one item on a PRO instrument. Compliance with the PRO assessments was defined as the proportion of patients who completed at least one item among those expected to complete the

	questionnaires (i.e., those who remained on treatment, and had a scheduled study visit) [20]. Mean changes from baseline to weeks 12 and 21 in the QLQ-C30 GHS/QOL score were evaluated using a constrained longitudinal data analysis model with the PRO score as the response variable and treatment by study visit interaction and randomisation stratification factors as covariates (supportive analyses of the effect of disease progression on PROs also included progression status as a time varied covariate). This model implicitly treats missing data as missing at random [20].
Subgroup analyses	

Table 53 NAVotrial 01

NAVotrial 01	
NCT number	NA. EudraCT: 2009-012001-19
Objective	Assess the feasibility of a platinum-based doublet with oral vinorelbine (ratio 1:2) in an investigational approach as first-line treatment in patients with NS NSCLC.
Publications – title, author, journal, year	Oral vinorelbine plus cisplatin as first-line chemotherapy in nonsquamous non-small-cell lung cancer: final results of an International randomized phase II study (NAVotrial 01), Bennouna et al., Clinical lung cancer, 2014.
Study type and design	International Randomized Phase 2 Study
Follow-up time	NA
Population (inclusion and exclusion criteria)	Inclusion Criteria: • Chemotherapy-naive patients with histologically/cytologically proven NS NSCLC, with disease classified as stage IIIB/IV (2009 TNM classification) or relapsing (locally or distantly) after local treatment that was not suitable for locoregional treatment • Karnofsky performance score ≥ 80% • Age from 18 to 75 years were eligible • Patients had to have at least 1 unidimensional measurable indicator lesion according to Response Evaluation Criteria in Solid Tumours (RECIST), version 1.1 that had not been previously irradiated. • A life expectancy longer than 12 weeks • Neutrophil levels ≥ 2.0 × 10^9/L, • Platelet levels ≥ 100 × 10^9/L • Haemoglobin value > 11 g/Dl • Total bilirubin levels ≤ 1.5 × the upper limit of normal (ULN) • Transaminase levels < 2.5 × the ULN • Alkaline phosphatase levels < 5 × the ULN • Serum creatinine levels ≤ the ULN, if limit value

	• Creatinine clearance ≥60 mL/m Exclusion Criteria: • Radiotherapy within the previous 4 weeks • Pregnancy • Brain metastasis or leptomeningeal involvement • Symptomatic peripheral neuropathy > grade 1 according to the National Cancer Institute Common Toxicity Criteria, version 2.0. • Women of childbearing potential had to use a medically accepted method of contraception during the 2 months preceding the beginning of the study, throughout the study period, and for up to 3 months after the last dose of study treatment [21].
Intervention	Patients received either cisplatin 75 mg/m2 plus pemetrexed 500 mg/m2 on day 1 (arm A, N=51) or cisplatin 80 mg/m2 on day 1 plus oral vinorelbine 80 mg/m2 on day 1 and day 8 (arm B, N=102) after the first cycle at 60 mg/m2 to test hematologic tolerance. Chemotherapy was administered every 3 weeks for 4 cycles until documented disease progression, unacceptable toxicity, or patient refusal. In case of objective response or disease stabilization, treatment was continued in each arm until disease progression or toxicity with either single agent pemetrexed or oral vinorelbine at the same doses and schedules as cycle 4, every 3 weeks. No dose reescalation was permitted after dose reduction of pemetrexed, oral vinorelbine or cisplatin. Dose reductions and omissions were allowed within cycles (day 8) for oral vinorelbine. Treatment was discontinued if it could not be administered after an additional 2 weeks' delay (cycle duration > 5 weeks) related to any toxicity. When disease progressed, further second-line treatment was dependent on the investigator's decision. Supportive treatments, such as antiemetic agents, transfusion of blood products, analgesics, antibiotics, antidiarrheal agents, granulocyte colony-stimulating factors (except for primary prophylactic use), and erythropoietic agents were allowed according to evidence-based recommendations. Patients treated with pemetrexed received oral folic acid 400 mg daily and a vitamin B12 injection every 9 weeks from 1 to 2 weeks before the first dose of treatment until 3 weeks after the last dose [21].

Baseline characteristics

Table 1 Main Patients Characteristics

Characteristic	Arm A (n = 51)	Arm B (n = 100)
Sex, No. of Patients (%)		
Male	33 (64.7)	62 (62.0)
Median age, years (range)	63.8 (40.3-75.5)	61.0 (38.4-75.1)
<65 (%)	60.8	71.0
≥65 (%)	39.2	29.0
Performance Status at Baseline (%)		
80%	41.2	42.0
90%	35.3	25.0
100%	23.5	33.0
Smoker at Randomization (%)	37.3	40.0
Histologic Subtype (%)		
Squamous cell carcinoma	–	1.0
Adenocarcinoma	82.4	88.0
Large cell carcinoma	7.8	10.0
Others	9.8	1.0
Stage at Randomization (%)		
IIIB	9.8	8.0
IV	88.2	88.0
Relapsed disease	2.0	4.0
Median Delay Between Diagnosis and Study Entry, mo (range)	0.9 (0.2-75.2)	0.7 (0.2-48.6)
Histopathologic Diagnosis		
Cytologic (%)	25.5	26.0
Histologic (%)	74.5	74.0
Number of Organs Involved (%)		
1	5.9	7.0
2	35.3	28.0
≥3	58.8	65.0

Primary and secondary endpoints

Primary endpoint:

The main end point of the study was DCR.

Secondary endpoint:

- Overall response rate (ORR)
- Progression-free survival (PFS, defined as the time elapsed from randomization until disease progression or death from any cause, whichever occurred first).
- Overall survival (OS)
- Time to treatment failure (TTF, defined as time elapsed from randomization until failure: disease progression, relapse, death, withdrawal because of an adverse event, patient refusal, loss to follow-up, start of a new anticancer therapy)
- Safety [21]

Method of analysis

The 1-sample multiple-testing procedure for phase II clinical trials described by Fleming was used with 2 prespecified analyses. The null hypothesis (H0) assumed a true DCR of 55% with an alternative hypothesis (H1) of 70%, a type I error $\alpha \leq 0.05$, and a type II error $\beta \leq 0.15$. All treated patients were included in the ITT analysis and were analysed for safety.

	The evaluable population was defined as all patients eligible for the trial who underwent a full evaluation of target and nontarget lesions and had received at least 2 cycles of study treatment (including patients with progressive disease documented before the second cycle). DCR and ORR were tabulated together with 95% confidence interval (CI), following the exact method. The Kaplan-Meier method was applied to PFS, TTF, and OS. Subset analysis, according to stratification factors, was performed for DCR, ORR, PFS, and OS [21].
Subgroup analyses	NA

Table 54 Kim et al. 2012

Kim et al. 2012	
NCT number	NA
Objective	Evaluate the safety and efficacy of pemetrexed and platinum agents for first-line chemotherapy of advanced ''non-squamous'' NSCLC
Publications – title, author, journal, year	Phase II study of carboplatin and pemetrexed in advanced non-squamous, non-small-cell lung cancer: Kyoto Thoracic Oncology Research Group Trial 0902, Kim et al., Cancer chemotherapy and pharmacology, 2012 [22]
Study type and design	Single-arm phase II
Follow-up time	The median follow-up duration was 15.5 months (0.9–27.5 months).
Population (inclusion and exclusion criteria)	Patients with histologically and/or cytologically documented non-squamous NSCLC were eligible for the study. Each patient was required to meet the following criteria: clinical stage IV or IIIB (including only patients with no indications for curative radiotherapy), an Eastern Cooperative Oncology Group performance status (PS) of 0 or 1, age\75 years, no prior chemotherapy, measurable lesions, adequate hematologic function [neutrophils C1,500/mm3; platelets C100,000/mm3; haemoglobin C8.5 g/dl], adequate hepatic function [total bilirubin B1.5 mg/dl, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) B100 IU/l], and adequate renal function (creatinine B1.5 mg/dl). Patients with active infection, severe heart disease, uncontrollable hypertension or diabetes mellitus, active concomitant malignancy, and pleural and/or pericardial effusion requiring drainage were excluded. The study was approved by the Institutional Review Board of each participating centre. Written informed consent was obtained from all patients.
Intervention	Chemotherapy consisted of pemetrexed (500 mg/m2) on day 1 and carboplatin (area under the curve: AUC 6) on day 1 every 3 weeks. Pemetrexed was infused over 10 min, and immediately after the completion of pemetrexed infusion, carboplatin was administered over 30 min. The actual dose of carboplatin was calculated based on the Cockcroft–Gault equation and Calvert formula for every course. In Japan, serum creatinine is measured enzymatically; therefore, the adjusted creatinine clearance was used for Calvert's formula based on the previous study. Patients were instructed to take a daily 1 g multivitamin with 500 lg folate beginning 1 week before day 1 of cycle 1 until study

discontinuation. Vitamin B12 (1,000 lg) was injected intramuscularly, starting 1 week before day 1 of cycle 1 and repeated every 9 weeks until study discontinuation. Maintenance chemotherapy with pemetrexed was permitted in patients whose disease did not progress after combination chemotherapy.

Baseline characteristics

Between November 2009 and March 2011, 51 patients were enrolled and 49 were evaluable for both safety and efficacy (Table 1). One patient was proved to have small cell lung cancer, and the other withdrew consent after one cycle of treatment. The median age of the patients was 63 years (range 41–74). There were 29 males and 20 females. Eighteen patients had PS 0 and 31 had PS 1. All but one patient had adenocarcinoma histology. Epidermal growth factor receptor (EGFR) mutation status was available in 44 patients: There were 13 mutants and 31 wild types.

Table 1 Patient characteristics ($n = 49$)

Characteristics	No. of patients
Age	
Median	63
Range	41–74
Gender	
Male	29
Female	20
Performance status	
0	18
1	31
Histology	
Adenocarcinoma	48
Pleomorphic carcinoma	1
Clinical stage	
IIIB	10
IV	39
Smoking history	
+	25
−	24
EGFR mutation	
+	13
−	31
Unknown	5

EGFR epidermal growth factor receptor

Primary and secondary endpoints

Primary endpoint:

- The overall response rate.

Secondary endpoints:

- progression-free survival (PFS),
- OS,
- 1-year survival rate
- toxicities

Method of analysis

A single-arm, two-stage, sequential phase II design was used to test the null hypothesis (H0) that the true response rate is 25 % versus the alternative hypothesis (Ha) that the true response rate is at least 40 %. At a risk alpha of 5 % and a power of 90 %, the study had to enrol 25 assessable patients in the first stage.

If less than 5 patients responded to the therapy, this regimen would be deemed not worthy of any further investigation in this patient population, unless clinical considerations suggested otherwise. If at

	least 5 of the first 25 patients responded to therapy, accrual had to continue until 20 additional assessable patients had been recruited. If \17 of the 45 patients responded to therapy, this regimen would be deemed not worthy of any further investigation in this patient population, unless clinical considerations suggested otherwise. If responses were seen in C17 of the 45 patients, this regimen would be recommended for further study. Considering that 10 % of patients would be nonassessable for response, five additional patients had to be enrolled for a total of 50 patients. p\0.05 was considered significant. All statistical analyses were performed using SPSS 11.0 statistical software (Dr. SPSS II for Windows, Standard version 11.0; SPSS Inc., Chicago, IL, USA).
Subgroup analyses	NA

Table 55 Manegold et al. 2000

Manegold et al. 2000	
NCT number	NA
Objective	The objective of this study was to explore the anti-tumour activity of MTA and cisplatin combination therapy when given to chemotherapy-naive patients with locally advanced or metastatic NSCLC.
Publications – title, author, journal, year	Front-line treatment of advanced non-small-cell lung cancer with MTA (LY231514, pemetrexed disodium, ALIMTA) and cisplatin: a multicentre phase II trial, Manegold et al., Annals of oncology, 2000 [23]
Study type and design	Multicentre, single trial, Phase II trial
Follow-up time	NA
Population (inclusion and exclusion criteria)	Patients were eligible if they met the following criteria: Histologic or cytologic diagnosis of stage IIIB or IV NSCLC with stage NIB or IV age bi-dimensionally measurable lesions; age ≥ 19 years; no prior chemotherapy; prior radiation therapy to less than 25% of the bone marrow; performance status ≤ on the scale; adequate bone marrow reserve (absolute neutrophil count ≥ 1.5 * 10^9/l, platelets ≥ 100 * 10^9/l, and haemoglobin ≥ g/dl); adequate renal function (calculated creatinine clearance of ≥ 45 ml/min using the modified Cockcroft and Gault formula); adequate hepatic function (bilirubin ≤ 1.5 times the upper limit of normal, and aspartate and alanine transaminases ≤ 3.0 times the upper limit of normal.) Patients were ineligible if they had and active infection, clinical evidence of NCS metastases or thirds space fluid collections, albumin < 2.5 g/dl, or were unable to interrupt aspiring or other NSAID administration on or around the day of MTA administration. The local ethical committees of each participating centre approved the protocol . Written informed consent was obtained from all patients before treatment.
Intervention	Patients with solid tumours received MTA intravenously over 10 minutes and cisplatin over 2 hours once every 21 days. The MTD was determined to be 600 mg/m2 MTA and 100 mg/m2 cisplatin, with dose-limiting toxicities of reversible neutropenia and leukopenia, and delayed fatigue. The dose selected for further evaluation in the phase II setting was 500 mg/m2 MTA and 75 mg/m2 cisplatin.

Baseline characteristics

From November 1997 to March 1998, 36 chemotherapy naive patients with NSCLC were enrolled. Patient characteristics are listed in Table 1. Ninety-seven percent of the patients had a WHO performance status of 0-1, and patients were distributed equally between stage IIIB and stage IV disease at baseline. Seventeen patients (47%) each had adenocarcinoma and squamous-cell carcinoma, with two patients (6%) having undifferentiated histology. The majority of patients had received no prior treatment for their cancer, with six (17%) having had prior surgery and one (3%) having received prior radiotherapy.

Table 1. Patient characteristics.

	Number of patients (%)
Total	36
Age (years)	
Median	
58	
Range	
26–73	
Sex	
Male	29 (81)
Female	7 (19)
Performance Status (WHO)	
0	8 (22)
1	27 (75)
2[a]	1 (3)
Stage at entry	
IIIB	18 (50)
IV	18 (50)
Histology	
Squamous	17 (47)
Adeno	17 (47)
NSCLC	2 (6)
Prior treatment	
None	29 (80)
Surgery	6 (17)
Radiotherapy	1 (3)
Number of involved sites	
1	12 (33)
2	12 (33)
3	9 (25)
4	3 (8)

[a] This patient was enrolled in violation of the protocol entry criteria, which required a performance status less than 2.

Primary and secondary endpoints

The primary objective of the study was to determine the tumour response rate for patients with stage IIIB or IV NSCLC who received treatment with MTA in combination with cisplatin.

Secondary objectives included the measurement of time to event variables such as duration of response for responding patients, time to progressive disease, and survival time.

According to SWOG-criteria the duration of response was calculated from the time of first objective assessment of CR/PR to the first time of progression or death due to any cause. The time to progressive disease was calculated from the time of study entry to the first observation of disease progression. Overall survival was measured from the time of study entry to the time of death due to any cause and was estimated by the method of Kaplan and Meier.

Method of analysis

Standard SWOG response criteria were used to define the antitumor effects; responses were assessed in alternate therapy cycles with CT scan or chest X-ray [21]. Responses had to be confirmed; in case of CR and PR a second assessment had to be scheduled for four weeks after the first documentation of response. All patients who received at least one dose of both MTA and cisplatin were assessable for response.

According to SWOG-criteria the duration of response was calculated from the time of first objective assessment of CR/PR to the first time of progression or death due to any cause. The time to progressive disease

	was calculated from the time of study entry to the first observation of disease progression. Overall survival was measured from the time of study entry to the time of death due to any cause and was estimated by the method of Kaplan and Meier.
Subgroup analyses	NA

Table 56 Scagliotti et al. 2008

Scagliotti et al. 2008	
NCT number	NA
Objective	The primary objective of this phase III non-inferiority study was to compare the overall survival of cisplatin/pemetrexed with cisplatin/gemcitabine in chemotherapy-naive patients with advanced NSCLC.
Publications – title, author, journal, year	Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naive patients with advanced-stage non-small-cell lung cancer, Scagliotti et al., Journal of clinical oncology, 2008 [25]
Study type and design	Non-inferiority, phase III, randomized study Eligible patients were randomly assigned to receive either cisplatin 75 mg/m2 on day 1 plus gemcitabine 1,250 mg/m2 on days 1 and 8 or cisplatin 75 mg/m2 plus pemetrexed 500 mg/m2 on day 1. Pocock and Simon random assignment was used according to disease stage (IIIBv IV), performance status (0 v 1), history of brain metastases (yes v no), sex (male v female), pathologic diagnosis (histologic v cytologic), and investigative centre. Chemotherapy was repeated every 3 weeks for a maximum of six cycles (unless there was earlier evidence of disease progression or intolerance of the study treatment). Patients on both arms received dexamethasone prophylaxis of 4 mg orally twice per day on the day before, the day of, and the day after each day-1 treatment. All patients received oral folic acid (350 to 1,000 mg) daily and a vitamin B12 injection (1,000 mg) every 9 weeks, beginning 1 to 2 weeks before the first dose and continuing until 3 weeks after the last dose of study treatment. Patients requiring a day-1 dose reduction of pemetrexed, gemcitabine, or cisplatin received the reduced dose for the remainder of the study. Patients who had two dose reductions on day 1 and who experienced toxicity requiring a third dose reduction were discontinued from study therapy. Cycle delays of up to 42 days were permitted for recovery from adverse events. Within-cycle (day 8) dose reductions and omissions were allowed for gemcitabine. Concomitant supportive therapies, such as erythropoietic agents or granulocyte. Colony-stimulating factors were allowed according to the American Society of Clinical Oncology guidelines. The study protocol requested, in a nonmandatory way, the collection of tumour samples for assessment of candidate biomarkers. Details about these data will be reported separately.
Follow-up time	The baseline assessment method was repeated every other cycle and then every 6 weeks after treatment discontinuation until disease progression. Disease status was assessed according to Response Evaluation Criteria in Solid Tumours.
Population (inclusion and exclusion criteria)	Chemotherapy-naive patients with histologically or cytologically confirmed NSCLC, classified as stage IIIB not amenable to curative treatment or stage IV, with at least one unidimensional measurable lesion according to the Response Evaluation Criteria in Solid Tumours, with an Eastern Cooperative

	Oncology Group performance status of 0 or 1,20 and at least 18 years of age were eligible. Patients had adequate bone marrow reserve and organ function including calculated creatinine clearance 45 mL/min based on the standard Cockcroft and Gault formula. Prior radiation therapy was permitted if it was completed at least 4 weeks before study treatment and patients had fully recovered from its acute effects. Exclusion criteria included peripheral neuropathy National Cancer Institute Common Toxicity Criteria grade 1, progressive brain metastases, or uncontrolled third-space fluid retention before study entry. Patients were also excluded if they were unable to interrupt aspirin and other nonsteroidal anti-inflammatory drugs or if they were unable or unwilling to take folic acid, vitamin B12, or corticosteroids.
Intervention	Eligible patients were randomly assigned to receive either cisplatin 75 mg/m2 on day 1 plus gemcitabine 1,250 mg/m2 on days 1 and 8 or cisplatin 75 mg/m2 plus pemetrexed 500 mg/m2 on day 1. Pocock and Simon random assignment was used according to disease stage (IIIBv IV), performance status (0 v 1), history of brain metastases (yes v no), sex (male v female), pathologic diagnosis (histologic v cytologic), and investigative centre. Chemotherapy was repeated every 3 weeks for a maximum of six cycles (unless there was earlier evidence of disease progression or intolerance of the study treatment). Patients on both arms received dexamethasone prophylaxis of 4 mg orally twice per day on the day before, the day of, and the day after each day-1 treatment. All patients received oral folic acid (350 to 1,000 mg) daily and a vitamin B12 injection (1,000 mg) every 9 weeks, beginning 1 to 2 weeks before the first dose and continuing until 3 weeks after the last dose of study treatment. Patients requiring a day-1 dose reduction of pemetrexed, gemcitabine, or cisplatin received the reduced dose for the remainder of the study. Patients who had two dose reductions on day 1 and who experienced toxicity requiring a third dose reduction were discontinued from study therapy. Cycle delays of up to 42 days were permitted for recovery from adverse events. Within-cycle (day 8) dose reductions and omissions were allowed for gemcitabine. Concomitant supportive therapies, such as erythropoietic agents or granulocyte. Colony-stimulating factors were allowed according to the American Society of Clinical Oncology guidelines. The study protocol requested, in a nonmandatory way, the collection of tumour samples for assessment of candidate biomarkers. Details about these data will be reported separately.

Baseline characteristics

Table 1. Baseline Patient and Disease Characteristics for Randomly Assigned Patients

Characteristic	Cisplatin/ Pemetrexed (n = 862) No. of Patients	%	Cisplatin/ Gemcitabine (n = 863) No. of Patients	%
Age, years				
Median	61.1		61.0	
Range	28.8-83.2		26.4-79.4	
Age < 65 years	541	62.8	577	66.9
Age ≥ 65 years	321	37.2	286	33.1
Sex				
Female	257	29.8	258	29.9
Male	605	70.2	605	70.1
Smoking status				
Former/current smoker	629	73.0	637	73.8
Never-smoker	128	14.8	122	14.1
Unknown	105	12.2	104	12.1
Stage of disease				
Stage IIIB, dry	138	16.0	159	18.4
Stage IIIB, wet	67	7.8	51	5.9
Stage IV	657	76.2	653	75.7
ECOG performance status				
0	305	35.4	307	35.6
1	556	64.5	554	64.2
Unknown	1	0.1	2	0.2
Pathologic diagnosis				
Histologic	573	66.5	575	66.6
Cytologic	289	33.5	288	33.4
Race				
African descent	18	2.1	18	2.1
White	669	77.6	680	78.8
East/South East Asian	116	13.5	104	12.1
Other	59	6.8	61	7.1
Histologic type*				
Adenocarcinoma	436	50.6	411	47.6
Large-cell carcinoma	76	8.8	77	8.9
Squamous cell carcinoma	244	28.3	229	26.5
Other: NSCLC, NOS	106	12.3	146	16.9

Abbreviations: ECOG, Eastern Cooperative Oncology Group; NSCLC, non–small-cell lung cancer; NOS, not otherwise specified.
*Histologic type was reported by the investigative site.

Primary and secondary endpoints

The primary endpoint was:

- Overall survival (OS)

The secondary endpoints were:

- Progression-free survival (PFS)
- time to progressive disease
- time to treatment failure
- objective tumour response rate
- duration of response
- toxicity

Method of analysis

Using a noninferiority design, this study compared overall survival between the two treatment arms using a fixed margin method. Assuming a hazard ratio (HR) of 1.0 and including all randomly assigned patients, when at least 1,190 deaths occurred, the analysis provided 80% power to reject the null hypothesis (H0). The H0 assumed that cisplatin/gemcitabine would provide a15% reduction in the risk of death over cisplatin/pemetrexed, corresponding to a fixed margin of 1.176. Using the Cox proportional hazards model26 (with preplanned adjustments for sex, diagnosis [histologic v

	cytologic], disease stage, and performance status) and two-tailed 95% CIs for the HR, rejection of the H0 occurred when the upper bound of the HR's 95% CI was less than 1.176. Cox proportional hazard models were also used to compare the other time-to-event end points between the treatment arms and to test for treatment-by-histology interaction; the Kaplan-Meier method was used to estimate the medians for time-to-event parameters. Tests were conducted as follows: noninferiority tests at one-sided α=025 level; superiority tests at two-sided α=.05 level; and two-sided CIs at 95%. Tumour response was compared using the normal approximation test for superiority. The incidences of toxicities, hospitalizations, and supportive care were analysed using Fisher's exact test and analysis of variance (as appropriate). Prespecified analyses of overall survival by random assignment factors included age group, race, smoking status, and histology. All HRs are reported as adjusted, unless otherwise specified. P values were not adjusted for multiple comparisons.
Subgroup analyses	NA

Table 57 Ohe et al. 2007

Ohe et al. 2007	
NCT number	NA
Objective	The objective of this study was to compare the efficacy and toxicity of three platinum-based combination regimens against cisplatin plus irinotecan (IP) in patients with untreated advanced non-small-cell lung cancer (NSCLC) by a non-inferiority design.
Publications – title, author, journal, year	Randomized phase III study of cisplatin plus irinotecan versus carboplatin plus paclitaxel, cisplatin plus gemcitabine, and cisplatin plus vinorelbine for advanced non-small-cell lung cancer: Four-Arm Cooperative Study in Japan, Ohe et al., Annals of oncology, 2007 [24]
Study type and design	Randomized phase III study All patients were randomly assigned to one of the four treatment groups by the central registration office by means of the minimization method. Stage, PS, gender, lactate dehydrogenase (LDH) and albumin values, and institution were used as adjustment variables. The first group received the reference treatment, 80 mg/m2 of cisplatin on day 1 and 60 mg/m2 of irinotecan on days 1, 8, and 15, and the cycle was repeated every 4 weeks. The second group received 200 mg/m2 of paclitaxel (Bristol-Myers K.K., Tokyo, Japan) over a 3-h period followed by carboplatin at a dose calculated to produce an area under the concentration–time curve of 6.0 min · mg/mL on day 1 and the cycle was repeated every 3 weeks. The third group received 80 mg/m2 of cisplatin on day 1 and 1000 mg/m2 of gemcitabine (Eli Lilly Japan K.K., Kobe, Japan) on days 1, 8 and the cycle was repeated every 3 weeks. The fourth group received 80 mg/m2 of cisplatin on day 1 and 25 mg/ m2 of vinorelbine (Kyowa Hakko Kogyo Co. Ltd., Tokyo, Japan) on days 1, 8 and the cycle was repeated every 3 weeks. Each treatment was repeated for three or more cycles unless the patient met the criteria for progressive disease or experienced unacceptable toxicity.
Follow-up time	2 years minimum follow up.
Population (inclusion and exclusion criteria)	Patients with histologically and/or cytologically documented NSCLC were eligible for participation in the study. Each patient had to meet the

following criteria: clinical stage IV or IIIB (including only patients with no indications for curative radiotherapy, such as malignant pleural effusion, pleural dissemination, malignant pericardiac effusion, or metastatic lesion in the same lobe), at least one target lesion >2 cm, no prior chemotherapy, no prior surgery and/or radiotherapy for the primary site, age 20–74 years, Eastern Cooperative Oncology Group performance status (PS) of 0 or 1, adequate haematological, hepatic and renal functions, partial pressure of arterial oxygen (paO2) ‡60 torr, expected survival >3 months, able to undergo first course treatment in an inpatient setting, and written informed consent. The study was approved by the Institutional Review Board at each hospital. Written informed consent was obtained from every patient.

Intervention

Patients were randomised to either:

- 80 mg/m2 of cisplatin on day 1 and 60 mg/m2 of irinotecan on days 1, 8, and 15
- 200 mg/m2 of paclitaxel over a 3-h period followed by carboplatin at a dose calculated to produce an area under the concentration–time curve of 6.0 min · mg/mL on day 1
- 80 mg/m2 of cisplatin on day 1 and 1000 mg/m2 of gemcitabine (Eli Lilly Japan K.K., Kobe, Japan) on days 1, 8
- 80 mg/m2 of cisplatin on day 1 and 25 mg/ m2 of vinorelbine on days 1, 8

Baseline characteristics

From October 2000 to June 2002, a total of 602 patients were registered by 44 hospitals in Japan. All patients had been followed up for >2 years, and 447 patients had died as of June 2004. Of the 602 patients registered, 151 were allocated to the reference treatment, IP, and 150, 151, and 150 patients were allocated to TC, GP, and NP, respectively. Since 10 patients did not receive chemotherapy and 11 patients were subsequently found to be ineligible, 592 patients were assessable for toxicity and 581 patients were assessable for efficacy. Four patients did not receive chemotherapy due to electrolytic disorder, fever, symptomatic brain metastases, and rapid tumour progression in IP, two patients due to refusal and pneumonia in TC, four patients due to lower WBC counts (two patients), rapid tumour progression, and nephritic syndrome in NP. Two patents were ineligible due to wrong stage in IP, two patients were wrong stage and one patient had double cancer in TC, two patients were wrong diagnosis, one patient had massive pleural effusion, one patient received prior chemotherapy in GP, one patient had no target lesions in NP. Age, gender, PS, stage, and LDH and albumin values were well balanced in each arm (Table 1). Fewer patients with adenocarcinoma and more patients with squamous cell carcinoma were, however, entered in three experimental arms than in IP.

Table 1. Patient characteristics and treatment delivery

	Cisplatin + irinotecan	Carboplatin + paclitaxel	Cisplatin + gemcitabine
Assessable patients	145	145	146
Gender (male/female)	97/48	99/46	101/45
Age, median (range)	62 (30–74)	63 (33–74)	61 (34–74)
PS (0/1)	44/101	44/101	45/101
Histology			
Adenocarcinoma	121	104	108
Squamous cell carcinoma	16	31	29
Others	8	10	9
Stage (IIIB/IV)	31/114	28/117	30/116
No. of cycles			
Mean ± SD	3.0 ± 1.3	3.5 ± 1.5	3.2 ± 1.2
Median	3	3	3
Range	1–7	1–10	1–7

PS, performance status; SD, standard deviation.

Primary and secondary endpoints	The primary end point of this study was overall survival (OS), and the secondary end points were response rate, response duration, time to progressive disease (TTP), time to treatment failure (TTTF), adverse event, and QoL.
Method of analysis	Response was evaluated according to the Response Evaluation Criteria in Solid Tumours, and tumour markers were excluded from the criteria. Objective tumour response in all responding patients was evaluated by an external review committee with no information on the treatment group. Toxicity grading criteria in National Cancer Institute Common Toxicity Criteria Ver 2.0 were used to evaluate toxicity. Quality of life (QoL) was evaluated by means of the Functional Assessment of Cancer Therapy—Lung (FACT-L) Japanese version and the QoL Questionnaire for Cancer Patients Treated with Anticancer Drugs (QoLACD), before treatment, immediately before the second cycles of chemotherapy, and 3 and 6 months after the start of treatment. The 1-year survival rate of the control group in this study was estimated to be 43% based on the data in published papers, and the 1-year survival rate in the other treatment group was expected to be 50%. The lower equivalence limit for 1-year survival rate was set as '10%'. The criterion for the non-inferiority of each treatment was a lower limit of the two-sided 95% confidence interval (CI) of the 1-year survival rate of treatment minus that of control larger than the lower equivalence limit. Because the noninferiority of each treatment versus the control was to be evaluated independently, a separate null hypothesis was stated for each treatment, and for that reason no multiple comparison adjustment was included in the study. Based on the above conditions and binomial distribution, 135 patients were needed per arm for a one-sided Type I error of 2.5% and 80.0% power. In view of the possibility of variance inflation due to censoring, the sample size was set at 600 (150 per arm). Central registration with randomization, monitoring, data collection, and the statistical analyses were independently carried out by a contract research organization (EPS Co., Ltd, Tokyo, Japan).
Subgroup analyses	NA

Table 58 Shen et al. 2020

Shen et al. 2020	
NCT number	NA
Objective	The objective of this study was to further explore the relationship between RET fusion gene sub-types and the efficacy of pemetrexed-based chemotherapy as a first or subsequent approach and overall survival (OS) in patients with advanced lung adenocarcinoma.
Publications – title, author, journal, year	Association Between RET Fusions and Efficacy of Pemetrexed-based Chemotherapy for Patients With Advanced NSCLC in China: A Multicentre Retrospective Study, Shen et al., Clinical lung cancer, 2020 [26]
Study type and design	Multicentre, retrospective study
Follow-up time	OS was measured from the date of confirmed stage IIIB/IV NSCLC to death or the last follow-up evaluation. The last follow-up date was April 12, 2019

Population (inclusion and exclusion criteria)	The histologic classification of NSCLC was determined using the World Health Organization criteria (2015 version), and the histologic subtype classification of adenocarcinoma was performed in accordance with the standards of International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society. Lung cancer staging was performed in accordance with the 7th TNM classification scheme, and measurable disease using the Response Evaluation Criteria in Solid Tumours (RECIST), version 1.1. Previous anti-cancer therapies were allowed. The institutional ethics committee at each investigation site approved the present study protocol. RET rearrangements were validated using molecular diagnostic testing performed at an accredited local laboratory. The accepted test method was next generation sequencing. For positive fluorescence in situ hybridization detection, the fusion subtype was confirmed by next generation sequencing.
Intervention	A total of 62 patients with NSCLC and RET rearrangements were enrolled in the present study. Of the 62 patients, 40 had received first-line chemotherapy regimen, including pemetrexed/platinum (n ¼ 19), pemetrexed monotherapy (n ¼ 3), paclitaxel/platinum (n ¼ 14), and gemcitabine/platinum (n ¼ 4). All chemotherapy regimens were calculated according to the standard dose of the National Comprehensive Cancer Network guideline (pemetrexed, 500 mg/m2 on day 1; gemcitabine, 1000-1250 mg/m2 on days 1 and 8; paclitaxel, 175 mg/m2 on day 1]; carboplatin, area under the curve of 5 on day 1); and cisplatin, 75 mg/m2 on day 1). Of the 40 patients, 7 had received chemotherapy combined with bevacizumab. No information on treatment received was available for 10 patients. Twenty-eight patients received second-line treatment, including pemetrexed-based chemotherapy for 10 and other treatment regimens for 18.
Baseline characteristics	Of the 62 patients, 33 were men and 29 were women, with a median age of 59 years (range, 25-78 years). The smoking history was divided into former or current (n ¼ 25) and never (n ¼ 37). Of the 62 patients, 18 had undergone surgery and 12 had not developed a relapse. Also, 6 patients had stage IIIB and 44 had stage IV using the International Association for the Study of Lung Cancer classification of lung adenocarcinoma. Detailed patient characteristics are listed in Table 1. All 62 patients had RET rearrangements, including KIF5B-RET fusions in 41 (66.1%) and CCDC6-RET fusions in 15 (24.2%). Other rare fusion types among the remaining 6 patients included ANK3-RET (n ¼ 1), ERC1-RET (n ¼ 1), RABEP1-RET (n ¼ 1), ALOX5-RET (n ¼ 1), and ATR-RET (n ¼ 2). The baseline characteristics of patients with lung cancer with KIF5B-RET (n ¼ 24) and noneKIF5B-RET (n ¼ 16) rearrangements who had received chemotherapy were compared (Table 2). No differences were found in gender, age, smoking status, or pemetrexed-based chemotherapy between the 2 groups.

Table 1 Clinical Characteristics of Study Population (n = 62)

Characteristic	n (%)
Gender	
Male	33 (53.2)
Female	29 (46.8)
Mean age, y	59.0
Age group, y	
≤60	34 (54.8)
>60	28 (45.2)
Smoking status	
No	37 (59.7)
Yes	25 (40.3)
RET fusion type	
KIF5B-RET	41 (66.1)
CCDC6-RET	15 (24.2)
Rare fusions	6 (9.7)
First-line regimen	40 (64.5)
Pemetrexed-based	22 (55.0)
Non–pemetrexed-based	18 (45.0)
Second-line regimen	28 (45.2)
Pemetrexed-based	10 (35.7)
Non–pemetrexed-based	18 (64.3)
Cabozantinib	
No	52 (82.9)
Yes	10 (16.1)
Brain metastases before treatment	
No	51 (82.3)
Yes	11 (17.7)

Abbreviation: RET = rearranged during transfection.

Table 2 Comparison of Clinical Characteristics of Patients With KIF5B-RET Versus Non–KIF5B-RET Who Had Received Chemotherapy (n = 40)

Characteristic	KIF5B-RET Fusion (n = 24)	Non–KIF5B-RET Fusion (n = 16)	*P* Value
Gender			.601
Male	13	10	
Female	11	6	
Age, y			.243
≤60	15	7	
>60	9	9	
Smoking status			.604
No	14	8	
Yes	10	8	
Brain metastases before treatment			.159
No	20	10	
Yes	4	6	
Pemetrexed-based chemotherapy			.295
No	5	6	
Yes	19	10	
Cabozantinib			.482
No	19	11	
Yes	5	5	

Data presented as number of patients.
Abbreviation: RET = rearranged during transfection.

Primary and secondary endpoints	The primary endpoint was: • OS

	The secondary endpoints were: • Progression free survival
Method of analysis	The authors collected the data from all patients during disease progression, including the chemotherapy regimen and targeted drugs used. The response to systemic therapies was assessed locally by each investigator and 1 radiologist using the RECIST, version 1.1, including the complete response (CR), partial response (PR), stable disease, and progressive disease. The ORR was defined as the sum of CR and PR. The disease control rate (DCR) was defined as the sum of the objective response and stabilization rates (CR plus PR plus stable disease). The tumour response was evaluated by computed tomography every 6 weeks in accordance with the RECIST, version 1.1. PFS was defined as the period from the initial date of drug treatment to the date of confirmation of disease progression, as evaluated by RECIST, version 1.1, or death. OS was measured from the date of confirmed stage IIIB/IV NSCLC to death or the last follow-up evaluation. Kaplan-Meier estimates and the log-rank test were applied to evaluate PFS and OS. Statistical analysis was performed using SPSS, version 19.0 (IBM Corp, Armonk, NY). Two-sided P values < .05 were considered to represent statistical significance.
Subgroup analyses	This study analysed the data from 32 patients with RET rearrangements who had received pemetrexed-based chemotherapy as first- (22 patients) or second-line (10 patients) treatment.

Table 59 Tan et al. 2020

Tan et al. 2020	
NCT number	NA
Objective	This study aimed to conduct a comparative analysis of FISH and next-generation sequencing (NGS) methods of molecular testing for RET rearrangements, to correlate their clinical and treatment outcomes to the different classes of systemic therapies, and to genomically characterize further this subset of patients.
Publications – title, author, journal, year	Molecular Characterization and Clinical Outcomes in RET-Rearranged NSCLC, Tan et al., Journal of thoracic oncology, 2020 [27]
Study type and design	Retrospective cohort study
Follow-up time	The median follow-up time (range) was 20.3 (0.2-113.5)
Population (inclusion and exclusion criteria)	Included patients were diagnosed with RET-rearranged NSCLC treated at the National Cancer Centre Singapore between April 2014 and March 2020
Intervention	17 (28%) patients received Immunotherapy; 14 (23%) received Multikinase RET TKI, 38 (62%) received Platinum-pemetrexed chemotherapy; 35 (58%) received Selective RET TKI.
Baseline characteristics	There were a total of 64 patients with RET-rearranged NSCLC included during the study period (Table 1). The median age of the patients at diagnosis was 62 years (range 25–85 y), with 36 patients (56%) who were women, 49 (77%) were of Chinese ethnicity, 61 (95%) had histologic diagnosis of adenocarcinoma, 50 (78%) had stage IV disease at diagnosis, and 44 (69%) were never smokers. Of the entire cohort, 33

were consecutive patients diagnosed by FISH at our institution—representing 2.1% (33 of 1603) of the patients newly diagnosed with advanced NSCLC who had RET FISH testing in the same time frame and 3.5% (27 of 773) of the patients negative for EGFR mutation.

Table 2. Known Molecular Profile

Characteristic	N (%)
Method of *RET* testing (n = 64)	
FISH only	21 (33)
NGS only	30 (47)
Both FISH and NGS	13 (20)
RET FISH testing (n = 34)	
Positive	30 (88)
Equivocal	2 (6)
Negative	2 (6)
RET NGS testing (n = 43)	
Positive	40 (93)
Negative	3 (7)
RET FISH and NGS testing (n = 13)	
FISH positive only	3 (23)
NGS positive and equivocal FISH	2 (15.5)
NGS positive only	2 (15.5)
Both FISH and NGS positive	6 (46)
RET fusion partner (n = 40)	
CCDC6-RET	12 (30)
CNTNAP2-RET	1 (2.5)
KIF5B-RET	25 (62.5)
KIF5B-RET + *CCDC6-RET*	1 (2.5)
KIF5B-RET + *THOC2-RET*	1 (2.5)
TMB (n = 17)	
Median (range)	5.4 mutations/Mbp (0.8-18.2)
PD-L1 status, % (n = 31)	

Primary and secondary endpoints	The primary endpoint was: • Median OS The secondary endpoints were: • Median PFS • Objective response rate
Method of analysis	Descriptive statistics, including median and range for continuous variables, and percentages for categorical variables were used. Kaplan-Meier survival analysis was performed to determine progression-free survival and overall survival (OS). Survival was tested using Cox proportional hazard model. Hazard ratio (HR) with its 95% confidence intervals (CIs) is displayed with the associated log-rank p value. Statistical analysis was conducted using GraphPad Prism 8 (GraphPad Software, San Diego, CA). The value of p less than 0.05 was considered statistically significant.
Subgroup analyses	NA

Table 60 REVEL

REVEL	
NCT number	NCT01168973
Objective	This study aimed to compare the survival of participants who receive chemotherapy and ramucirumab versus chemotherapy alone as second line treatment for NSCLC after prior first line platinum-based chemotherapy.
Publications – title, author, journal, year	Ramucirumab plus docetaxel versus placebo plus docetaxel for second-line treatment of stage IV non-small-cell lung cancer after disease progression on platinum-based therapy (REVEL): a multicentre, double-blind, randomised phase 3 trial, Garon et al., Lancet, 2014[28]
Study type and design	Randomized, Double-Blind, Phase 3 Study
Follow-up time	The median follow-up time (range) was 9.5 months (IQR 4.4–14.9),
Population (inclusion and exclusion criteria)	Inclusion criteria: • Disease progression during or after one prior first-line platinum-based chemotherapy with or without maintenance therapy • Prior bevacizumab as first-line and/or maintenance therapy is allowed • Signed informed consent • Eastern Cooperative Oncology Group (ECOG) performance status of 0-1 • Histologically or cytologically confirmed NSCLC • Stage IV NSCLC disease • Participants have measurable or nonmeasurable disease • Adequate organ function • Disease progression during or after one prior first-line platinum-based chemotherapy with or without maintenance therapy • Prior bevacizumab as first-line and/or maintenance therapy is allowed • Signed informed consent • Eastern Cooperative Oncology Group (ECOG) performance status of 0-1 • Histologically or cytologically confirmed NSCLC • Stage IV NSCLC disease • Participants have measurable or nonmeasurable disease • Adequate organ function Exclusion criteria: • Disease progression on more than 1 prior chemotherapy regimens • Participants whose only prior treatment was a tyrosine kinase inhibitor

- The participant's tumor wholly or partially contains small cell lung cancer
- Major surgery within 28 days prior to randomization, or subcutaneous venous access device placement within 7 days prior to randomization. Postoperative bleeding complications or wound complications from a surgical procedure performed in the last 2 months.
- Concurrent treatment with other anticancer therapy, including other chemotherapy, immunotherapy, hormonal therapy, chemoembolization, or targeted therapy
- Last dose of bevacizumab must be at least 28 days from time of randomization
- Last dose of cytotoxic chemotherapy must be at least 14 days from time of randomization
- The participant has untreated CNS metastases. Participants with treated brain metastases are eligible if they are clinically stable with regard to neurologic function, off steroids after cranial irradiation ending at least 2 weeks prior to randomization, or after surgical resection performed at least 28 days prior to randomization. No evidence of Grade greater than or equal to 1 CNS hemorrhage based on pretreatment Magnetic Resonance Imaging (MRI) or IV contrast Computed Tomography (CT) scan.
- Radiologically documented evidence of major blood vessel invasion or encasement by cancer
- Radiographic evidence of intratumor cavitation
- History of uncontrolled hereditary or acquired thrombotic disorder
- Chronic therapy with nonsteroidal anti-inflammatory drug (NSAIDs) or other antiplatelet agents; Aspirin use at doses up to 325 milligrams per day (mg/day) is permitted
- History of gross hemoptysis (defined as bright red blood or greater than or equal to 1/2 teaspoon) within 2 months prior to randomization
- Clinically relevant congestive heart failure [New York Heart Association (NYHA II-IV)] or symptomatic or poorly controlled cardiac arrhythmia
- Any arterial thrombotic event, including myocardial infarction, unstable angina, cerebrovascular accident, or transient ischemic attack, within 6 months prior to randomization
- Uncontrolled arterial hypertension greater than or equal to 150 / greater than or equal to 90 millimeters of mercury (mm Hg) despite standard medical management
- Serious or nonhealing wound, ulcer, or bone fracture within 28 days prior to randomization
- Significant bleeding disorders, vasculitis, or Grade 3/4 gastrointestinal bleeding within 3 months prior to randomization
- Gastrointestinal (GI) perforation and/or fistulae within 6 months prior to randomization

	• Bowel obstruction, history or presence of inflammatory enteropathy or extensive intestinal resection Crohn's disease, ulcerative colitis, or chronic diarrhea • Peripheral neuropathy greater than or equal to Grade 2 [National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.02] • Serious illness or medical condition(s) including, but not limited to: Human immunodeficiency virus (HIV) infection or acquired immunodeficiency syndrome (AIDS)-related illness; Active or uncontrolled clinically serious infection; Severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or study drug administration • Known allergy or hypersensitivity reaction to any of the treatment components • The participant is pregnant or breastfeeding • Current or recent (within 28 days prior to randomization) treatment with an investigational drug or device that has not received regulatory approval for any indication at the time of randomization, or participation in another interventional clinical trial • Prior therapy with docetaxel
Intervention	intravenous docetaxel 75 mg/m² plus intravenous ramucirumab 10 mg/kg (ramucirumab group; n=628) or intravenous docetaxel 75 mg/m² plus placebo (control group; n=625) on day 1 of a 21 day cycle

Baseline characteristics

	Ramucirumab plus docetaxel group (n=628)	Placebo plus docetaxel group (n=625)
Age, years		
Median (range)	62 (21–85)	61 (25–86)
<65 years	391 (62%)	407 (65%)
≥65 years	237 (38%)	218 (35%)
Sex		
Male	419 (67%)	415 (66%)
Female	209 (33%)	210 (34%)
Race (self-reported)*		
White	526 (84%)	503 (80%)
Asian	74 (12%)	86 (14%)
Black	17 (3%)	16 (3%)
Other	10 (2%)	20 (3%)
Region of origin		
East Asia (South Korea or Taiwan)	43 (7%)	46 (7%)
Other	585 (93%)	579 (93%)
ECOG performance status†		
0	207 (33%)	199 (32%)
1	420 (67%)	425 (68%)
Disease		
Measurable	606 (96%)	603 (96%)
Non-measurable	22 (4%)	22 (4%)
Smoking history		
Ever	518 (82%)	483 (77%)
Never	109 (17%)	141 (23%)
Unknown	1 (<1%)	1 (<1%)
Histological subtype		
Non-squamous	465 (74%)	447 (72%)
Squamous	157 (25%)	171 (27%)
Unknown	6 (1%)	7 (1%)

EGFR status		
Wild type	207 (33%)	197 (32%)
Mutant	15 (2%)	18 (3%)
Unknown or missing	406 (65%)	410 (66%)
Best response to platinum-based chemotherapy		
CR, PR, or SD	420 (67%)	417 (67%)
PD	178 (28%)	182 (29%)
Missing	30 (5%)	26 (4%)
Previous maintenance treatment		
No	493 (79%)	482 (77%)
Yes‡	135 (21%)	143 (23%)
Previous taxane		
No	475 (76%)	476 (76%)
Yes	153 (24%)	149 (24%)
Previous bevacizumab treatment		
No	540 (86%)	533 (85%)
Yes	88 (14%)	92 (15%)
Time since previous therapy		
<9 months	400 (64%)	374 (60%)
≥9 months	226 (36%)	251 (40%)
Missing	2 (<1%)	0

Data are n (%), unless otherwise stated. ECOG=Eastern Cooperative Oncology Group. CR=complete response. PR=partial response. SD=stable disease. PD=progressive disease. *Data not available for one patient in the ramucirumab group. †Data not available for one patient in each group. ‡Maintenance therapy in the ramucirumab group included pemetrexed (54 patients [9%]), bevacizumab (30 patients [5%]), EGFR tyrosine kinase inhibitor (16 patients [3%]), investigational drug (14 patients [2%]), and other (18 patients [3%]) and in the control group included pemetrexed (53 patients [9%]), bevacizumab (43 patients [7%]), EGFR tyrosine kinase inhibitor (14 patients [2%]), investigational drug (22 patients [4%]), and other (13 patients [2%]).

Primary and secondary endpoints	The primary endpoint was: • Median OS The secondary endpoints were: • Progression-Free Survival (PFS) Percentage of Participants Achieving an Objective Response (Objective Response Rate) • Percentage of Participants Achieving Disease Control (Disease Control Rate) • Maximum Improvement on Lung Cancer Symptom Scale (LCSS) • Change From Baseline to 30-Day Follow-Up Visit on European Quality of Life Questionnaire-5 Dimension (EQ-5D) Health State Scores • Maximum and Minimum Serum Concentrations (Cmax and Cmin) of Ramucirumab • Number of Participants With Anti-Ramucirumab Antibodies • Number of Participants Who Had Treatment-Emergent Adverse Events (TEAEs) or Died
Method of analysis	The primary endpoint was overall survival (time from randomisation until death). Secondary endpoints included PFS (time from

	randomisation until disease progression or death) and ORR as assessed by investigators according to RECIST 1.1 at baseline, and every 6 weeks thereafter. We reported adverse events according to NCI-CTCAE. Primary efficacy analysis was conducted through a stratified logrank comparison of overall survival in the intention-to-treat population. Safety analyses included all patients who received at least one dose of study drug. Overall survival and PFS survival curves were created with the Kaplan-Meier method, and HRs were estimated with stratified Cox proportional hazards models. Multivariable analysis with a stepwise Cox regression model of predefined baseline characteristics were used to examine the effect of treatment after adjustment for other significant prognostic factors. Comparison of ORRs (percentage of patients in the intention-to-treat population with a complete response or partial response) in each treatment group with the CochranMantel-Haenszel test.
Subgroup analyses	NA

8.5 Results of studies (Table A3)

Table A3a Results of study LIBRETTO-001 (RET-altered thyroid cancer)											
Trial name:	LIBRETTO-001										
NCT number:	NCT03157128										
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Median overall survival	Selpercatinib	19	[redacted]	NA	NA	NA	NA	NA	NA	Kaplan–Meier Plots were used to estimate median overall survival.	Data on file
	NA	NA	NA								
OS rate at 24 months	Selpercatinib	19	[redacted]	NA	NA	NA	NA	NA	NA	Kaplan–Meier Plots were used to estimate overall survival at 24 months.	Data on file
	NA	NA	NA								
	Selpercatinib	19	[redacted]	NA	NA	NA	NA	NA	NA	Objective Response Rate were assessed by RECIST v1.1 or	Data on file

Table A3a Results of study LIBRETTO-001 (RET-altered thyroid cancer)											
Objective response rate	NA									RANO, as appropriate to tumor type, as assessed by independent review committee (IRC).	
Median progression-free survival	Selpercatinib NA	NA	[redacted]	NA	NA	NA	NA	NA	NA	*For the previously treated *RET* fusion-positive thyroid cancer patients followed for at least 6 months from first dose, the median PFS by IRC was 20.07 months (95% CI: 10.8-NE) with a median follow-up of 16.5 months at the 30th March 2020 data cut-off. Kaplan–Meier Plots were used to estimate Progression-free survival.	Data on file
Grade 3-4 adverse events	Selpercatinib NA	162	56.2%							CTCAE version 4.03. Reported AE terms were coded using MedDRA version 21.0	Data on file

Table A3a Results of study DECISION	
Trial name:	DECISION

Table A3a Results of study DECISION

NCT number:	NCT00984282										
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Median overall survival	NR NR	NR NR	NR NR	NR	NR	NR	NR	NR	NR		
OS rate at 24 months	Sorafenib NA	196 NA	73% NA	NA	NA	NA	NA	NA	NA		Brose et al. 2014.
Objective response rate	Sorafenib Placebo	24/196 1/201	12.2% (24/196) 0.5%	NA	NA	P < 0.0001	NA	NA	NA	Assessed by Cochran–Mantel–Haenszel test (one-sided significance level: 0.025) in patients who received study medication and had a baseline and a post-baseline tumour evaluation..	Brose et al. 2014.
	Sorafenib		10.8	NA	NA	NA	HR: 0.59	0.45–0.76			

Table A3a Results of study DECISION											
Median progression-free survival	Placebo		5.8						P<0.0001	Assessed by log-rank test using one-sided significance levels of 0.01. Hazard ratios (HR) and confidence intervals (CI) were derived from a Cox proportional hazards model.	Brose et al. 2014.
Grade 3-4 adverse events	Sorafenib	207	64.3%	NA	NA	NA	NA	NA	NA		Brose et al. 2014.
	NA	NA	NA								

Table A3a Results of study Kloos et al. 2009.											
Trial name:	NA										
NCT number:	NA										
				Estimated absolute difference in effect			**Estimated relative difference in effect**			**Description of methods used for estimation**	**References**
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		

Table A3a Results of study Kloos et al. 2009.											
Median overall survival	Treatment naïve Sorafenib	33	23 (18 – 34)	NA	NA	P = .4787	NA	NA	NA	The median survival is based on log-rank test to compare the curves for OS.	Kloos et al. (2009)
	Treatment experience sorafenib	41	37.5 (4-42.5)								
OS rate at 24 months	Treatment naïve Sorafenib	33	45%	NA	NA	NA	NA	NA	NA		
	Treatment experience sorafenib	41	62%								
Objective response rate	Treatment naïve Sorafenib	33	15% (5/33)	NA	NA	NA	NA	NA	NA	The objective response rate is based on RECIST (Response Evaluation Criteria in Solid Tumors).	Kloos et al. (2009)
	Treatment experience sorafenib	8	13% (1/8)								
Median progressio	Treatment naïve Sorafenib	33	16 (8-27.5)	NA	NA	P = .8627	NA	NA	NA	The median progression-free survival is based on the log-	Kloos et al. (2009)

Table A3a Results of study Kloos et al. 2009.											
n-free survival	Treatment experience sorafenib	8	10 (4-28)							rank test to compare the curves for PFS.	
Grade 3-4 adverse events	NA NA	NA NA	NA NA	NA	NA	NA	NA	NA	NA		

Table A3a Results of study Leboulleux et al. 2012											
Trial name:	NA										
NCT number:	NCT00537095										
				Estimated absolute difference in effect			**Estimated relative difference in effect**			**Description of methods used for estimation**	**References**
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Median overall survival	Vandetanib Placebo	72 73	NR NR	NA	NA	NA	HR: 0.92*	0.4–2.15	0.80	*At data cut-off, overall survival did not differ between treatment groups although data were immature.	Leboulleux et al. 2012
	Vandetanib	72	62%	NA	NA	NA	NA	NA	NA		

Table A3a Results of study Leboulleux et al. 2012

OS rate at 24 months	Placebo	73	60%								
Objective response rate	Vandetanib	72	6	NA	NA	NA	OR: 1.57	0.42-5.81	0.501	Investigator assessed according to RECIST version 1.1.	Leboulleux et al. 2012
	Placebo	73	26								
Median progression-free survival	Vandetanib	72	11.1 (7.7–14.0) months	NA	NA	NA	HR: 0.63	0.54–0.74	one-sided p=0.008	PFS were analyzed with the log-rank test (unadjusted model with treatment factor only) in the intention-to-treat population.	Leboulleux et al. 2012
	Placebo	73	5.9 (4.0–8.9) months								
Grade 3-4 adverse events	Vandetanib	72	53% (39/73)*	NA	NA	NA	NA	NA	NA	*QTc prolongation adverse events were assessed by the investigators and were graded according to US National Cancer Institute Common Terminology Criteria for Adverse Events: grade 1 was 450–470 ms; grade 2 was >470–500 ms or ≥60 ms longer than baseline; grade 3 was >500 ms; and grade 4 was >500 ms with life-threatening signs or symptoms, or Torsade de pointes.	Leboulleux et al. 2012
	Placebo	73	19% (14/72)								

Table A3a Results of study LIBRETTO (MTC thyroid cancer – clinical question 2)											
Trial name:	LIBRETTO										
NCT number:	NCT03157128										
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		Wirth et al. 2020
Median overall survival	Selpercatinib	55	33.3 (33.2 - NE) months	NA	NA	NA	NA	NA	NA	Median overall survival is estimated using the Kaplan–Meier method.	Wirth et al. 2020
	NA	NA	NA								
OS rate at 24 months	Selpercatinib	55	77.1% (63.1-86.3)	NA	NA	NA	NA	NA	NA	OS rate at 24 months is estimated using the Kaplan–Meier method.	
	NA	NA	NA								
Mean CFB in EORTC-QLQ-C30	NA	NA	NA	NA	NA	NA	NA	NA	NA		
	NA	NA	NA								
	Selpercatinib	55	69.1 (55.2 - 80.9)*	NA	NA	NA	NA	NA	NA	*At the 30th March 2020 data cut-off the ORR was 69.1 (55.2	

Table A3a Results of study LIBRETTO (MTC thyroid cancer – clinical question 2)											
Objective response rate	NA	NA	NA							- 80.9) in the PAS population, respectively. Of these 10.9% were complete responses (CR) and 58.2% were partial responses (PR) in the PAS population, respectively.	Wirth et al. 2020
Median progression-free survival	Selpercatinib NA	55 NA	NE (24.4-NE)* NA	NA	NA	NA	NA	NA	NAS	*At the 30th March 2020 data cut-off the median PFS was not reached. Progression-free survival is estimated by means of the Kaplan–Meier method.	Wirth et al. 2020
Grade 3-4 adverse events	Selpercatinib NA	299 NA	168 (56.2%) NA							In the MTC safety analysis group (N = 299 patients), Grade 3 or 4 TEAEs.	Data on file

Table A3a Results of study EXAM	
Trial name:	EXAM
NCT number:	NCT00704730

Table A3a Results of study EXAM

Outcome	Study arm	N	Result (CI)	Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
				Difference	95% CI	*P* value	Difference	95% CI	*P* value		
Median overall survival	Cabozantinib	81	44.3 months	NA	NA	NA	HR: 0.60	0.38-0.94	<0.03	The median survival is based on the Kaplan-Meier method and the stratified log-rank test for inference testing. The stratified Cox proportional hazards model was used to estimate hazard ratios (HRs).	Schlumberger et al. 2017
	Placebo	45	18.9 months								
OS rate at 24 months	Cabozantinib	81	70%	NA	NA	NA	NA	NA	NA		
	Placebo	45	42%								
Mean CFB in EORTC-QLQ-C30	Cabozantinib	NA	NA	NA	NA	NA	NA	NA	NA		
	Placebo	NA	NA								
Objective response rate	Cabozantinib	81	32 %* and 34 %**	NA	NA	NA	NA	NA	NA	* in the RET mutation–positive patients treated with cabozantinib **in the RET M918T–positive subgroup.	*Sherman et al. (2016) **Schlumberger et al. 2017

Table A3a Results of study EXAM

	Placebo	NA	NA							The objective response rate is based on mRECIST v1.0 by the Independent Review Committee (IRC).	
Median progression-free survival	Cabozantinib	81	13.9 months**	NA	NA	NA	HR: 0.15**	0.08-0.28**	<.0001*	**in the RET M918T–positive subgroup. The median progression-free survival used the Kaplan-Meier method and the stratified log-rank test for inference testing. The stratified Cox proportional hazards model was used to estimate hazard ratios (HRs).	**Schlumberger et al. 2017
	Placebo	45	4.0 months								
Grade 3-4 adverse events	Cabozantinib	214	69%	NA	NA	NA	NA	NAN	NA	Both RET-positive and negative, safety was not different based on RET-mutational status. Data in EXAM trial was reported for AEs (any grade), that occurred in ≥ 10 % of cabozantinib patients	Elisei et al. 2013.
	Placebo	109	33%								

Table A3a Results of study Park et al. 2018											
Trial name:	NA										
NCT number:	NA										
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Median overall survival	Platinum-based therapy as salvage chemotherapy after immunotherapy	24	10.9	NA	NA	NA	NA	NA	NA	Not reported in the publication.	Park et al. 2018
	NA	NA	NA								
OS rate at 24 months	NA	NA	NA	NA	NA	NA	NA	NA	NA		
	NA	NA	NA								
	NA	NA	NA	NA	NA	NA	NA	NA	NA		

Table A3a Results of study Park et al. 2018										
Mean CFB in EORTC-QLQ-C30	NA	NA	NA							
Objective response rate	Platinum-based therapy as salvage chemotherapy after immunotherapy NA	24	66.7%	NA	NA	NA	NA	NA	NA	Assessed by investigators using RECIST.	Park et al. 2018
Median progression-free survival	Platinum-based therapy as salvage chemotherapy after immunotherapy NA	24 NA	4.5 NA	NA	NA	NA	NA	NA	NA	Defined as time from the start of SCAI to disease progression or death due to any cause.	Park et al. 2018
Grade 3-4 adverse events	NA NA	NA NA	NA NA	NA	NA	NA	NA	NA	NA		

Table A3a Results of study Metro et al. 2019											
Trial name:	NA										
NCT number:	NA										
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Median overall survival	NA NA	NA NA	NA NA	NA	NA	NA	NA	NA	NA		
OS rate at 24 months	NA NA	NA NA	NA NA	NA	NA	NA	NA	NA	NA		
Mean CFB in EORTC-QLQ-C30	NA NA	NA NA	NA NA	NA	NA	NA	NA	NA	NA		
Objective response rate	Platinum-based chemotherapy	21	42.9% (25.5 – 67.0)	NA	NA	NA	NA	NA	NA	The ORR is based on RECIST version 1.1.	Metro et al. 2019

Table A3a Results of study Metro et al. 2019											
	NA	NA	NA								
Median progression-free survival	Salvage chemotherapy	42	4.5 (3.1–6.5) months	NA	NA	NA	NA	NA	NA	PFS were analysed according to Kaplan-Meier method and survival curves were compared using the log-rank test. Cox model was used to estimate hazard ratio and related 95% confidence interval (CI). Given the retrospective nature of the study, statistical significance should be used in an exploratory view and median time estimation with their 95% CI: reported to better interpret the data.	Metro et al. 2019
	NA	NA	NA								
Grade 3-4 adverse events	NA	NA	NA	NA	NA	NA	NA	NA	NA		
	NA	NA	NA								

Table A3a Results of study Bersanelli et al. (2020)	
Trial name:	NA

Table A3a Results of study Bersanelli et al. (2020)

NCT number:	NA										
				Estimated absolute difference in effect			**Estimated relative difference in effect**			**Description of methods used for estimation**	**References**
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Median overall survival	Chemotherapy as second line treatment		8.4 (5.6−11.2) months	NA	NA	NA	NA	NA	NA	The median survival is based on the Kaplan–Meier estimator and compared using log-rank test.	Bersanelli et al. 2020
	NA	NA	NA								
OS rate at 24 months	NA	NA	NA	NA	NA	NA	NA	NA	NA		
	NA	NA	NA								
Mean CFB in EORTC-QLQ-C30	NA	NA	NA	NA	NA	NA	NA	NA	NA		
	NA	NA	NA								
Objective response rate	Chemotherapy as second line treatment		22.8%*	NA	NA	NA	NA	NA	NA	*77 partial responses and 1 complete response The ORR is based on RECIST version 1.1.	Bersanelli et al. 2020
	NA	NA	NA								

Table A3a Results of study Bersanelli et al. (2020)											
Median progression-free survival	Chemotherapy as second line treatment		4.1 (3.4–4.8)	NA	NA	NA	NA	NA	NA	The PFS is based on RECIST version 1.1 using Kaplan Meier.	Bersanelli et al. 2020
	NA	NA	NA								
Grade 3-4 adverse events	NA	NA	NA	NA	NA	NA	NA	NA	NA		
	NA	NA	NA								

Table A3a Results of study Gautschi et al 2017											
Trial name:	Gautschi et al 2017										
NCT number:	NA										
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
	Platinum + pemetrexed	66	23.6 (13.4-33.2) months	NA	NA	NA	NA	NA	NA	Overall survival was measured as the time from the first	Gautschi et al. 2017

Table A3a Results of study Gautschi et al 2017												
Median overall survival	NA	NA	NA								administration of RET inhibitor therapy to death from any cause. Patients who were alive at the time of analysis were censored at their last follow-up. Survival rates were estimated by using the Kaplan-Meier method	
OS rate at 24 months	NA NA	NA NA	NA NA	NA	NA	NA	NA	NA	NA			
Mean CFB in EORTC-QLQ-C30	NA NA	NA NA	NA NA	NA	NA	NA	NA	NA	NA			
Objective response rate	Platinum + pemetrexed NA	55 NA	49% (27/55) NA	NA	NA	NA	NA	NA	NA		Only 55 were evaluable. The ORR is based on RECIST version 1.1.	Gautschi et al. 2017
Median progressio	Platinum + pemetrexed	66	6.4 (4.3-8.8)	NA	NA	NA	NA	NA	NA		Progression-free survival was measured as the time from	Gautschi et al. 2017

Table A3a Results of study Gautschi et al 2017											
n-free survival	NA	NA	NA							the first administration of RET inhibitor therapy to progression defined by RECIST v1.1 or death from any cause. Survival rates were estimated by using the Kaplan-Meier method.	
Grade 3-4 adverse events	NA NA	NA NA	NA NA	NA	NA	NA	NA	NA	NA		

Table A3a Results of study KEYNOTE-189											
Trial name:	KEYNOTE-189										
NCT number:	NCT02578680										
				Estimated absolute difference in effect			**Estimated relative difference in effect**			**Description of methods used for estimation**	**References**
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		

Table A3a Results of study KEYNOTE-189											
Median overall survival	1L pemetrexed in combination with platinum	206	10.7 (8.7-13.6) months	NA	NA	NA	NA	NA	NA	The median survival is based on the Kaplan–Meier estimator. A stratified Cox proportional hazards model with Efron's method of tie handling was used to determine HRs and 95% CIs.	Gadgeel et al. 2020
	NA	NA	NA								
OS rate at 24 months	1L pemetrexed in combination with platinum	206	29.9%	NA	NA	NA	NA	NA	NA	The OS rate at 24 months is based on the Kaplan–Meier estimator.	Gadgeel et al. 2020
	NA	NA	NA								
Mean CFB in EORTC-QLQ-C30	1L pemetrexed in combination with platinum	200	-2.6 (-5.8 – 0.5)	NA	NA	NA	NA	NA	NA	Based on mean changes from baseline in QLQ-C30 global status/quality of life score.	Garassino et al. 2020
	NA	NA	NA								

Table A3a Results of study KEYNOTE-189											
Objective response rate	1L pemetrexed in combination with platinum	206	ORR: 40/206 (19.4%) CR: 1 PR: 39	NA	NA	NA	NA	NA	NA	The ORR is based on RECIST version 1.1 .	Gadgeel et al. 2020
	NA	NA	NA								
Median progression-free survival	1L pemetrexed in combination with platinum	206	4.9 (4.7-5.5) PFS-2**: 9.0 (7.6-10.4)	NA	NA	NA	NA	NA	NA	**PFS-2: was defined as the time from randomization to objective tumour progression on next-line treatment (including subsequent anti–PD-[L]1 therapy) or death from any cause, whichever occurs first.	Gadgeel et al. 2020
	NA	NA	NA								
Grade 3-4* adverse events	1L pemetrexed in combination with platinum	206	135/202 (66.8%)	NA	NA	NA	NA	NA	NA	*The result is only available for grade 3-5 adverse events.	Gadgeel et al. 2020
	NA	NA	NA								

Table A3a Results of study KEYNOTE-21												
Trial name:	KEYNOTE-21											
NCT number:	NCT02039674											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Median overall survival	1L pemetrexed in combination with platinum	63	21.1 (14.9-NR)	NA	NA	NA	NA	NA	NA	The Kaplan-Meier method was used to estimate median overall survival.	Borghaei et al. 2019
	NA	NA	NA								
OS rate at 24 months	1L pemetrexed in combination with platinum	63	48%	NA	NA	NA	NA	NA	NA	The Kaplan-Meier method was used to estimate OS rate at 24 months.	Awad et al. 2021
	NA	NA	NA								

Table A3a Results of study KEYNOTE-21											
Mean CFB in EORTC-QLQ-C30	NA NA	NA NA	NA NA	NA	NA	NA	NA	NA	NA		
Objective response rate	1L pemetrexed in combination with platinum NA	63 NA	ORR: 21/63 (33%; 22-46) CR: 2 PR: 19 NA	NA	NA	NA	NA	NA	NA	The ORR is based on RECIST version 1.1.	Awad et al. 2021
Median progression-free survival	1L pemetrexed in combination with platinum NA	63 NA	9.9 (6.2-15.2) NA	NA	NA	NA	NA	NA	NA	The Kaplan-Meier method was used to estimate progression-free survival. Treatment differences were assessed with a stratified log-rank test.	Awad et al. 2021
Grade 3-4 adverse events*	1L pemetrexed in combination with platinum	62	19/62 (31%)	NA	NA	NA	NA	NA	NA	*Measured as grade 3 or worse severity.	Langer et al. 2016

Table A3a Results of study KEYNOTE-21			
	NA	NA	NA

Table A3a Results of study Kim et al. 2012	
Trial name:	Kyoto Thoracic Oncology Research Group Trial 0902
NCT number:	NA

				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Median overall survival	1L pemetrexed in combination with platinum	49	24.3 (18.7-29.9)	NA	NA	NA	NA	NA	NA	The median overall survival is based on the Kaplan–Meier estimator.	Kim et al. 2012
	NA	NA	NA								
	NA	NA	NA	NA	NA	NA	NA	NA	NA		

Table A3a Results of study Kim et al. 2012											
OS rate at 24 months	NA	NA	NA								
Mean CFB in EORTC-QLQ-C30	NA NA	NA NA	NA NA	NA	NA	NA	NA	NA	NA		
Objective response rate	1L pemetrexed in combination with platinum NA	49 NA	ORR: 51% CR: 0 PR: 25/49 NA	NA	NA	NA	NA	NA	NA	Tumor response was assessed by the Response Evaluation Criteria in Solid Tumors (RECIST) criteria.	Kim et al. 2012
Median progression-free survival	1L pemetrexed in combination with platinum NA	49 NA	6.3 (4.0-8.6) NA	NA	NA	NA	NA	NA	NA	The median progression-free survival is based on the Kaplan–Meier estimator.	Kim et al. 2012
Grade 3-4 adverse events	NA NA	NA NA	NA NA	NA	NA	NA	NA	NA	NA		

Table A3a Results of study Manegold et al. (2000)											
Trial name:	NA										
NCT number:	NA										
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Median overall survival	1L pemetrexed plus cisplatin NA	36 NA	10.9 (6.8-16.9) Na	NA	NA	NA	NA	NA	NA	The median overall survival is based on the Kaplan–Meier estimator.	Manegold et al. 2000.
OS rate at 24 months	NA NA	NA NA	NA NA	NA	NA	NA	NA	NA	NA		
Mean CFB in EORTC-QLQ-C30	NA NA	NA NA	NA NA	NA	NA	NA	NA	NA	NA		

Table A3a Results of study Manegold et al. (2000)											
Objective response rate	1L pemetrexed plus cisplatin	36	ORR: 39% CR: 0 PR: 14/36	NA	NA	NA	NA	NA	NA	Objective response rate was assessed by the standard SWOG response criteria.	Manegold et al. 2000.
	NA	NA	NA								
Median progression-free survival*	1L pemetrexed plus cisplatin	36	TTP*: 6.3 months (2.9-14.1)	NA	NA	NA	NA	NA	NA	* TTP: time to progression. The time to progressive disease was calculated from the time of study entry to the first observation of disease progression.	Manegold et al. 2000.
	NA	NA	NA								
Grade 3-4 adverse events	1L pemetrexed plus cisplatin	36	24%* 121**	NA	NA	NA	NA	NA	NA	* Nonhematologic toxicity. ** Hematologic toxicity. Graded using the NCI common toxicity criteria (CTC) scale.	Manegold et al. 2000.
	NA	NA	NA								

Table A3a Results of study Scagliotti et al. (2008)	
Trial name:	NA
NCT number:	NA

Table A3a Results of study Scagliotti et al. (2008)

Outcome	Study arm	N	Result (CI)	Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
				Difference	95% CI	*P* value	Difference	95% CI	*P* value		Scagliotti et al. 2008
Median overall survival	1L pemetrexed in combination with platinum	839	10.3 Smokers: 10.0 (9.4-11.1) Non-smokers: 15.9 (13.8-20.2)	NA	NA	NA	NA	NA	NA	The median overall survival is based on the Kaplan–Meier estimator. The HR is based on a Cox proportional hazards model.	Scagliotti et al. 2008
	NA	NA	NA								
OS rate at 24 months	1L pemetrexed in combination with platinum	839	18.9%	NA	NA	NA	NA	NA	NA	The survival rates are based on the Kaplan–Meier estimator. The HR is based on a Cox proportional hazards model.	Scagliotti et al. 2008
	NA	NA	NA								
Mean CFB in EORTC-QLQ-C30	NA	NA	NA	NA	NA	NA	NA	NA	NA	.	
	NA	NA	NA								

Table A3a Results of study Scagliotti et al. (2008)											
Objective response rate	1L pemetrexed in combination with platinum	839	30.6%	NA	NA	NA	NA	NA	NA	Objective response rate was assessed according to Response Evaluation Criteria in Solid Tumors and analysed using Fisher's exact test and analysis of variance.	Scagliotti et al. 2008
	NA	NA	NA								
Median progression-free survival	1L pemetrexed in combination with platinum	839	4.8	NA	NA	NA	NA	NA	NA	The progression-free survival are based on the Kaplan–Meier estimator.	Scagliotti et al. 2008
	NA	NA	NA								
Grade 3-4 adverse events	1L pemetrexed in combination with platinum	839	556/839 (66.3%)	NA	NA	NA	NA	NA	NA	Grade 3-4 events was assessed according to the National Cancer Institute Common Toxicity Criteria, version 2.0.	Scagliotti et al. 2008
	NA	NA	NA								

Table A3a Results of study LIBRETTO-001 (clinical question 3+4)												
Trial name:	**LIBRETTO-001**											
NCT number:	NCT03157128											
				Estimated absolute difference in effect			**Estimated relative difference in effect**			**Description of methods used for estimation**	**References**
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Median overall survival	Selpercatinib NA	105 NA	NE (25.7–NE) NA	NA	NA	NA	NA	NA	NA	The median survival is based on the Kaplan–Meier estimator.	EMA's EPAR
OS rate at 24 months	Selpercatinib NA	105 NA	68.0% NA	NA	NA	NA	NA	NA	NA	The OS rate at 24 months is based on the Kaplan–Meier estimator.	EMA's EPAR
Mean CFB in EORTC-QLQ-C30	NA NA	NA NA	NA NA	NA	NA	NA	NA	NA	NA		
Objective response rate	Selpercatinib NA	105 NA	64% (53.9–73.0) NA	NA	NA	NA	NA	NA	NA	The ORR is defined as the proportion of patients with BOR of confirmed CR or PR based on RECIST v1.1.	EMA's EPAR
	Selpercatinib	105	19.3 (13.9–NE)	NA	NA	NA	NA	NA	NA		EMA's EPAR

Table A3a Results of study LIBRETTO-001 (clinical question 3+4)												
Median progression-free survival	NA	NA	NA							The median progression-free survival is based on the Kaplan–Meier estimator.		
Grade 3-4 adverse events	Selpercatinib NA	329 NA	[redacted] NA	NA	NA	NA	NA	NA	NA	*Based on the *RET* fusion-positive NSCLC Safety Analysis Set (SAS) (N = 329)	Data on file	

Table A3a Results of study NAVotrial 01											
Trial name:	NAVotrial 01										
NCT number:	EudraCT: 2009-012001-19										
				Estimated absolute difference in effect			**Estimated relative difference in effect**			**Description of methods used for estimation**	**References**
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Median overall survival	1L oral vinorelbine plus cisplatin NA	100 NA	10.2 months (7.8 to 11.9) NA	NA	NA	NA	NA	NA	NA	The median overall survival is based on the Kaplan–Meier estimator.	Bennouna et al. 2014

Table A3a Results of study NAVotrial 01											
OS rate at 24 months	NA NA	NA NA	NA NA	NA	NA	NA	NA	NA	NA		
Mean CFB in EORTC-QLQ-C30	NA NA	NA NA	NA NA	NA	NA	NA	NA	NA	NA		
Objective response rate	NA NA	NA NA	NA NA	NA	NA	NA	NA	NA	NA		
Median progression-free survival	1L oral vinorelbine plus cisplatin NA	100 NA	4.2 months (3.6 to 4.7) NA	NA	NA	NA	NA	NA	NA	The median progression-free survival is based on the Kaplan–Meier estimator.	Bennouna et al. 2014
Grade 3-4 adverse events	NA NA	NA NA	NA NA	NA	NA	NA	NA	NA	NA		

Table A3a Results of study Ohe et al. (2007)	
Trial name:	NA

Table A3a Results of study Ohe et al. (2007)

NCT number:	NA

				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Median overall survival	1L vinorelbine plus cisplatin	145	11.4	NA	NA	NA	NA	NA	NA	Not reported.	Ohe et al. 2007
	NA	NA	NA								
OS rate at 24 months	1L vinorelbine plus cisplatin	145	21.4	NA	NA	NA	NA	NA	NA	Not reported.	Ohe et al. 2007
	NA	NA	NA								
Mean CFB in EORTC-QLQ-C30	NA	NA	NA	NA	NA	NA	NA	NA	NA		
	NA	NA	NA								
Objective response rate	1L vinorelbine plus cisplatin	145	31.1%	NA	NA	NA	NA	NA	NA	Response was evaluated according to the Response Evaluation Criteria in Solid Tumors.	Ohe et al. 2007
	NA	NA	NA								

Table A3a Results of study Ohe et al. (2007)											
Median progression-free survival	1L vinorelbine plus cisplatin	145	4.1**	NA	NA	NA	NA	NA	NA	**TTP, time to progressive disease. Method not reported.	Ohe et al. 2007
	NA	NA	NA								
Grade 3-4 adverse events	NA	NA	NA	NA	NA	NA	NA	NA	NA	Toxicity grading criteria in National Cancer Institute Common Toxicity Criteria Ver 2.0 were used to evaluate toxicity.	Ohe et al. 2007
	NA	NA	NA								

Table A3a Results of study Shen et al. 2020											
Trial name:	NA										
NCT number:	NA										
				Estimated absolute difference in effect			**Estimated relative difference in effect**			**Description of methods used for estimation**	**References**
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		

Table A3a Results of study Shen et al. 2020											
Median overall survival	Pemetrexed-based chemotherapy	38	26.4 months	NA	NA	NA	NA	NA	NA	Kaplan-Meier estimates and the log-rank test were applied to evaluate median OS.	Shen et al. 2020
	NA	NA	NA								
OS rate at 24 months	NR	NR	NR	NA	NA	NA	NA	NA	NA		
	NA	NA	NA								
Mean CFB in EORTC-QLQ-C30	NR	NR	NR	NA	NA	NA	NA	NA	NA		
	NA	NA	NA								
Objective response rate	Pemetrexed-based chemotherapy	22	50%	NA	NA	NA	NA	NA	NA	RECIST version 1.1 including the complete response (CR), partial response (PR), stable disease, and progressive disease were used as estimator. The ORR was defined as the sum of CR and PR. The disease control rate (DCR) was defined as the sum of the objective response and stabilization rates (CR plus PR plus stable disease).	Shen et al. 2020
	NA	NA	NA								

Table A3a Results of study Shen et al. 2020											
Median progression-free survival*	Pemetrexed-based chemotherapy	10	4.9	NA	NA	NA	NA	NA	NA	*Second-line chemotherapy. Kaplan-Meier estimates and the log-rank test were applied to evaluate median PFS.	Shen et al. 2020
	NA	NA	NA								
Grade 3-4 adverse events	NR	NR	NR	NA	NA	NA	NA	NA	NA		
	NA	NA	NA								

Table A3a Results of study Tan et al. 2020											
Trial name:	NA										
NCT number:	NA										
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		

Table A3a Results of study Tan et al. 2020											
Median overall survival	Platinum-pemetrexed chemotherapy	38	37.7	NA	NA	NA	NA	NA	NA	Kaplan-Meier survival analysis was performed to determine overall survival.	Tan et al. 2020
	NA	NA	NA								
OS rate at 24 months	NR	NR	NR	NA	NA	NA	NA	NA	NA		
	NA	NA	NA								
Mean CFB in EORTC-QLQ-C30	NR	NR	NR	NA	NA	NA	NA	NA	NA		
	NA	NA	NA								
Objective response rate	Platinum-pemetrexed chemotherapy	38	54%	NA	NA	NA	NA	NA	NA	Not reported	Tan et al. 2020
	NA	NA	NA								
Median progression-free survival	Platinum-pemetrexed chemotherapy	38	7.7	NA	NA	NA	NA	NA	NA	Kaplan-Meier survival analysis was performed to determine progression-free survival.	Tan et al. 2020
	NA	NA	NA								

Table A3a Results of study Tan et al. 2020										
Grade 3-4 adverse events	NR NA	NR NA	NR NA	NA	NA	NA	NA	NA	NA	

Table A3a Results of study REVEL											
Trial name:	REVEL										
NCT number:	NCT01168973										
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Median overall survival	Ramucirumab + docetaxel Placebo + docetaxel	[redacted] [redacted]	[redacted] [redacted]	NA	NA	NA	[redacted]	[redacted]	[redacted]	Subgroup analysis of non-squamous population. Stratified logrank comparison of overall survival in the intention-to-treat population. Kaplan-Meier survival analysis was performed to determine overall survival. HR estimated with stratified Cox proportional hazards models	[28]Data of file (REVEL CSR)

Table A3a Results of study REVEL

OS rate at 24 months	Ramucirumab + docetaxel	628	21%	NA	NA	NA	NA	NA	NA		Garon et al. 2014[28]
	Placebo + docetaxel	625	18%								
Mean CFB in EORTC-QLQ-C30	NR	NR	NR	NA	NA	NA	NA	NA	NA		
	NA	NA	NA								
Objective response rate	Ramucirumab + docetaxel	628	23% (144/628)	NA	NA	NA	OR: 1.89	1.41-2.54	0.0001	Cochran-Mantel-Haenszel test.	Garon et al. 2014[28]
	Placebo + docetaxel	625	14% (85/625)								
Median progression-free survival	Ramucirumab + docetaxel	[redacted]	[redacted]	NA	NA	NA	[redacted]	[redacted]	[redacted]	Subgroup analysis of non-squamous population. logrank comparison of overall survival in the intention-to-treat population. Kaplan-Meier survival analysis was performed to determine overall survival. HR estimated with stratified Cox proportional hazards models	Data of file (REVEL CSR)[28]
	Placebo + docetaxel	[redacted]	[redacted]								

Table A3a Results of study REVEL

Grade 3-4 adverse events	Ramucirumab + docetaxel	627	33% (204/627)	NA	NA	NA	NA	NA	NA		Garon et al. 2014[28]
	Placebo + docetaxel	618	71% (444/618)								

8.6 Supportive data for MAIC clinical question 2

Table 61: Comparison of study characteristics between LIBRETTO-001 and EXAM

Trial	LIBRETTO-001 (NCT03157128)	EXAM (NCT00704730)
Study arms	Selpercatinib	Cabozantinib Placebo
Line of therapy	Any line (results not reported for any line; reported separately for first-line[a] and ≥second-line therapy)	Any line
Population	Patients with a variety of advanced solid tumours, including NSCLC, MTC, and PTC with activating RET alterations (gene fusions and/or mutations)	Patients with progressive MTC
Key subgroups of interest for which data are available	First-line[a] MTC ≥Second-line MTC	*RET*-mutation *RET* M918T-mutation
Key inclusion criteria	**Inclusion criteria for Phase I** 1. Locally advanced or metastatic solid tumour who: Have progressed on or are intolerant to standard therapy, or No standard therapy exists, or in the opinion of the Investigator, are not candidates for or would be unlikely to tolerate or derive significant clinical benefit from Standard therapy, or Decline standard therapy 2. Prior MKIs with anti-RET activity are allowed; prior selective RET inhibitor(s) are prohibited. 3. A *RET* gene alteration is not required initially. Once adequate PK exposure is achieved, evidence of *RET* gene alteration in tumour and/or blood required. 4. Measurable or non-measurable disease as determined by RECIST 1.1 or RANO as appropriate to tumour type. 5. At least 18 years of age. For countries and sites where approved, patients as young as 12 years of age may be enrolled. 6. ECOG PS 0, 1, or 2 (age ≥16 years) or Lansky Performance Score ≥40% (age <16 years) with no sudden deterioration 2 weeks prior to the first dose of study treatment. 7. Life expectancy of at least 3 months. 8. Archived tumour tissue sample available. **Inclusion criteria for Phase II:** Inclusion criteria were the same as for Phase I, with the following modifications:	1. Histologically confirmed MTC that is unresectable, locally advanced, or metastatic, and disease that is measurable or non-measurable per mRECIST. 2. ≥18 years old. 3. ECOG PS ≤2 4. Documented PD on CT, MRI, bone scan, or X-ray (determined by the Investigator) per mRECIST at screening compared with a previous image done within 14 months of screening. 5. Recovered to NCI CTCAE v3.0 grade ≤1 from clinically significant AEs due to antineoplastic agents, investigational drugs, or other medications that were administered prior to randomisation. Additional criteria, e.g., for organ function, no other malignancy.

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	1. Cohorts 1 and 3: failed or intolerant to standard of care.	
Key exclusion criteria	1. Phase II cohorts 1 through 4: an additional validated oncogenic driver that could cause resistance to selpercatinib treatment. 2. Prior treatment with a selective *RET* inhibitor(s) (including investigational selective *RET* inhibitor[s]). 3. Investigational agent or anticancer therapy within 5 half-lives or 2 weeks (whichever is shorter) prior to planned start of selpercatinib. In addition, no concurrent investigational anticancer therapy is permitted. 4. Major surgery (excluding placement of vascular access) within 4 weeks prior to planned start of selpercatinib. 5. Radiotherapy with a limited field of radiation for palliation within 1 week of the first dose of study treatment, with the exception of patients receiving radiation to more than 30% of the bone marrow or with a wide field of radiation, which must be completed at least 4 weeks prior to the first dose of study treatment. 6. Any unresolved toxicities from prior therapy greater than NCI CTCAE grade 1 at the time of starting study treatment with the exception of alopecia and grade 2, prior platinum-therapy related neuropathy. 7. Symptomatic primary CNS tumour, metastases, leptomeningeal carcinomatosis, or untreated spinal cord compression. Other criteria e.g., concurrent cardiovascular disease, infection, active second malignancy	1. Prior systemic antitumour therapy (e.g., chemotherapy, biologic modifiers, or antiangiogenic therapy) within 4 weeks of randomisation (6 weeks for nitrosoureas or mitomycin C). 2. Radiation to ≥25% of bone marrow. 3. Treatment with other investigational agents within 4 weeks of randomisation. 4. Treatment with cabozantinib. 5. Brain metastases or spinal cord compression, unless completed radiation therapy ≥4 weeks prior to randomisation and stable without steroid and without anticonvulsant treatment for ≥10 days. Other criteria e.g., renal function, serious intercurrent illness, infection.
Location	65 centres in Australia, Canada, Denmark, Germany, Japan, Hong Kong, Israel, Singapore, France, Italy, Spain, South Korea, Switzerland, Taiwan, and the US (15 countries)	140 active enrolling clinical sites including, but not limited to, the US, Europe, Canada, Latin America, Asia-Pacific, and Australia (specific number of countries not recorded)
Randomisation stratified for *RET* mutation	NA	No
***RET*-mutation subgroup analysis pre-planned**	NA	Yes
Primary outcome measure	ORR	PFS
Other key outcome measures	PFS, OS	ORR, OS
Treatment switching	NA	No
Publications	Wirth et al. (2019)	Elisei et al. (2013)[9] Sherman et al. (2016)[10] Schlumberger et al. (2017)[30]

Table 62: Comparison of baseline characteristics in LIBRETTO-001 and EXAM

Characteristic	LIBRETTO-001 MTC			EXAM (*RET*-mutant subgroup)[c]
	Pre-treated (N=55)	Treatment-naive[b] (N=88)	Any-line (N=212)	Cabozantinib (N=107)
Male (n, %)	36 (65.5)	58 (65.9)	[redacted]	73 (68.2)
Age				
Mean (SD)	[redacted]	[redacted]	[redacted]	NR (NR)
Median (min, max)	57 (17, 84)	58 (15, 82)	[redacted]	55 (20, 86)
Age category				
≤65 years	[redacted]	[redacted]	[redacted]	84 (78.5%)
>65 years	[redacted]	[redacted]	[redacted]	23 (21.5%)
Weight (kg), mean	[redacted]	[redacted]	[redacted]	74
Patients with measurable disease (n, %)	[redacted]	[redacted]	[redacted]	101 (94.4)
Sum of the longest diameter (mm)				
n	[redacted]	[redacted]	[redacted]	101
Mean (SD)				120.5 (80.5)
Median (min, max)				111.7 (10.7, 420.2)
WHO performance status (n, %)	[redacted]	[redacted]	[redacted]	NR
ECOG PS (n, %)	0: 11 (20) 1: 41 (74.5) 2: 3 (5.5)	0: 43 (48.9) 1: 42 (47.7) 2: 3 (3.4)	[redacted]	0: 66 (61.7) 1: 39 (36.4) 2: 2 (1.9)
Calcitonin (pg/mL)				
Mean (SD)	[redacted]	[redacted]	[redacted]	NR
Median (min, max)	[redacted]	[redacted]	[redacted]	NR
Carcino-embryonic antigen (ng/mL)				
Mean (SD)	[redacted]	[redacted]	[redacted]	NR
Median (min, max)	[redacted]	[redacted]	[redacted]	NR
RET-mutation status (n, %)				
Positive	[redacted]	[redacted]	[redacted]	107 (100)
Negative	[redacted]	[redacted]	[redacted]	0 (0)
Unknown	[redacted]	[redacted]	[redacted]	0 (0)
***RET* M918T mutation status**	33 (60%)	49 (55.7%)	[redacted]	81 (75.7%)
MTC disease type (n, %)				
Hereditary	[redacted]	[redacted]	[redacted]	NR
Sporadic/unknown				
Locally advanced				

Patients with prior anticancer therapy (n, %)	[redacted]	[redacted]	[redacted]	NR ITT = 85/219 (38.8%)
Patients with prior systemic therapy for MTC (n, %)	[redacted]	[redacted]	[redacted]	NR ITT = 81/219 (37.0%)
Prior therapies (n, %)				
1 or 2	[redacted]	[redacted]	[redacted]	NR
2 or more	[redacted]	[redacted]	[redacted]	NR
3 or more	[redacted]	[redacted]	[redacted]	NR
Patients with prior thyroidectomy	[redacted]	[redacted]	[redacted]	NR
Prior TKI status (n, %)	55 (100)	7 (8)	[redacted]	23 (21.5)
No. of organs and anatomic locations involved at enrolment (n, %)	[redacted]	[redacted]	[redacted]	NR
Main sites of metastatic disease (n, %)				
Hepatic	[redacted]	[redacted]	[redacted]	NR
Lymph nodes				
Respiratory				
Bone				
Neck				
Smoking				
Never	[redacted]	[redacted]	[redacted]	55 (51.4)
Former	[redacted]	[redacted]	[redacted]	43 (40.2)
Current	[redacted]	[redacted]	[redacted]	9 (8.4)
Publications	Eli Lilly Data on File (16th December 2019 data cut-off)[43] Wirth *et al.* (2020)[4]			Elisei et al. (2013)[9] Table S1 and S2

[a] Baseline characteristics for the RET-mutation or RET M918T-mutation subgroups of the ZETA trial have not been identified. b Cabozantinib and vandetanib-naïve patients, 81.8% of whom had no prior treatment. c Data for the RET-mutation-positive patients in the placebo arm of the EXAM trial are not available. d Safety analysis set, Table 17, interim CSR (28th Nov 2019).24

Abbreviations: ECOG PS: Eastern Cooperative Oncology Group Performance Status; Max: maximum; Min: minimum; MTC: medullary thyroid cancer; NR: not reported; RET: rearranged during transfection; SD: standard deviation; TKI: tyrosine kinase inhibitor.

Table 63: Comparison of prognostic factors between LIBRETTO-001 and EXAM trials used for MAIC adjustment

Prognostic Factor	Details	Source	Comparison of LIBRETTO-001 With Other Trial Populations
Age	Older age associated with worse disease-free survival and OS	Jayakody et al. (2018)[44] Meng et al. (2019)[45]	LIBRETTO-001 population a little older than in EXAM
Stage	More advanced stage associated with worse outcomes	ESMO guideline (Filetti et al., 2019)[46]	All patients had locally advanced or metastatic disease per inclusion criteria

Performance status	Higher performance status associated with worse outcomes	ESMO guideline (Filetti et al., 2019)[46]	A higher proportion of patients in the pre-treated MTC group of the LIBRETTO-001 trial had worse performance status than in the EXAM trial populations
Macroscopically evident extrathyroidal extension	Associated with worse outcomes	ESMO guideline (Filetti et al., 2019)[46] Clark et al. (2005)[47]	Not reported
Tumour size	Larger size associated with worse outcomes	ESMO guideline (Filetti et al., 2019)[46]	Not reported
Post-operative calcitonin doubling time	Calcitonin doubling time > 6 months is associated with 5- and 10-year survival rates of 92% and 37%, respectively; shorter doubling times predict markedly worse survival (25% and 8% at 5 and 10 years, respectively)	ESMO guideline (Filetti et al., 2019)[46]	Not reported
Post-operative carcinoembryonic antigen doubling time	Shorter doubling time associated with worse outcomes	ESMO guideline (Filetti et al., 2019)[46] Clark et al. (2005)[47]	Not reported
***RET*-mutation**	The presence of somatic *RET*-mutation, particularly M918T, has been associated with worse prognosis in some studies	Elisei et al. (2008)[9] Schilling et al. (2001)[48]	All patients have *RET*-mutation in LIBRETTO-001 and the subgroups of EXAM
	Hereditary MTC due to *RET*-mutation associated with better outcomes than sporadic MTC (approximately 50% *RET*-mutation 40% *RAS*-mutation)	Jayakody et al. (2018)[44]	
	RET and particularly *RET* M918T mutation is predictive of increased treatment effect for cabozantinib and vandetanib	Sherman et al. (2016)[10] Schlumberger et al. (2017)[30] Wells et al. (2012)[49] Krajewska et al. (2016)[50]	
***RAS*-mutation**	In sporadic MTC, patients with *RAS* mutations have an intermediate risk between those with ATA level D *RET* mutations, which are associated with the worst prognosis, and cases with other *RET* mutations, that have the most indolent course	Moura et al. (2019)[51]	Reported for EXAM (Supplement Table S1) but not the other trials
Circulating *RET* M918T mutated tumour DNA	The detection of *RET* M918T cfDNA strongly correlated with worse OS and more accurately predicted a worse outcome than calcitonin doubling time	Cote et al. (2017)[52]	Not reported
CA19-9	Predictor of worse outcomes	Alencar et al. (2019)[53]	Not reported
Multiple endocrine neoplasia type 2	Predictor of worse disease-free survival and OS	Jayakody et al. (2018)[44]	Not reported
CDKN2C copy number	Somatic CDKN2C loss is associated with decreased OS, a relationship	Grubbs et al. (2016)[54]	Not reported

	enhanced by concomitant RET*RET* M918T mutation. CDKN2C loss has been associated with *RET*-mediated MTC		
Oestrogen receptor α expression	Predictor of disease-free survival	Ahmed et al. (2015)[55]	Not reported
Vascular invasion	Adverse predictor for disease-free survival	Abraham et al. (2011)[56] Clark et al. (2005)[47]	Not reported
Multiple endocrine neoplasia syndrome type IIB	Predicted decreased disease-specific survival	Clark et al. (2005)[47]	Not reported
Perineural invasion	Predicted decreased PFS	Clark et al. (2005)[47]	Not reported
PD-1, PD-L1	Coexpression of PD-1 and PD-L1 correlated with advanced stage and distant metastases at surgery. However, there was no other clinicopathologic and prognostic relevance	Bi et al. (2019)[57]	Not reported
CD133, CD44	CD133 and CD44 were unfavourable prognostic predictors for OS. CD44 was a significant predictor for DFS	Bi et al. (2016)[57]	Not reported
Number of involved lymph nodes	≥ 11 positive lymph nodes associated with worse OS	Meng et al. (2019)[45]	Not reported

Cost Effectiveness Model Report for Selpercatinib (LOXO-292)

Adapted for Denmark

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ABBREVIATIONS

1L	first line
2L	second line
AC	Appraisal Committee
AE	adverse event
AIC	Akaike information criterion
ALK	anaplastic lymphoma kinase
ALT	alanine aminotransferase
ASAS	additional supportive analysis set
AST	aspartate aminotransferase
AUC	area under the curve
BI	budget impact
BIC	Bayesian information criterion
BMI	body mass index
BSA	body surface area
BSC	best supportive care
CI	confidence interval
CLIA	Clinical Laboratory Improvement Amendments
CPI	checkpoint inhibitor
CR	complete response
CrI	credible interval
CSR	clinical study report
CT	computerised tomography
DMC	Danish Medical Council
DSU	Decision Support Unit

DTC	differentiated thyroid cancer
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EGFR	epidermal growth factor receptor
EHR	electronic health record
ERG	evidence review group
GP	general practitioner
HR	hazard ratio
HTA	health technology assessment
IAS	integrated analysis set
IC	incremental cost
IRC	independent review committee
ITT	intention to treat
IV	intravenous
KM	Kaplan-Meier
LOT	line of treatment
MKI	multikinase inhibitor
MR	median ratio
MST	median survival time
MTC	medullary thyroid cancer
NA	not applicable
NE	not evaluable
NGS	next generation sequencing
NICE	National Institute for Health and Care Excellence
NMA	network meta-analysis
NOS	not otherwise specified
NR	not reported
NSCLC	non–small cell lung cancer
OMERACT	Outcome Measures in Rheumatology Clinical Trials
ORR	overall response rate
OS	overall survival
PAS	primary analysis set
PD-1	programmed cell death protein 1
PD-L1	programmed death-ligand 1
PFS	progression-free survival
PH	proportional hazards
PPS	postprogression survival
PR	partial response
PSA	probabilistic sensitivity analysis
PSW	propensity score weighting

PTC	papillary thyroid cancer
QALY	quality-adjusted life-year
RCT	randomised controlled trial
RECIST	Response Evaluation Criteria in Solid Tumors
RET	Rearranged during Transfection
RPSFTM	rank-preserving structural failure time model
RR	response rate
RTI-HS	RTI Health Solutions
RWE	real world evidence
SAP	statistical analysis plan
SAS1	Supplemental Analysis Set 1
SCE	Summary of Clinical Efficacy
SD	standard deviation
SE	standard error
SLR	systematic literature review
TC	thyroid cancer
TKI	tyrosine kinase inhibitor
TMLE	targeted minimum loss-based estimation
TPS	tumour proportion score
TTD	time-to-treatment discontinuation
UK	United Kingdom
US	United States
VEGF	vascular endothelial growth factor

1 BACKGROUND

Rearranged during Transfection (*RET*) is a receptor tyrosine kinase with critical roles in normal organogenesis and in the maintenance of several adult tissue types (Mulligan 2014). *RET* is an oncogenic driver, and mutation-mediated activation of *RET* or *RET* fusion may contribute to the growth and survival of some human cancers. Patients with *RET* fusion-positive cancers (e.g., non–small cell lung cancer [NSCLC], thyroid cancer [TC], colon cancer) and *RET*-mutation cancers (such as medullary thyroid cancer [MTC]) may benefit from *RET*-targeted therapy. Therefore. There is an urgent need to identify new targeted therapies that potently inhibit *RET* in tumours, while sparing other kinase and non-kinase off-targets that contribute to significant toxicity (Clinical protocol LOXO-RET-17001 2018).

Eli Lilly & Company (Lilly) is developing selpercatinib (LOXO-292), an oral drug for the treatment of patients with cancers that harbour abnormalities in the *RET* kinase. Selpercatinib is currently being evaluated in an ongoing single-arm global study (LOXO-RET-17001, or LIBRETTO-001) initiated in May 2017 (Cabanillas, Wirth et al. 2020). The study is recruiting patients with a variety of advanced solid tumours, including NSCLC, MTC, and other tumours. Given that biologically significant exposures of selpercatinib were achieved by the second level of dose-escalation, trial eligibility was limited to patients with activating *RET* alterations (gene fusions and/or mutations) most likely to clinically benefit from this therapy. The patients were required to have either disease progression or inadequate response or were considered ineligible for, or to have declined standard therapy. The study includes a dose-escalation phase (Phase 1) and a dose-expansion phase (Phase 2).

Selpercatinib has been approved by the United States Food and Drug Administration in May 2020, and conditional marketing authorisation was approved by the European Medicines Agency in February 2021 based on Phase 2 data collected in the LIBRETTO-001 trial. To support health technology assessment (HTA) submission in Denmark, incremental cost (IC) and budget impact (BI) analyses are required for selpercatinib in the *RET* fusion-positive NSCLC, *RET*-mutant MTC, and *RET* fusion-positive TC (predominantly papillary TC [PTC]). This document presents a economic model for selpercatinib, populated with country-specific data for Denmark.

2 OBJECTIVES

The objective of the economic model is to estimate the incremental cost and BI for selpercatinib, with separate analyses in each of the following indications:

- Pretreated *RET* fusion-positive NSCLC
- *RET*-mutant MTC
- Pretreated *RET* fusion-positive TC

The country-specific data in the model are populated for Denmark. The model design and input data were informed by the following research:

- A targeted review of oncology models submitted to National Institute for Health and Care Excellence (NICE) which were based on response or progression data (i.e., no or very immature OS data were available for the intervention being appraised); such models were useful to identify approaches for prediction of survival and to ascertain whether the approaches were accepted by NICE .
- A systematic literature review (SLR) to identify efficacy and safety data for selpercatinib and comparators (Bull and Ahdesmaki 2020).
- An SLR identifying prognostic factors and predictive factors (treatment effect modifiers), to inform indirect treatment comparisons using the single-arm LIBRETTO-001 study, and to identify data to support modelling of survival from response or PFS data.
- Indirect treatment comparisons, survival analyses, and other statistical analyses performed by Lilly, including a network meta-analysis (NMA) in pretreated NSCLC (update of the analysis reported by (Vickers, Winfree et al. 2019)).
- Reviews performed during the development of a health economics and outcomes research plan previously developed by RTI-HS for selpercatinib in NSCLC and MTC.

3 METHODS

3.1 Decision Problem

The purpose of the analysis is to estimate the incremental costs of selpercatinib versus comparators in the following populations:

1. Pretreated *RET* fusion-positive NSCLC
2. *RET*-mutant MTC
3. Pretreated *RET* fusion-positive TC

Details of the population definitions are provided in Section 3.1.3. Details of the patient populations in which selpercatinib has been investigated are provided in section 3.2.

3.1.1 Analysis Perspective

The analysis was performed using restricted societal perspective where direct medical costs and costs associated with patient time and transport were included.

3.1.2 Interventions

The interventions included in the analyses are presented in Table 1 to Table 3.

Table 1. Dosages, Routes of Administration, and Durations of Interventions: Pretreated *RET* Fusion-Positive NSCLC

Drug (Patient Subgroup)	Planned Dosage per Treatment Cycle	Duration of Treatment	Route	Source
Selpercatinib	160 mg, twice daily	In 28-day cycles until progressive disease or unacceptable toxicity, or other reason for treatment discontinuation	Oral	Clinical protocol LOXO-RET-17001 (2018), Version 7.0
Pemetrexed + carboplatin	Pemetrexed: 500 mg/m^2 of body surface area on day 1 Carboplatin: AUC 5 mg/mL/min on day 1	In 21-day cycles Pemetrexed is given until disease progression or unacceptable toxicity Carboplatin is given for up to 6 cycles, disease progression or unacceptable toxicity	IV	EMA SmPC
Docetaxel	75 mg/m^2	On the first day of each 21-day cycle given for up to 6 cycles until disease progression or unacceptable toxicity	IV	EMA SmPC
Pemetrexed	500 mg/m^2	On the first day of each 21-day cycle until disease progression or unacceptable toxicity	IV	EMA SmPC

AE = adverse event; AUC = area under the curve; EMA = European Medicines Agency; IV = intravenous; NSCLC = non–small cell lung cancer; SmPC =Summary of product characteristics

Table 2. Dosages, Routes of Administration, and Durations of Interventions: *RET*-Mutant Medullary Thyroid Cancer

Drug	Planned Dosage per Treatment Cycle	Duration of Treatment	Route	Source
Selpercatinib	160 mg twice daily	In 28-day cycles until progressive disease or unacceptable toxicity, or other reason for treatment discontinuation	Oral	Clinical protocol LOXO-RET-17001 (2018), Version 7.0
Cabozantinib	140 mg once daily	Until disease progression or unacceptable toxicity	Oral	EMA SmPC
Best supportive care	Monitoring and palliative care[a]	NA	NA	NA

BSC = best supportive care; EMA = European Medicines Agency; NA = not applicable; SmPC =Summary of product characteristics

Note: selpercatinib is expected to be indicated in patients aged 12 years and older. Cabozantinib is indicated for adults only.

[a] BSC will be assumed to be monitoring and palliative care, consistent with the Assessment Group model in TA516.

Table 3. Dosages, Routes of Administration, and Durations of Interventions: Pretreated *RET* Fusion-positive Thyroid Cancer

Drug	Planned Dosage per Treatment Cycle	Duration of Treatment	Route	Source
Selpercatinib	160 mg twice daily	In 28-day cycles until progressive disease or unacceptable toxicity, or other reason for treatment discontinuation	Oral	Clinical protocol LOXO-RET-17001 (2018), Version 7.0
Vandetanib	300 mg once daily	Until disease progression or unacceptable toxicity	Oral	EMA SmPC
Sorafenib	400 mg twice daily	In 28-day cycles until progressive disease or unacceptable toxicity, or other reason for treatment discontinuation	Oral	EMA SmPC
Best supportive care	No systemic anticancer therapy	NA	NA	NA

BSC = best supportive care; EMA = European Medicines Agency; NA = not applicable; SmPC =Summary of product characteristics

3.1.3 Patient Population

The populations of interest are as follows:

1. Adults (i.e., at least 18 years of age) requiring second- or subsequent-line systemic treatment for metastatic *RET* fusion-positive NSCLC
2. Patients (at least 12 years of age) requiring systemic treatment for advanced or metastatic *RET*-mutant MTC
3. Adults (i.e., at least 18 years of age) requiring second- or subsequent-line systemic treatment for advanced or metastatic *RET* fusion-positive TC (predominantly PTC)

Because *RET* fusions are very rare in squamous NSCLC (none were identified in studies by (Zhao, Choi et al. 2016) and (Mazieres, Drilon et al. 2019); one patient with squamous NSCLC was enrolled in LIBRETTO-001), analyses for NSCLC focus on nonsquamous patients.

Note that PD-L1 status was not assessed in the LIBRETTO-001 trial. The efficacy of selpercatinib in PD-L1-positive patients is assumed to be the same as in the overall *RET*-fusion-positive population.

3.1.4 Analysis Time Frame

The time frame encompasses the lifetime of the patient cohort from the initiation of treatment (25 years). The models are programmed to allow the user to enter alternative analysis time frames up to a maximum number of years defined by the default lifetime time horizon.

3.1.5 Cost-Year

The economic analysis is conducted using the most recent estimates of resource use and treatment costs available from published sources (2021).

3.1.6 Discounting

The default discount rate for costs was taken as 3.5% for Denmark based on the guideline of finance ministry on the socio-economic discount rate (FINANSMINISTERIET 2021). In the one-way sensitivity analysis, lower and upper bound value of 0% and 6% respectively were used for discount rates.

3.2 Clinical Evidence for Selpercatinib

Selpercatinib is currently being evaluated in an ongoing single-arm global study (LOXO-RET-17001, or LIBRETTO-001) initiated in May 2017. The study is recruiting patients with a variety of advanced solid tumours, including NSCLC, MTC, and TC with activating *RET* alterations (gene fusions and/or mutations). To be eligible for standard therapy, patients are required to have either disease progression, inadequate response, or must be considered ineligible for, or to have declined, standard therapy. The study includes a dose-escalation phase (Phase 1) and a dose-expansion phase (Phase 2). Results of the LIBRETTO-001 trial have been presented at the World Conference on Lung Cancer and the European Society for Medical Oncology (Drilon, Oxnard et al. 2019, Wirth, Sherman et al. 2019) and in peer reviewed journal articles (Drilon, Oxnard et al. 2020, Wirth, Sherman et al. 2020).

A variety of analysis sets were analysed for the populations relevant to the economic evaluation. The efficacy analysis sets (including patients who have potential follow up for more than 6 months) are presented in Table 4.

Table 4. Analysis Sets for Relevant Populations in LIBRETTO-001

Indication	Analysis sets
[redacted]	[redacted]
[redacted]	[redacted]

Indication	Analysis sets
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

ASAS = additional supportive analysis set; CLIA = Clinical Laboratory Improvement Amendments; CSR = clinical study report; IAS = integrated analysis set; MTC = medullary thyroid cancer; NSCLC = non–small cell lung cancer; PAS = primary analysis set; RECIST = Response Evaluation Criteria in Solid Tumors; SAS1 = supplementary analysis set 1; TC = thyroid cancer; TKI = tyrosine kinase inhibitor; US = United States.

Source: Loxo data on file (2019), Loxo data on file (2019). Note: additional analysis sets also were analysed which are not relevant to the decision problem; details are provided in the CSRs.

For the pretreated NSCLC, the IAS data were included in the model rather than the PAS data because the IAS data sets are the larger of the two data sets. There was no specific analysis set for MTC patients receiving any line of treatment (as included in the economic model); the MTC analyses are based on combined data for IAS and SAS1. Independent

review committee (IRC)-assessed PFS was used rather than investigator-assessed PFS because the IRC assessment provides a more rigorous and independent assessment of progression. Data at the December 2019 data cutoff were used in the model.

Table 5 presents patient baseline characteristics, and Table 6 presents response rates. PFS and OS are presented in Figure 1 through Figure 3.

Table 5. Patient Characteristics

Characteristic	Pretreated *RET* fusion-positive NSCLC[a] (n = 184)	Pretreated *RET*-mutant MTC[b] (n = 124)	TKI-naïve *RET*-mutant MTC[c] (n = 88)	Pretreated *RET* fusion-positive TC[d] (n = 19)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]				
[redacted]	[redacted]			[redacted]
[redacted]	[redacted]			[redacted]

Characteristic	Pretreated *RET* fusion-positive NSCLC[a] (n = 184)	Pretreated *RET*-mutant MTC[b] (n = 124)	TKI-naïve *RET*-mutant MTC[c] (n = 88)	Pretreated *RET* fusion-positive TC[d] (n = 19)
[redacted]				

ECOG = Eastern Cooperative Oncology Group; MKI = multikinase inhibitor; MTC = medullary thyroid cancer; NA = not available; NSCLC = non–small cell lung cancer; PD-1 = programmed cell death protein 1; PD-L1 = programmed death-ligand 1; PTC = papillary thyroid cancer; TKI = tyrosine kinase inhibitor.

[a] Integrated analysis set (n = 184).

[b] Integrated analysis set (n = 124).

[c] Supplemental Analysis Set 1 (n = 88) consisting of cabozantinib/vandetanib-naïve patients; 81.8% had no prior treatment.

[d] Additional supportive analysis set for patients with *RET* fusion-positive thyroid cancers (n = 27), of whom 21 had PTC. Patients had a variety of thyroid cancers, including PTC: 21 (77.8%); poorly differentiated thyroid cancer: 3 (11.1%); anaplastic thyroid cancer; 2 (7.4%); Hürthle cell thyroid cancer: 1 (3.7%). A total of 19 patients received prior anticancer treatment.

Sources: Lilly data on file (2020); Dec 2019 data cut;
RET_Fusion_Positive_NSCLC_ThyCA_Demographics_Baseline_Characteristics_DEC2019DataCut_NRB_11MAR2020;
RET_Fusion_Positive_NSCLC_ThyCA_Prior_CATx_DEC2019DataCut_NRB_11MAR2020;
RET_Fusion_Positive_NSCLC_ThyCA_CancerHistory_DEC2019DataCut_NRB_11MAR2020;
RET_Mutant_MTC_Demographics_Baseline_Characteristics_DEC2019DataCut_NRB_11MAR2020;
RET_Mutant_MTC_Prior_CATx_DEC2019DataCut_NRB_11MAR2020; RET_Mutant_MTC_Cancer_History_DEC2019DataCut_NRB_11MAR2020; t2lpritrt_pre_ptc.
NSCLC_PTC_T14.2.4; MTC_PTC_T14.2.4

Table 6. Response Rates for Selpercatinib

Response	Pretreated *RET* fusion-positive NSCLC (n = 184)	Pretreated *RET*-mutant MTC (n = 124)	TKI-naïve *RET*-mutant MTC (n = 88)	Pretreated *RET* fusion-positive TC[a] (n = 19)
[redacted]	[redacted]	[redacted]	73% (62%-82%)	79% (54%-94%)
[redacted]	[redacted]	[redacted]	11%	5%
[redacted]	[redacted]	[redacted]	61%	74%
[redacted]	[redacted]	[redacted]	23%	21%
[redacted]	[redacted]	[redacted]	2%	0%
[redacted]	[redacted]	[redacted]	2%	0%
Source	[redacted]	[redacted]	Wirth, Sherman et al. (2020)	Wirth, Sherman et al. (2020)

CI = confidence interval; MTC = medullary thyroid cancer; NSCLC = non–small cell lung cancer; ORR = overall response rate; PTC = papillary thyroid cancer; SCE = summary of clinical efficacy; TKI = tyrosine kinase inhibitor.

[a] Patients with *RET* fusion-positive TC (N = 27) had a variety of thyroid cancers, including PTC: 21 (77.8%); poorly differentiated thyroid cancer: 3 (11.1%); anaplastic thyroid cancer; 2 (7.4%); Hürthle cell thyroid cancer: 1 (3.7%). 19 patients received prior anticancer treatment. All patients were eligible at the data cutoff date.

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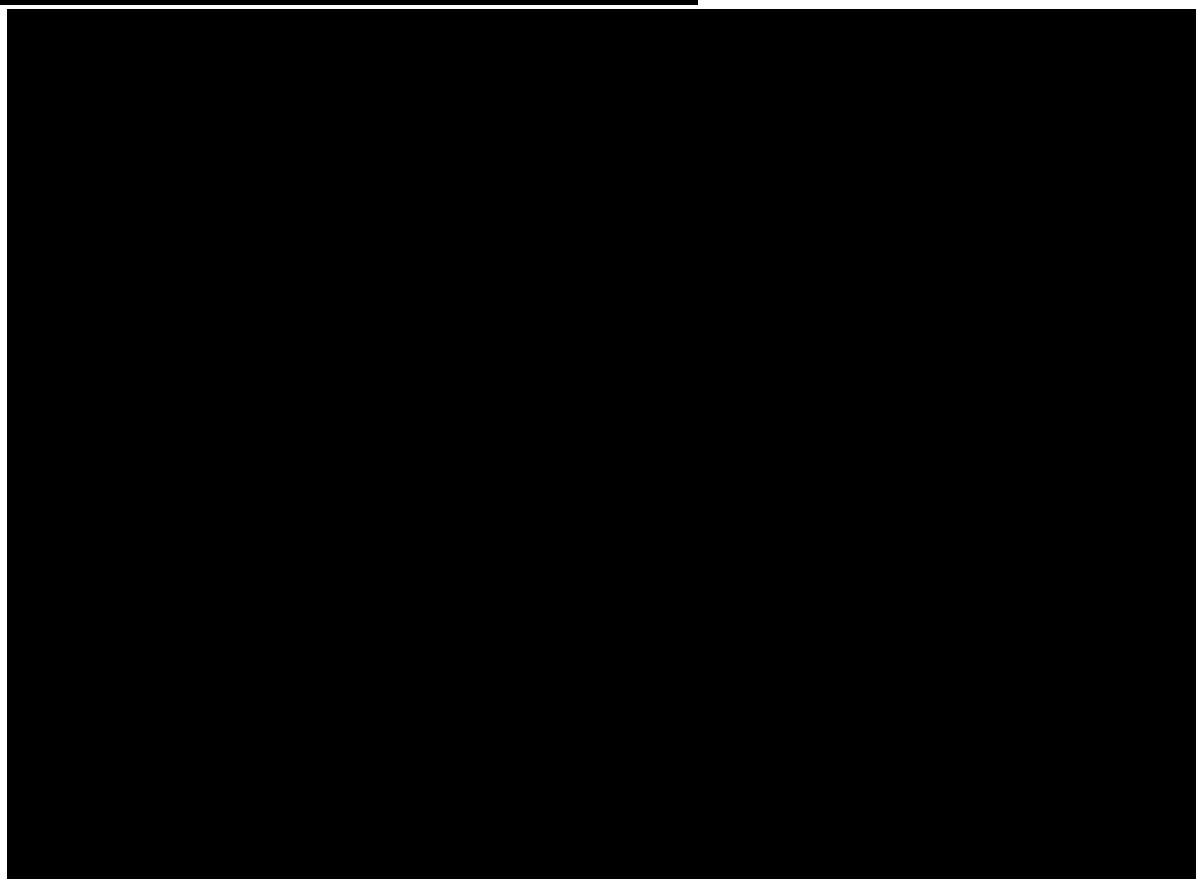


[redacted]

[redacted]

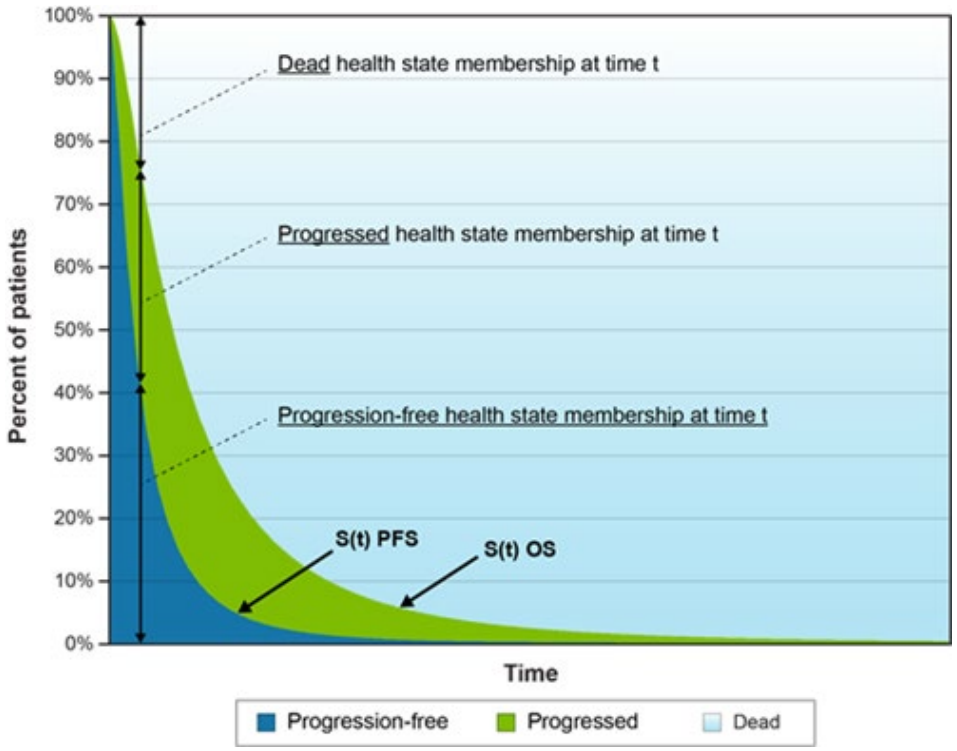
[redacted]

3.3 Model Approach and Structure

Survival partition models are used for all indications, consisting of three health states: progression-free, progressed, and dead (Woods, Sideris et al. 2017). The approach is presented in Figure 4. The health states are defined as follows:

- Progression free: Patients disease is in a stable or responding state and not actively progressing. Patients in this state are assumed to incur costs associated with treatment, administration, medical management of the condition and the management of Grade 3/4 adverse events (AEs).
- Progressed: Patients have met Response Evaluation Criteria in Solid Tumors (RECIST) criteria for disease progression. Patients in this state may continue their allocated therapy for a time (see section 3.5.3.2) and/or have subsequent anticancer therapy and incur costs associated with treatment, administration, medical management of the condition and terminal care.

Figure 4. Model Structure



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

Note: The data in the figure are fictitious and used for illustrative purposes only. S(t) PFS is the survival function describing the probability that a patient remains in the progression-free health state beyond a specific time point (t) from model entry. S(t) OS is the survival function describing the probability that a patient survives in the progression-free or the progressed health states beyond a specific time point (t) from model entry. Membership in the progressed health state is determined by subtracting the progression-free state membership from the dead state membership.

The model structure is consistent with that used in previous economic evaluations in NSCLC, MTC and differentiated TC (e.g., NICE (2017), NICE (2018), NICE (2018), NICE (2019)).

3.4 Indirect Comparisons and Survival Estimation

Comparator trial data were identified by an SLR (clinical SLR 1 (Bull and Ahdesmaki 2020)). The approaches to estimation of PFS and OS for selpercatinib and comparators are described in Sections 3.4.1 to 3.4.3. Section 3.4.4 presents a tabulated summary of the approaches across the five indications.

The terminology used for the range of approaches to survival estimation is defined in Table 7.

Table 7. Survival Estimation Approach Terminology

Approach	Definition
Trial survival extrapolation	Survival functions fitted to trial PFS and OS data. OS is capped in the model using general population mortality rates, adjusted using a mortality ratio for cancer patients.

OS = overall survival; PFS = progression-free survival; PPS = postprogression survival;

Survival functions were fitted to Kaplan-Meier data as recommended by the NICE Decision Support Unit (Latimer 2011). Stratified functions and unstratified function (with treatment as an indicator variable) were fitted. Stratified functions were used rather than separate functions for each treatment arm to allow comparison of model fit statistics (Akaike information criterion and Bayesian information criterion) with those for the unstratified functions. The visual fit to the data was evaluated by comparison of the parametric curve overlaid with the Kaplan-Meier curve. Long-term predicted survival was compared with long-term studies of a similar patient population (where available).

3.4.1 Pretreated *RET* Fusion-positive NSCLC

PFS and OS data are available for selpercatinib from the LIBRETTO-001 trial (IAS n = 184). PFS and OS data for each of the comparator interventions also are available in second- and subsequent-line nonsquamous NSCLC (clinical SLR 1 (Bull and Ahdesmaki 2020)).

No comparator data specific to *RET*-fusion patients were identified by clinical SLR 1. Based on the prevalence of *RET* fusions in NSCLC, up to approximately 2% of patients in the comparator trials would be expected to have *RET* fusion-positive tumours. It is unclear whether *RET* fusion status is a prognostic factor on survival. Several studies have reported numerically superior outcomes for NSCLC patients with *RET* fusion (e.g., (Cong, Yang et al. 2019)). Although differences are not statistically significant, this may be due to the small

numbers of *RET*-fusion patients. Other studies have noted an association between *RET* fusion and known prognostic factors, such as "never smoked" (e.g., (Tsuta, Kohno et al. 2014) and (Lin, Wang et al. 2015)). The pattern of other prognostic factors differs between the LIBRETTO-001 trial and comparator trials (e.g., the proportion "never smoked" is much larger in LIBRETTO-001 than in the comparator trials). Analyses were performed to explore the independent effect of *RET* fusion status on outcomes using data from the Flatiron database and to estimate a control arm for the LIBRETTO-001 study (adjusting for *RET* and other patient characteristics) using patient-level data for selpercatinib and a comparator treatment. The LIBRETTO-001 data and estimated control arm were then included in an NMA. An overview of these analyses is provided in Sections 3.4.1.1 to 3.4.1.3.

3.4.1.1 Estimation of a Control Arm for the LIBRETTO-001 Study

Flatiron Health's longitudinal, demographically and geographically diverse database contains electronic health record (EHR) data from over 265 cancer clinics (~800 sites of care), including more than 2 million active United States patients with cancer. The patient cohort included patients in the Flatiron Health database who underwent comprehensive genomic profiling by Foundation Medicine. The deidentified patient-level clinical data from the EHR include structured data (e.g., laboratory values and prescribed drugs) in addition to unstructured data collected via technology-enabled chart abstraction from physicians' notes and other unstructured documents (e.g., detailed biomarkers). Deidentified patient-level genomic data include specimen features (e.g., tumour mutation burden, pathologic purity), alteration-level details (e.g., genomic position, reference and alternate alleles, mutant allele count, minor allele frequency), and therapeutic recommendations that were reported to the clinician at the time of testing.

Patients were selected from this database who had advanced/metastatic NSCLC and who were *RET* fusion-positive or negative and received systemic therapy. Details of the patient characteristics are presented in Table 8.

Table 8. Patient Characteristics and Treatments Received for Pretreated *RET* Fusion-positive NSCLC in the Flatiron Data Set

Variable	***RET*-positive (n = 23)**	***RET*-negative (n = 2,214)**	***P* value**
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	

Variable	*RET*-positive (n = 23)	*RET*-negative (n = 2,214)	*P* value
[redacted]			

Variable	*RET*-positive (n = 23)	*RET*-negative (n = 2,214)	*P* value
[redacted]		[redacted]	

BMI = body mass index; CPI = checkpoint inhibitor; ECOG = Eastern Cooperative Oncology Group; EGFR = epidermal growth factor receptor; NSCLC = non–small cell lung cancer; OS = overall survival; PD-L1 = programmed death-ligand 1; PFS = progression-free survival; *RET* = REarranged during Transfection; VEGF = vascular endothelial growth factor.

Source: Lilly data on file, 20 April 2020. P420025_table02_SummaryTable_LOT2; p420025_table03_RegimenClass_LOT2.

Patient-level data for a comparator treatment available to support the estimation of a control arm for the LIBRETTO-001 study was taken from the REVEL trial, which investigated ramucirumab + docetaxel versus placebo + docetaxel (Garon, Ciuleanu et al. 2014). The placebo + docetaxel arm of this trial was used to estimate a control arm for LIBRETTO-001. This process was performed as follows.

- The effect of *RET* was explored using Flatiron data as follows:
  a) Variable cluster analysis of the Flatiron data was performed to check for correlated covariates
  b) Investigative analyses of the Flatiron data were performed using random survival forests to provide information on how to fit multivariable survival models for PFS and OS
  c) Survival trees were produced to check whether simple-shaped survival curves exist in the Flatiron data that will be suitable for parametric survival modelling
  d) Cox regression models were fitted to the Flatiron data with multiple imputation of missing data to determine how best to handle nonlinear relationships and determine whether all variables are needed in the model
  e) Multivariable acceleration failure time models were fitted to the Flatiron data with multiple imputation of missing data to obtain an estimate of the time acceleration factor for *RET*-fusion–positive status after taking into account other variables. The model fit statistics are presented in Table 9; loglogistic models were selected. The time acceleration factors are presented in Table 10.
  f) Point estimates of the time acceleration factors were used to adjust the survival times for PFS and OS for the REVEL placebo plus docetaxel arm, and recensoring at the study end time for each patient was performed

Table 9. Multivariable Parametric Survival Models Fit Results: Estimation of Time Acceleration Factors for *RET* Fusion-Positive Status in Pretreated NSCLC Using Flatiron Data

Survival model	PFS R^2	OS R^2
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

NSCLC = non–small cell lung cancer; OS = overall survival; PFS = progression-free survival; *RET* = REarranged during Transfection.

Source: Lilly data on file (19 May 2020): pfs2 console content; os2_console_content.

Table 10. Time Acceleration Factors for *RET* Fusion-Positive Status in Pretreated NSCLC Estimated from the Flatiron Data (Loglogistic Model)

Survival model	PFS	OS
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

NSCLC = non–small cell lung cancer; OS = overall survival; PFS = progression-free survival; *RET* = REarranged during Transfection; SE = standard error.

Source: Lilly data on file (19 May 2020): pfs2 console content; os2_console_content.

- An estimated control arm for LIBRETTO-001 was constructed using the time acceleration adjusted patient-level data from the REVEL trial (placebo plus docetaxel arm) data to account for *RET* and using the following methods to account for other prognostic factors:

  a) Propensity score matching (PSM) was performed using the time-accelerated adjusted values to simultaneously model the matched covariates in the two trial arms

  b) As recommended in the NICE DSU guidelines (Faria, Alava et al. 2015), alternative approaches also were explored, using genetic matching, targeted minimum loss-based estimation (TMLE), propensity score weighting (PSW) using a generalised boosted model, and PSW using a logistic regression

  c) Kaplan-Meier survival plots were produced from the output for the counterfactual data for PFS and OS, for selpercatinib and placebo plus docetaxel

  d) For the simulated control arm, PFS and OS plots were produced, using the predictions from the alternative methods

This process resulted in Kaplan-Meier PFS and OS data for selpercatinib and an estimated control arm (placebo plus docetaxel); the latter was based on the REVEL trial data, adjusted

for the effect of *RET* (using the Flatiron analysis) and other prognostic factors (using PSM and other methods). These data before RET-adjustment are presented in Figure 5, and after multivariate regression propensity score matching (PSM)-adjustment for other prognostic factors in Figure 6.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

(A) [redacted]

(B) OS

[redacted]

[redacted]

Nonparametric log-rank test and Cox regression models were performed on the data from step 2 to obtain significance tests for the treatment effect and estimate log (hazard ratios [HRs]) and standard errors.

The HRs for PFS and OS estimated from steps 2 and 3 using PSM, TMLE, and the alternative methods for step 3 are presented in Table 11. Based on clinical expert opinion, the PSM-adjusted data gave the most clinically plausible prediction for docetaxel and retains a higher effective sample size and follow-up period, and were therefore included in the model as the base case.

Table 11. Estimated Treatment Effects for Selpercatinib Versus Docetaxel in Pretreated NSCLC (Alternative Methods)

	PFS		OS	
Method	Hazard ratio (95% CIs)	*P* value	Hazard ratio (95% CIs)	*P* value
[redacted]				

CI = confidence interval; NSCLC = non–small cell lung cancer; OS = overall survival; PFS = progression-free survival; PSW = propensity score weighting; TMLE = targeted minimum loss-based estimation.

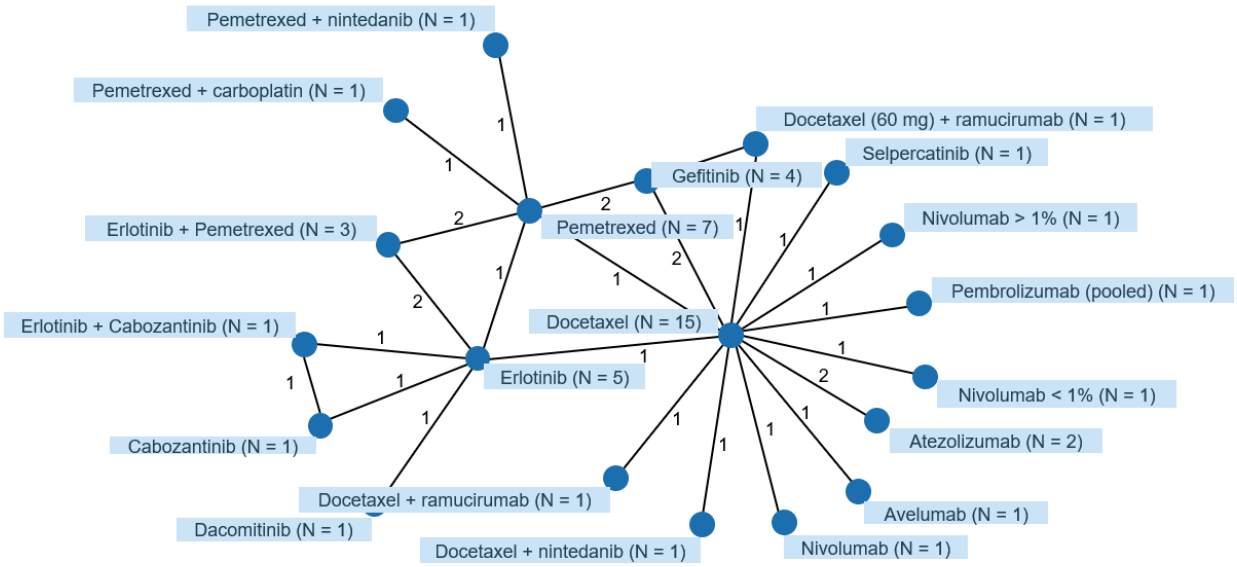
Source: Lilly data on file, 9 August 2020, parameter_estimates.xls.

3.4.1.2 Network Meta-analysis

The data from section 3.4.1.1 (PSM and TMLE methods) were included in an NMA, alongside trials for the comparator interventions identified by clinical SLR 1 (Bull and Ahdesmaki 2020).

The network diagram for the NMA is presented in Figure 7.

Figure 7. Evidence Network for Pretreated NSCLC, OS Endpoint



NSCLC = non–small cell lung cancer.

Note: atezolizumab was not represented in the PFS network. Many of the comparator trials investigated specifically second-line treatment. The network diagram represents the OS endpoint data.

Source: Lilly data on file, 4 September 2020. 2nd Line NMA Results.xls

An update of the NMA performed by Vickers, Winfree et al. (2019) was performed that focussed on data from patients with non-squamous tumours. In the analyses by Vickers and colleagues, HRs were meta-analysed for OS, while for PFS a fractional polynomial NMA was conducted due to nonproportional hazards in the PFS network. In the updated NMA, HRs were analysed for both PFS and OS. The rationale for this difference is as follows:

- For the pretreated NSCLC cohort, the populations of interest are patients with PD-L1 ≥ 1% for both nivolumab and pembrolizumab, and the overall non-squamous population for atezolizumab, nintedanib plus docetaxel, and docetaxel.
- Proportional hazards (PH) tests for the survival data available in these populations indicated no violation of the PH assumption in most cases.

The base case NMA results derived using the PSM-adjusted data are summarised in Table 12.

Table 12. Network Meta-Analysis Results in Pretreated *RET* fusion-positive NSCLC: PSM

Drug (Patient Subgroup)	PFS	OS
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Drug (Patient Subgroup)	PFS	OS
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

CrI = credible interval; HR = hazard ratio; NA = not available; NSCLC = non–small cell lung cancer; OS = overall survival; PD-L1 = programmed death-ligand 1; PFS = progression-free survival; PSM = propensity score matching *RET* = REarranged during Transfection.

The table presents HRs versus docetaxel and 95% CrIs.

[a] The OS results suggest that atezolizumab is similar in efficacy to pembrolizumab (OS HR for atezolizumab vs. pembrolizumab = 1.07 [95% CrIs, 0.80-1.43]), and this has been noted in the literature (ICER 2016, Vickers, Winfree et al. 2019). Therefore, the PFS HR for atezolizumab was assumed to be the same as for pembrolizumab.

Source: Lilly data on file, 13 January 2021; pfs_he_ps.xls; os_he_ps.xls. NMA performed by Lilly (update of analysis by Vickers, Winfree et al. (2019)).

Survival functions for the comparators (with the exception of selpercatinib) were constructed in the economic model by applying these HRs to the docetaxel survival functions described below in Section 3.4.1.3 (PH functions only, as application of HRs to non-PH survival functions is not appropriate).

3.4.1.3 Survival Analysis

Progression-Free Survival and Overall Survival

A range of parametric functions were fitted to the selpercatinib and PSM-estimated control arm PFS and OS data (Figure 5). The fit test results are presented in Table 13. Visual fit to the Kaplan-Meier data is presented in Figure 8 and Figure 9.

Table 13. PFS and OS Model Evaluation Results for the Selpercatinib and Estimated Control (Docetaxel) Arm in Pretreated *RET* fusion-positive NSCLC: PSM

	PFS				OS			
Function	AIC	BIC	Rank (AIC)	Rank (BIC)	AIC	BIC	Rank (AIC)	Rank (BIC)
[redacted]								

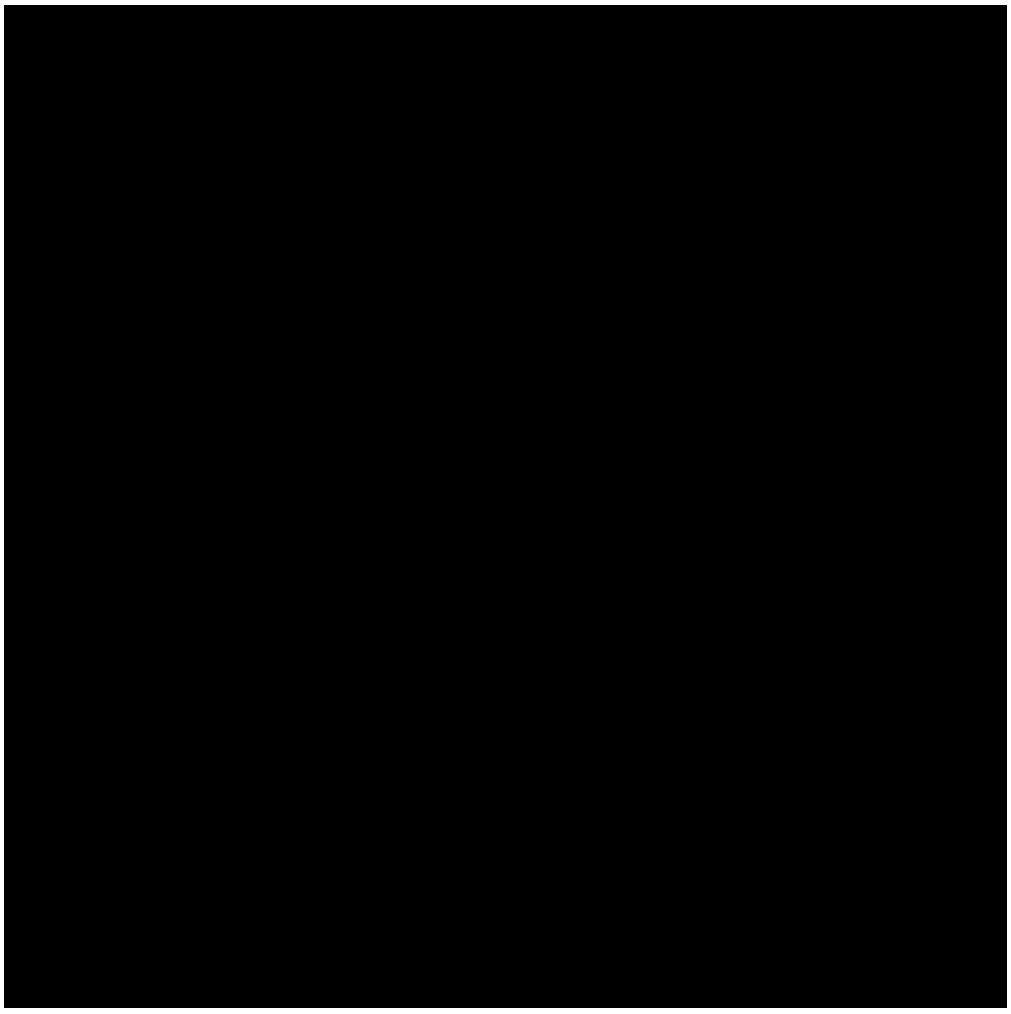
AIC = Akaike information criterion; BIC = Bayesian information criterion; NSCLC = non–small cell lung cancer; OS = overall survival; PFS = progression-free survival; PSM = propensity score matching; *RET* = REarranged during Transfection.

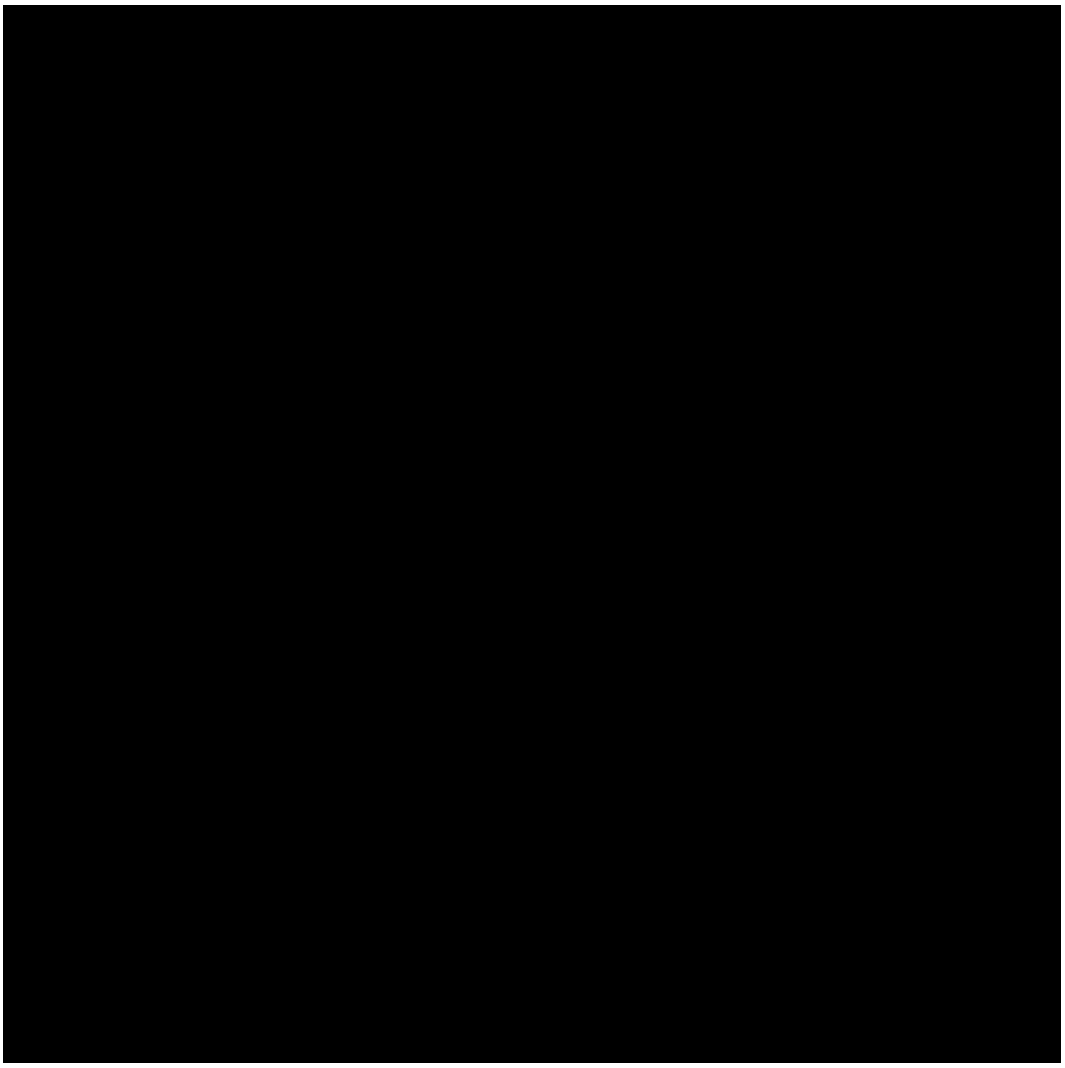
Source: Lilly data on file, 21 October 2020; Pretreated-Propensity score matching-paramsurv-unstratified-FitStatistics; Pretreated-Propensity score matching-paramsurv-stratified-FitStatistics.

[redacted]

([redacted]

[redacted]





Functions were selected for the base case analysis based on the model fit statistics and clinical plausibility of the survival (Table 14). The extrapolations using the PFS parametric survival functions were shared with an expert clinician from UK. Of these, expert clinical feedback suggested that the docetaxel arm projections, using the Gamma function, were realistic but that the selpercatinib PFS projection was overly optimistic. The tail for the Spline/knot=1 and Spline/knot=2 selpercatinib functions were similarly predicting overly optimistic PFS estimates. As a result, the stratified Gompertz function was selected for the base case selpercatinib extrapolation, as well as the reference arm (and therefore carboplatin plus pemetrexed arm, and pemetrexed), as this was considered to provide the most clinically plausible extrapolation for both arms.

For OS, expert clinical feedback suggested that the most plausible extrapolations for OS for both arms was achieved using the stratified Gamma or stratified Weibull survival functions. For the current analysis, the Spline/Knot=1 function was applied as it produced an extrapolation in-between the stratified Weibull and stratified Gamma distributions and was deemed to provide a clinically plausible function for the selpercatinib, reference and other comparators (carboplatin + pemetrexed and pemetrexed).

Table 14. Selected Base Case Survival Functions for Pretreated NSCLC

Endpoint	Selpercatinib	Docetaxel	Other Comparators (Docetaxel)
PFS	Stratified gompertz	Stratified gompertz	Stratified gompertz
OS	Spline/Knot=1	Spline/Knot=1	Spline/Knot=1

NSCLC = non–small cell lung cancer; OS = overall survival; PFS = progression-free survival.

The long-term survival prediction was compared with Flatiron data (Figure 10).

For the other comparators, the HRs for PFS and OS from the NMA (vs. docetaxel; Table 12) were applied to the estimated control (docetaxel) functions (Figure 8).

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Time-to-Treatment Discontinuation

In the base case analysis, the PFS curve was used to govern treatment discontinuation.

3.4.2 RET-Mutant Medullary Thyroid Cancer

PFS and OS data are available for selpercatinib from the LIBRETTO-001 trial (pooled IAS and SAS1 analysis sets [N = 212], Section 3.2). PFS and OS data for cabozantinib, vandetanib and best supportive care (BSC; represented by trial placebo arms) are also available in *RET*-mutant MTC in the EXAM trial (Elisei, Schlumberger et al. 2013, Sherman, Clary et al. 2016, Schlumberger, Elisei et al. 2017) and ZETA trial (Wells, Robinson et al. 2012, Massicotte, Borget et al. 2013), respectively (clinical SLR 1 (Bull and Ahdesmaki 2020)).

3.4.2.1 Estimation of a Control Arm for the LIBRETTO-001 Study

The feasibility of an adjusted indirect comparison was evaluated. From the available data, it appears that the key differences in patient characteristics are the line of therapy, age and performance status. The definition and ascertainment of study endpoints were similar among the trials.

Patient-level data for a control treatment are not available; therefore, an approach similar to that used for NSCLC was not feasible. Propensity score weighting (PSW), specifically method of moments weighting as described in the NICE Decision Support Unit (DSU) guidelines (Phillippo, Ades et al. 2016) for an "unanchored" matched adjusted indirect comparison, was performed. This allows a study arm with patient-level data to be matched to another study arm with only summary data. This method was performed using the LIBRETTO-001 any-line MTC data (pooled IAS and SAS1) and the EXAM trial placebo arm (for PFS and OS) and cabozantinib arm (PFS only), such that the LIBRETTO-001 outcomes were adjusted to reflect the EXAM trial population characteristics for the *RET*-mutation–positive subgroup. The rationale for this approach was as follows:

- The EXAM trial was used rather than the ZETA trial because patient characteristics for the ZETA trial are available only for the intention-to-treat populations and not for the *RET*-mutation–positive subgroup. Furthermore, OS in the ZETA trial is confounded by crossover after disease progression.
- The placebo arm of the EXAM trial (representing BSC) was selected rather than the cabozantinib arm for the OS endpoint for the following reasons: Kaplan-Meier OS data are not available for the *RET*-mutation population in the EXAM trial but are available for the *RET* M918T population. OS for cabozantinib in the *RET* M918T population is not generalisable to the *RET*-mutation population overall because cabozantinib is more effective in the *RET* M918T population than in the overall *RET*-mutation population. Outcomes for the placebo arm in the *RET* M918T population

are more likely to be generalisable to the *RET*-mutation population overall (UK clinical expert, personal communication June 23, 2020).

The results of the PSW are summarised in Table 15 and Figure 11.

Table 15. MTC Patient Characteristics Before and After PSW

Variable	LIBRETTO-001 Unweighted	LIBRETTO-001 Weighted	EXAM
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

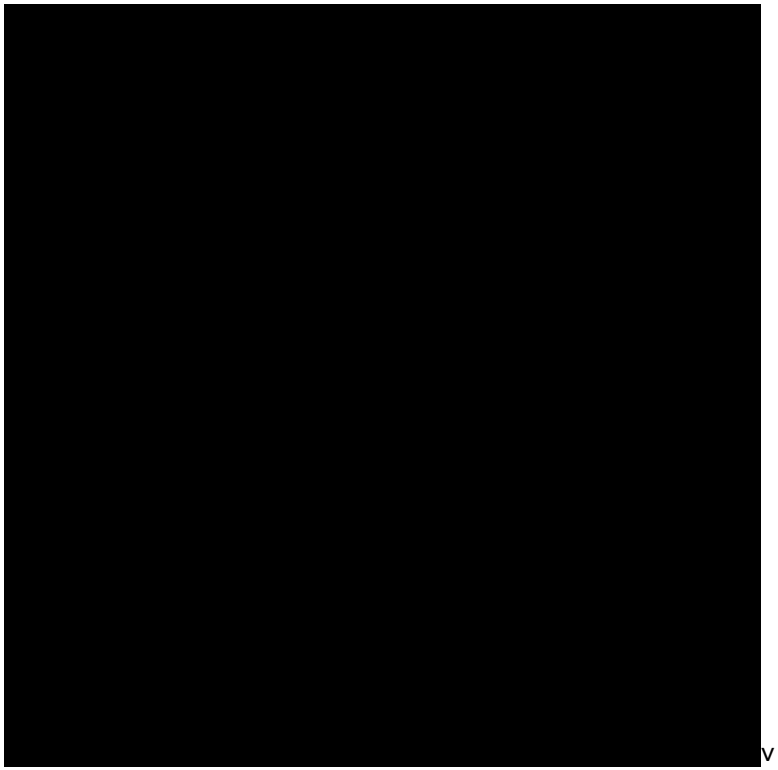
ECOG = Eastern Cooperative Oncology Group; MTC = medullary thyroid cancer; SD = standard deviation; TKI = tyrosine kinase inhibitor.

Source: Lilly data on file (October 20, 2020) balancing-AllComer-check-balancing.csv.

[redacted]

[redacted]

(B) OS



v

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

The treatment effect for was estimated (log-rank test and Cox regression model). The results are summarised in Table 16.

Table 16. Estimated Treatment Effects for Selpercatinib in MTC

	PFS		OS	
Endpoint	**HR (95% CI)**	***P* Value**	**HR (95% CI)**	***P* Value**
[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

BSC = best supportive care; CI = confidence intervals; HR = hazard ratio; MTC = medullary thyroid cancer; OS = overall survival; PFS = progression-free survival; PSW = propensity score weighting; *RET* = REarranged during Transfection.

Source: Lilly data on file (20 October 2020); balancing-AllComer-tte-Summary.

[a] Note that the treatment effect on OS for selpercatinib versus cabozantinib is expected to be underestimated because the data for cabozantinib were for patients with *RET* M918T. Cabozantinib is known to be more effective in the M918T population than in the overall *RET*-mutation population in the economic model.

These results reflect "any line of therapy" (39% with prior anticancer therapy, as in the EXAM study *RET*-mutation subgroup); therefore, the economic evaluation using these data also reflects any line of therapy for MTC. It is recognised as a limitation that the best available data comparing selpercatinib with relevant comparators for these economic analyses reflects any line of therapy.

3.4.2.2 Survival Analysis

Progression-Free Survival and Overall Survival

A range of parametric functions were fitted to the Kaplan-Meier data in Figure 12 and Figure 13 for PFS for unstratified and stratified models respectively. Figure 14 and Figure 15 present the results for OS for unstratified and stratified models, respectively. The fit test results are presented in Table 17.

Table 17. PFS and OS Model Evaluation Results for *RET*-Mutant MTC

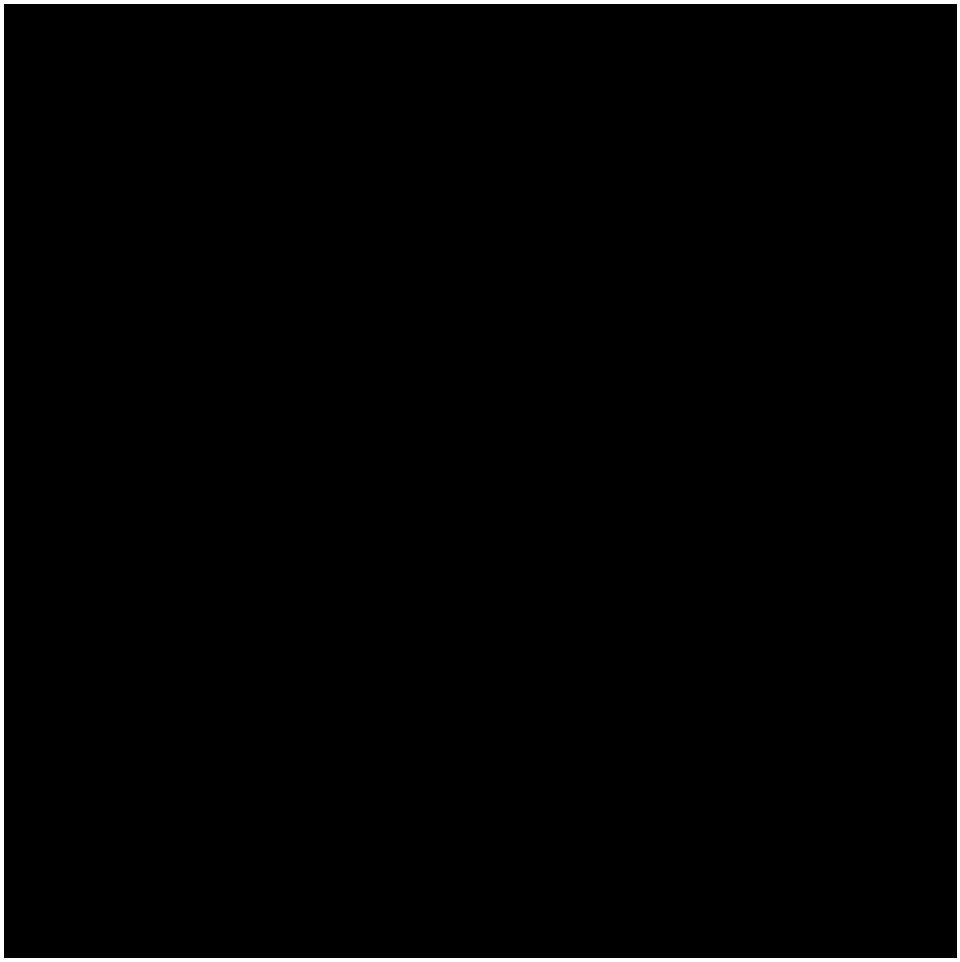
	PFS				OS			
Function	AIC	BIC	Rank (AIC)	Rank (BIC)	AIC	BIC	Rank (AIC)	Rank (BIC)
[redacted]								

AIC = Akaike information criterion; BIC = Bayesian information criterion; NSCLC = non–small cell lung cancer; OS = overall survival; PFS = progression-free survival; *RET* = REarranged during Transfection.

Source: Lilly data on file, 20 October 2020; paramsurv-unstratified-FitStatistics.csv, paramsurv-stratified-FitStatistics.csv.

[redacted]

[redacted]

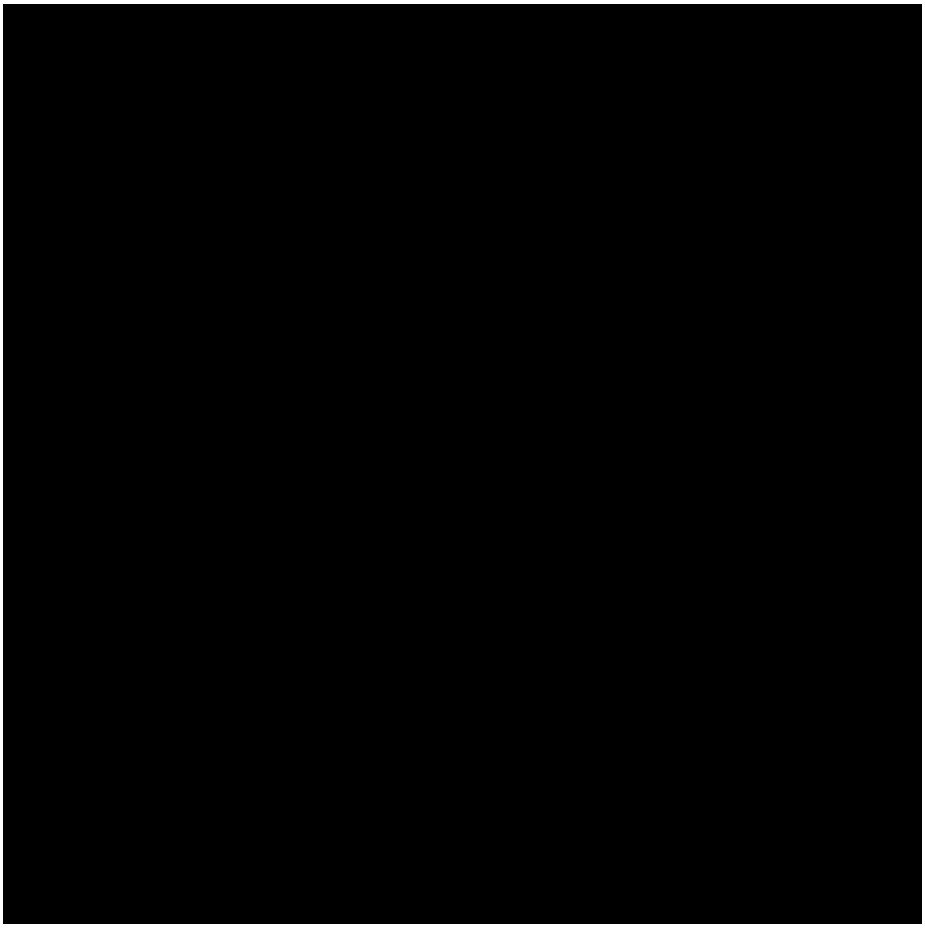


[redacted]

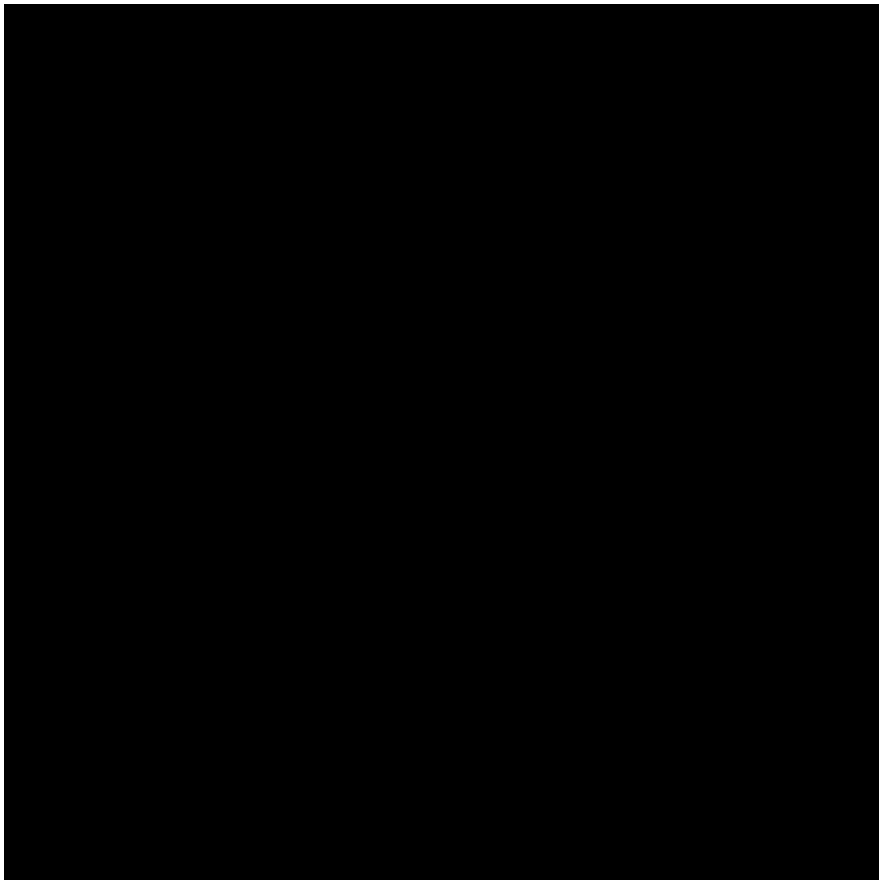
[redacted]

[redacted]

[redacted]



[redacted]



For PFS, statistical fit was similar between survival functions, and thus the choice of curve for the base case analysis was based on visual fit and clinical plausibility (Table 18). Stratified, spline and accelerated failure time functions were considered across all treatment arms. All functions appeared to provide a very similar visual fit to the Kaplan–Meier data for BSC. The loglogistic was selected as it provided a good visual fit to the early KM-data. This is aligned with the base case curve selected by the ERG in NICE TA516.

As for PFS, statistical fit was similar between survival functions, and thus the choice of OS curve for the base case analysis was based on visual fit and clinical plausibility. Stratified Weibull, Gamma and loglogistic extrapolations were explored, and the stratified loglogistic was selected for Selpercatinib as it provided a good visual fit to the early Kaplan–Meier data. Stratified Weibull curve was selected for BSC since it satisfies the PH assumption, which was required because OS for cabozantinib was predicted by applying HR to BSC survival function.

For cabozantinib (OS only), HRs for the *RET*-mutation subgroup from the EXAM trial was applied to the BSC/placebo survival functions (see Section 3.4.2.3, Table 19). Stratified

Weibull was used for the control (BSC) arm to predict the HRs, as choosing same curve as BSC would prevent the OS curves for BSC and cabozantinib crossing each other. More details on the rationale for selection of statistical distributions for OS extrapolation in RET-Mutant MTC can be found in Appendix B.

Table 18. Selected Base Case Survival Functions for *RET*-Mutant MTC

Endpoint	Selpercatinib	Cabozantinib	BSC/placebo
PFS	Loglogistic	Loglogistic	Loglogistic
OS	Stratified Loglogistic	Stratified Weibull[a]	Stratified Weibull

BSC = best supportive care; HR = hazard ratio; MTC = medullary thyroid cancer; NA = not applicable; OS = overall survival; PFS = progression-free survival; *RET* = REarranged during Transfection.

[a] Kaplan-Meier data were not available for the *RET*-mutation subgroup; OS for cabozantinib was estimated by applying the HR in the *RET*-mutation population to the BSC/placebo function.

The long-term survival prediction is presented in Figure 16, alongside the PSW KM data.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Note that no OS function is shown for cabozantinib because no KM data were available for the *RET*-mutation subgroup. OS for cabozantinib was estimated by applying the HR in the *RET*-mutation population to the BSC/placebo function (see section 3.4.2.3).

Time-to-Treatment Discontinuation

In the base case analysis, the PFS curve was used to govern treatment discontinuation.

3.4.2.3 Indirect Comparison

For cabozantinib (OS only), survival functions were constructed in the economic model by applying HRs versus BSC (placebo) for the *RET*-mutation subgroup to the BSC (placebo) functions described in 3.4.2.2 (PH functions only). This is a common method for indirect comparison in oncology and was used for PFS by the Assessment Group in the appraisal of cabozantinib (TA516, NICE 2017). The HRs are presented in Table 19.

Table 19. Treatment Effects for Cabozantinib in *RET*-Mutant Medullary Thyroid Cancer

	PFS	OS	
Intervention	**HR (95% CI)**	**HR (95% CI)**	**Source**
Cabozantinib	0.23 (0.14-0.38)[a]	0.79 (0.54-1.17)[b]	EXAM (Schlumberger, Elisei et al. 2017)

CI = confidence interval; NICE = National Institute for Health and Care Excellence; OS = overall survival; PFS = progression-free survival; *RET* = REarranged during Transfection.

[a] Not used in the economic model because Kaplan-Meier data were available and survival functions were fitted to these data to avoid assuming proportional hazards.

[b] Note that there was imbalance in postprogression therapy. This was not mentioned in TA516. If this imbalance might also be expected in routine practice, this may not be an issue. It is recommended to seek clinical opinion on whether this imbalance might also be expected in routine practice.

3.4.3 Pretreated RET Fusion-positive Thyroid Cancer

PFS and OS data are available for selpercatinib from the LIBRETTO-001 trial for a small group of patients (ASAS pretreated group, n = 19; Figure 3). The OS data are particularly immature. The majority of these patients had PTC.

PFS and OS data for sorafenib versus BSC (represented by trial placebo arms) are available in differentiated TC from the DECISION trial (Brose, Nutting et al. 2014) (clinical SLR 1 (Bull and Ahdesmaki 2020)). The Decision trial included predominantly first-line patients. Overall survival was confounded by crossover; however, adjusted OS estimates based on rank-preserving structural failure time models (RPSFTM) are available (NICE 2018). No randomised controlled trial data have been identified in patients with *RET* fusion-positive TC.

The prognostic significance of *RET*-fusion in TC is unclear (Punda, Bedekovic et al. 2018). Some authors have demonstrated *RET*-mutation to be present at a higher frequency in small, slow progressing and less aggressive tumours, while others have reported that *RET* was associated with histologic and clinical short-term aggressiveness in PTC or high-risk groups (Punda, Bedekovic et al. 2018). A clinical expert also confirmed that the prognostic significance of *RET*-fusion in TC is unknown (personal communication, 23 June 2020).

Patient-level data for a control treatment are not available, and data for only 19 patients in LIBRETTO-001 are available. Therefore, adjustment for *RET* status and/or other baseline characteristics for matching patient populations was not feasible. A naïve indirect comparison was performed.

In Denmark, vandetanib is also recommended in second line for patients with RET Fusion-positive Thyroid Cancer. Therefore, vandetanib was also included in the analysis. The efficacy of vandetanib was assumed to be the same as that for sorafenib.

Progression-Free Survival and Overall Survival

A range of survival functions were fitted to trial data as reported, with OS for BSC estimated using the RPSFTM-estimated placebo Kaplan-Meier data from SELECT trial (equivalent data are not reported for the DECISION trial placebo arm). Briefly, the approach was as follows:

- In TA535 (NICE 2018), the Assessment Group's analyses showed that, within the DECISION trial, the PH assumption did not hold for the majority of survival outcomes (p191 of the Committee Papers). Therefore, stratified survival models were fitted.
- In Denmark, since the comparator of interest is sorafenib, the PFS data for placebo was taken from the intention-to-treat (ITT) population in DECISION trial.
- In TA535, the ERG argued that long-term OS was consistent with an exponential function, and fitted exponential functions starting at 6 months to predict the long-term risk of death (Figure 2B). Therefore, we have taken a similar approach for OS functions, with piecewise exponential functions fitted to data for 0 to 6 months and for 6 months onwards. A range of standard (non-piecewise) functions also were fitted as recommended by the NICE DSU guidelines.

The data used are summarised in Table 20.

Table 20. PFS and OS Data Sources for *RET* Fusion-positive Thyroid Cancer

Intervention	Selpercatinib	Sorafenib and placebo
PFS	Pretreated IRC (Figure 3A)	ITT (Figure 2A in (Brose, Nutting et al. 2014))
OS	Pretreated (Figure 3C)	ITT (Figure 3A in (Brose, Nutting et al. 2014)), sorafenib arm only (RPSFTM-adjusted placebo not available)
TTD	same as PFS	Same as PFS

DTC = differentiated thyroid cancer; IRC = independent review committee; ITT = intention to treat; OS = overall survival; PFS = progression-free survival; *RET* = REarranged during Transfection; RPSFTM = rank-preserving structural failure time model; TKI = tyrosine kinase inhibitor; TTD = time-to-treatment discontinuation.

Note: Data for sorafenib and placebo are for patients with DTC with or without *RET* fusion. For vandetanib, PFS and OS data was assumed to be same as sorafenib

For PFS and OS, the fit test results are presented in Table 22. Visual fit to the Kaplan-Meier data is presented in Figure 17, and Figure 18.

Table 21. PFS and OS Model Evaluation Results for Pretreated *RET* Fusion-positive Thyroid Cancer

	PFS				OS			
Function	AIC	BIC	Rank (AIC)	Rank (BIC)	AIC	BIC	Rank (AIC)	Rank (BIC)
[redacted]								
[redacted]								
[redacted]								
[redacted]								
[redacted]								
[redacted]								

AIC = Akaike information criterion; BIC = Bayesian information criterion; OS = overall survival; PFS = progression-free survival; *RET* = REarranged during Transfection.

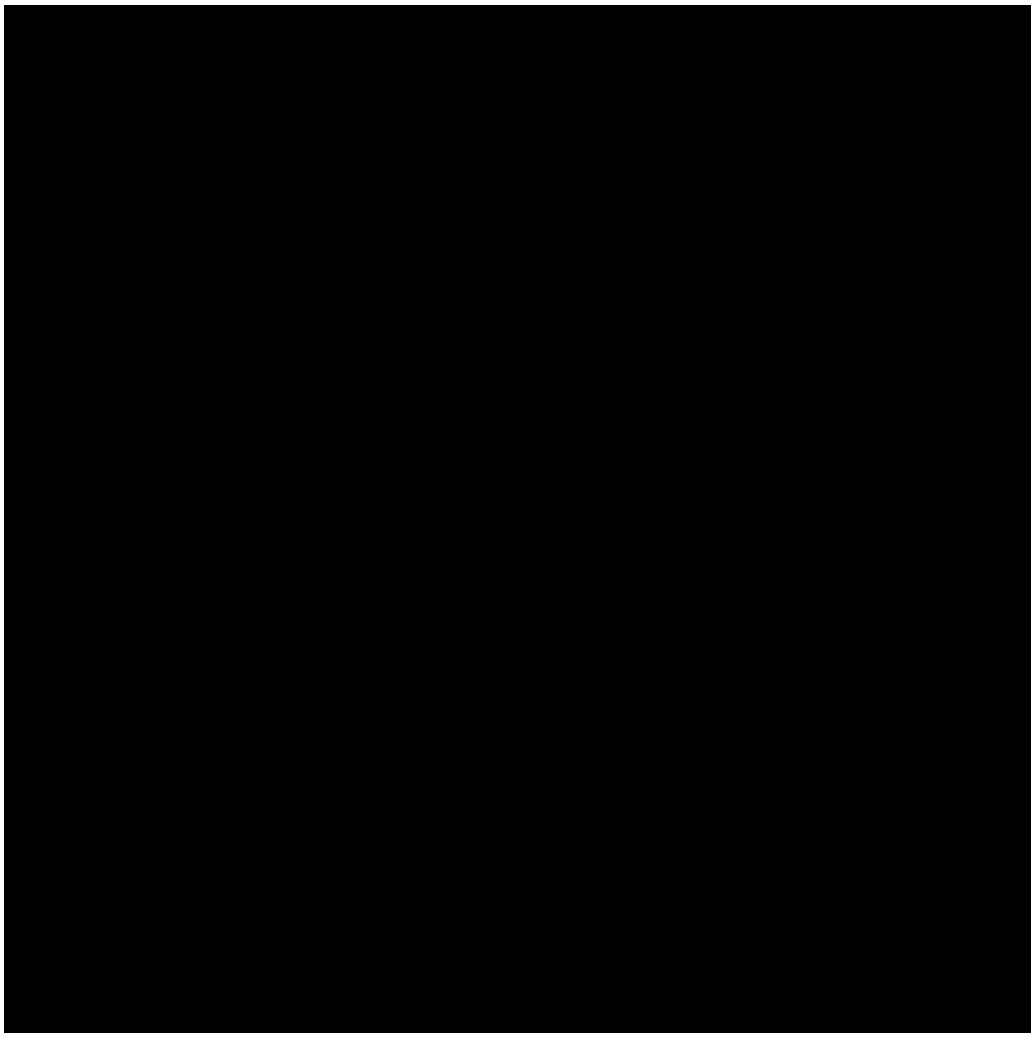
Source: Lilly data on file, 24 August 2020; PFS-paramsurv-FitStatistics.csv; OS-paramsurv-FitStatistics.csv.

[redacted]

[redacted]

[redacted]

[redacted]



[redacted]

Functions were selected for the base case analysis based on the model fit statistics and clinical plausibility of the survival predictions (personal communication [redacted], 24 September 2020), (Table 22).

Table 22. Selected Base Case Survival Functions for Pretreated *RET* Fusion-positive Thyroid Cancer

Endpoint	Selpercatinib	BSC/placebo	Sorafenib
PFS	Stratified Weibull	Stratified Weibull (SELECT, all patients)	Stratified Weibull
OS	Piecewise exponential	Piecewise exponential (SELECT, all patients, RPSFTM-adjusted)	Piecewise exponential

OS = overall survival; PFS = progression-free survival; *RET* = REarranged during Transfection; RPSFTM = rank-preserving structural failure time models.

The long-term survival prediction is presented in Figure 19, alongside the trial KM data.

[redacted]

[redacted]

[redacted]

[redacted]

Time-to-Treatment Discontinuation

In the base case analysis, the PFS curve was used to govern treatment discontinuation.

3.4.4 Summary of Survival Estimation Approaches

Table 23 presents a summary of the survival estimation approaches in each of the indications.

Table 23. Summary of Approaches for the Estimation of Progression-Free Survival and Overall Survival in the Economic Model

	Pretreated *RET* Fusion-positive NSCLC	*RET*-Mutant MTC	Pretreated *RET* Fusion-positive TC
Sample size	[redacted]	[redacted]	[redacted]
PFS available	Yes	Yes	Yes
OS available	Yes	Yes	Very immature
Comparator data	Multiple RCTs identified by clinical SLR 1 (Bull and Ahdesmaki 2020)	RCTs identified by clinical SLR 1 (Bull and Ahdesmaki 2020) Cabozantinib and BSC: EXAM trial Vandetanib: ZETA trial	RCTs identified by clinical SLR 1 (Bull and Ahdesmaki 2020) Trials in differentiated thyroid cancer (lenvatinib = SELECT; sorafenib = DECISION)
Comparator data available for *RET* patients	Trial data not available RWE blended comparator arm (survival analysis of Flatiron data)	Yes	No
RET adjustment	Flatiron analysis	Not required	No data available
Comparative effectiveness approach for the economic model	Estimated control arm based on REVEL docetaxel arm, adjusted for *RET* (time acceleration factor estimated from Flatiron data) and other variables to match the LIBRETTO-001 cohort (PSM). NMA performed (HR for PFS and OS). HRs applied to survival function for estimated control arm	Propensity score weighting to adjust the any-line MTC data in LIBRETTO-001 for the patient characteristics in the EXAM trial	Naïve indirect comparison (insufficient data for other approaches)
Modelling approach for primary analysis	Trial survival extrapolation	Trial survival extrapolation	Trial survival extrapolation

1L = first line; 2L = second line; BSC = best supportive care; ERG = evidence review group; HR = hazard ratio; LOT = line of treatment; MTC = medullary thyroid cancer; NA = not applicable; NMA = network meta-analysis; NSCLC = non–small cell lung cancer; OS = overall survival; PFS = progression-free survival; PPS = postprogression survival; PSW = propensity score weighing; RCT = randomised controlled trial; *RET* = REarranged during Transfection; RWE = real=world evidence; SLR = systematic literature review; TC = thyroid cancer; TKI = tyrosine kinase inhibitor;.

3.5 Data Inputs

3.5.1 Progression-Free Survival and Overall Survival

PFS and OS were estimated as described in Section 3.4. The functions selected for the base-case analysis are summarised in Table 24.

Table 24. Base-Case Survival Functions

Indication	PFS Selpercatinib	PFS Comparators	OS Selpercatinib	OS Comparators
Pretreated *RET* fusion-positive NSCLC	Stratified Gompertz	Stratified Gompertz	Spline Knot 1	Spline Knot 1
RET-mutant MTC	Loglogistic	Loglogistic	Stratified Loglogistic	Stratified Weibull
Pretreated *RET* fusion-positive TC	Stratified Weibull	Stratified Weibull [a]	Piecewise exponential	Piecewise exponential[a]

MTC = medullary thyroid cancer; NSCLC = non–small cell lung cancer; OS = overall survival; PFS = progression-free survival; PPS = postprogression survival; *RET* = REarranged during Transfection; TC = thyroid cancer;

[a] For vandetanib, the survival data was assumed same as that for Sorafenib

3.5.2 Adverse Events

Probabilities of individual AEs for each intervention were based on trial data. In order to focus on AEs, which are likely to have an important impact on costs, grade ≥ 3 AEs with at least 2% difference in frequency between interventions (as reported in the source trials) were included. Costs (if any) associated with each AE were included in the model and were attributed to the first model cycle.

The incidence data for AEs are presented in Table 25 to Table 27. For all interventions other than selpercatinib, these data are not specific to patients with *RET* alterations.

Costs of AEs are presented in Table 28 to Table 30. In the OWSA, the standard error was assumed to be 10% of the mean value.

Table 25. Incidence of Grade ≥ 3 Adverse Events Included in the Pretreated *RET* Fusion-positive NSCLC Model

Adverse Event	Selpercatinib LIB*RET*TO-001 N = 329	Pemetrexed + Platinum GOIRC-02 N = 112	Docetaxel REVEL N = 618	Pemetrexed GOIRC-02 N = 117
Diarrhoea	[redacted]	0.89%	3.07%	1.71%
Hypertension	[redacted]	0.00%	2.10%	0.00%
ECG QT prolonged	[redacted]	0.00%	0.00%	0.00%
Haemorrhage	[redacted]	0.00%	2.27%	0.00%
Fatigue	[redacted]	5.36%	10.52%	6.84%
Dyspnoea	[redacted]	0.00%	8.25%	0.00%
Alanine aminotransferase increased	[redacted]	0.00%	0.00%	0.00%
Aspartate aminotransferase increased	[redacted]	0.00%	0.00%	0.00%
Hyponatraemia	[redacted]	0.00%	0.00%	0.00%
Lymphopenia	[redacted]	0.00%	0.00%	0.00%
Pneumonia	[redacted]	0.00%	0.00%	0.00%
Thrombocytopenia	[redacted]	8.04%	0.65%	5.98%
Neutropenia	[redacted]	11.61%	39.81%	10.26%
Anaemia	[redacted]	5.36%	5.66%	8.55%
Pleural effusion	[redacted]	0.00%	0.00%	0.00%
Febrile neutropenia	[redacted]	2.68%	10.03%	3.42%
Urinary tract infection	[redacted]	0.00%	0.00%	0.00%
Leucopenia (Leukopenia)	[redacted]	8.04%	12.46%	13.68%
Venous thromboembolic	[redacted]	0.00%	2.91%	0.00%

NSCLC = non–small cell lung cancer; *RET* = REarranged during Transfection.

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Table 26. Incidence of Grade ≥ 3 Adverse Events Included in the *RET*-Mutant Medullary Thyroid Cancer Model

Adverse Event	Selpercatinib LIBRETTO-001 N = 299	Cabozantinib EXAM N = 214	BSC/Placebo EXAM N = 109
Diarrhoea	[redacted]	21.50%	1.83%
Hand foot syndrome	[redacted]	12.62%	0.00%
Hypertension	[redacted]	8.88%	0.00%
ECG QT prolonged	[redacted]	0.00%	0.00%
Decreased weight	[redacted]	9.81%	0.00%
Abdominal pain	[redacted]	3.27%	0.92%
Haemorrhage	[redacted]	3.27%	0.92%
Dysphagia	[redacted]	4.21%	0.92%
Fatigue	[redacted]	9.81%	2.75%
Decreased appetite	[redacted]	7.01%	0.92%
Asthenia	[redacted]	6.54%	1.83%
Mucosal inflammation	[redacted]	3.27%	0.00%
Vomiting	[redacted]	2.34%	0.92%
Dyspnoea	[redacted]	2.34%	0.00%
Headache	[redacted]	0.47%	10.09%
Back pain	[redacted]	4.21%	0.92%
Alanine aminotransferase increased	[redacted]	5.14%	1.83%
Aspartate aminotransferase increased	[redacted]	1.87%	0.00%
Hyponatraemia	[redacted]	0.93%	0.00%
Lymphopenia	[redacted]	7.48%	10.09%
Pneumonia	[redacted]	0.00%	0.00%
Hypocalcaemia	[redacted]	10.75%	0.00%
Dehydration	[redacted]	0.00%	0.00%
Weight increased	[redacted]	0.00%	0.00%

RET = REarranged during Transfection.

Sources: LIBRETTO-001 (Loxo data on file 2020); EXAM (Elisei, Schlumberger et al. 2013, Schlumberger, Elisei et al. 2017); ZETA (Wells, Robinson et al. 2012).

Table 27. Incidence of Grade ≥ 3 Adverse Events Included in the Pretreated *RET* Fusion-positive Thyroid Cancer Model

Adverse Event	Selpercatinib LIBRETTO-001 N = 299	Sorafenib DECISION N = 207	Vandetanib ZETA N = 231	BSC/Placebo DECISION[a] N = 209
Diarrhoea	[redacted]	5.80%	10.82%	0.96%
Hand foot syndrome	[redacted]	19.32%	0.00%	0.00%
Hypertension	[redacted]	9.18%	8.66%	1.91%
ECG QT prolonged	[redacted]	0.00%	7.79%	0.00%
Decreased weight	[redacted]	5.80%	0.00%	0.96%
Fatigue	[redacted]	4.83%	5.63%	0.96%
Decreased appetite	[redacted]	1.93%	3.90%	0.00%
Rash	[redacted]	4.83%	3.46%	0.00%
Asthenia	[redacted]	0.00%	2.60%	0.00%
Dyspnoea	[redacted]	4.35%	0.43%	3.35%
Headache	[redacted]	0.00%	0.00%	0.00%
Alanine aminotransferase increased	[redacted]	2.90%	0.00%	0.00%
Aspartate aminotransferase increased	[redacted]	0.97%	0.00%	0.00%
Hyponatraemia	[redacted]	0.00%	0.00%	0.00%
Lymphopenia	[redacted]	0.00%	0.00%	0.00%
Pneumonia	[redacted]	0.00%	0.00%	0.00%
Hypocalcaemia	[redacted]	8.70%	0.00%	1.44%
Dehydration	[redacted]	0.00%	0.00%	0.00%

AE = adverse event; BSC = best supportive care; *RET* = REarranged during Transfection.

Sources: LIBRETTO-001 (Loxo data on file 2020); ZETA trial(NICE 2018); DECISION (NICE 2018).

Table 28. Costs for Grade ≥ 3 Adverse Events: Pretreated NSCLC

Adverse Event	Cost per Episode (DKK)	Source
Diarrhoea	5,130.00	DRG 2021, 06MA11: Malabsorption og betændelse i spiserør, mave og tarm, pat. mindst 18 år, u. kompl. bidiag., Diagnosis: DK529B: Ikke-infektiøs diaré UNS
Hypertension	1,153.00	DRG 2021, 05MA98: MDC05 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DI109: Essentiel hypertension
ECG QT prolonged	15,488.00	DRG 2021, 05MA07: Hjertearytmi og synkope, Diagnosis: DI458: Anden ledningsforstyrrelse i hjertet
Haemorrhage	1,837.00	DRG 2021, 05MA08: Andre hjertesygdomme, Diagnosis: DR589: Blødning UNS
Fatigue	3,987.00	DRG 2021, 23MA03: Symptomer og fund, u. kompl. bidiag., Diagnosis: DR539A: Udmattelse
Dyspnoea	1,732.00	DRG 2021, 04MA98: MDC04 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DR060: Dyspnø
ALT increased	1,626.00	DRG 2021, 23MA98: MDC23 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DR740: Transaminase- og laktatdehydrogenaseforhøjelse
AST increased	1,626.00	DRG 2021, 23MA98: MDC23 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DR740: Transaminase- og laktatdehydrogenaseforhøjelse
Hyponatraemia	1,518.00	DRG 2021, 10MA98: MDC10 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DE871A: Hyponatriæmi
Lymphopenia	3,114.00	DRG 2021, 16MA98: MDC16 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DD728: Anden forstyrrelse i hvide blodlegemer
Pneumonia	25,695.00	DRG 2021, 04MA14: Lungebetændelse og pleurit, pat. 18-59 år, Diagnosis: DJ189: Pneumoni UNS
Thrombocytopenia	3,114.00	DRG 2021, 16MA98: MDC16 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DD696: Trombocytopeni UNS
Neutropenia	3,114.00	DRG 2021, 16MA98: MDC16 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DD709: Neutropeni UNS
Anaemia	3,114.00	DRG 2021, 16MA98: MDC16 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DD592: Hæmolytisk ikke-autoimmun anæmi forårsaget af lægemiddel
Pleural effusion	34,259.00	DRG 2021, 04MA09: Pleuritis exsudativa, Diagnosis: DJ919: Pleuraeffusion ved sygdom klassificeret andetsteds
Febrile neutropenia	3,114.00	DKK 3114 Kilde: DRG 2021, 16MA98: MDC16 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DD709A: Neutropeni og agranulocytose forårsaget af lægemiddel
Urinary tract infection	24,431.00	DRG 2021, 11MA07: Infektioner i nyrer og urinvej, pat. mindst 16 år, Diagnosis: DN390: Urinvejsinfektion uden angivelse af lokalisation
Leucopenia (Leukopenia)	3,114.00	DRG 2021, 16MA98: MDC16 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DD728H: Leukopeni
Venous thromboembolic	20,946.00	DRG 2021, 05MA12: Perifer karsygdom, Diagnosis: DI829: Emboli eller trombose i vene UNS

ALT = alanine aminotransferase; AST = aspartate aminotransferase; ECG = electrocardiogram; GP = general practitioner; NICE = National Institute for Health and Care Excellence; NSCLC = non–small cell lung cancer.

Table 29. Costs for Grade ≥ 3 Adverse Events: Medullary Thyroid Cancer

Adverse Event	Cost per Episode (DKK)	Source
Diarrhoea	5,130.00	DRG 2021, 06MA11: Malabsorption og betændelse i spiserør, mave og tarm, pat. mindst 18 år, u. kompl. bidiag., Diagnosis: DK529B: Ikke-infektiøs diaré UNS
Hand foot syndrome	1,735.00	DRG 2021, 09MA98: MDC09 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DL271: Lokaliseret dermatitis forårsaget af indtaget lægemiddel
Hypertension	1,153.00	DRG 2021, 05MA98: MDC05 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DI109: Essentiel hypertension
ECG QT prolonged	15,488.00	DRG 2021, 05MA07: Hjertearytmi og synkope, Diagnosis: DI458: Anden ledningsforstyrrelse i hjertet
Decreased weight	1,518.00	DRG 2021, 10MA98: MDC10 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DR634: Abnormt vægttab
Abdominal pain	5,130.00	DRG 2021, 06MA11: Malabsorption og betændelse i spiserør, mave og tarm, pat. mindst 18 år, u. kompl. bidiag., Diagnosis: DR100: Akutte mavesmerter
Haemorrhage	1,837.00	DRG 2021, 05MA08: Andre hjertesygdomme, Diagnosis: DR589: Blødning UNS
Dysphagia	5,130.00	DRG 2021, 06MA11: Malabsorption og betændelse i spiserør, mave og tarm, pat. mindst 18 år, u. kompl. bidiag., Diagnosis: DR139: Synkebesvær UNS
Fatigue	3,987.00	DRG 2021, 23MA03: Symptomer og fund, u. kompl. bidiag., Diagnosis: DR539A: Udmattelse
Decreased appetite	1,518.00	DRG 2021, 10MA98: MDC10 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DR630: Appetitløshed
Asthenia	3,987.00	DRG 2021, 09MA98: MDC09 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DL271: Lokaliseret dermatitis forårsaget af indtaget lægemiddel
Mucosal inflammation	5,130.00	DRG 2021, 23MA03: Symptomer og fund, u. kompl. bidiag., Diagnosis: DR539A: Udmattelse
Vomiting	5,130.00	DRG 2021, 06MA11: Malabsorption og betændelse i spiserør, mave og tarm, pat. mindst 18 år, u. kompl. bidiag., Diagnosis: DK529: Anden ikke-infektiøs gastroenteritis eller colitis UNS
Dyspnoea	1,732.00	DRG 2021, 06MA11: Malabsorption og betændelse i spiserør, mave og tarm, pat. mindst 18 år, u. kompl. bidiag., Diagnosis: DR119C: Opkastning
Headache	3,987.00	DRG 2021, 04MA98: MDC04 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DR060: Dyspnø
Back pain	1,617.00	DRG 2021, 23MA03: Symptomer og fund, u. kompl. bidiag., Diagnosis: DR519: Hovedpine UNS
Syncope[a]	864.83	DRG 2021, 08MA98: MDC08 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DM549: Rygsmerter UNS
ALT increased	1,626.00	DRG 2021, 05ma07: Hjertearytmi og synkope
AST increased	1,626.00	DRG 2021, 23MA98: MDC23 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DR740: Transaminase- og laktatdehydrogenaseforhøjelse
Hyponatraemia	1,518.00	DRG 2021, 23MA98: MDC23 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DR740: Transaminase- og laktatdehydrogenaseforhøjelse
Lymphopenia	3,114.00	DRG 2021, 10MA98: MDC10 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DE871A: Hyponatriæmi

Adverse Event	Cost per Episode (DKK)	Source
Pneumonia	25,695.00	DRG 2021, 16MA98: MDC16 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DD728: Anden forstyrrelse i hvide blodlegemer
Hypocalcaemia	1,518.00	DRG 2021, 04MA14: Lungebetændelse og pleurit, pat. 18-59 år, Diagnosis: DJ189: Pneumoni UNS
Dehydration	1,518.00	DRG 2021, 10MA98: MDC10 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DE835D: Hypokalcæmi UNS
Weight increased	1,518.00	DRG 2021, 10MA98: MDC10 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DE869A: Dehydrering

AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; ECG = electrocardiogram; NICE = National Institute for Health and Care Excellence.

Table 30. Costs for Grade ≥ 3 Adverse Events: Pretreated Thyroid Cancer

Adverse Event	Cost per Episode (DKK)	Source
Diarrhoea	5130.00	DRG 2021, 06MA11: Malabsorption og betændelse i spiserør, mave og tarm, pat. mindst 18 år, u. kompl. bidiag., Diagnosis: DK529B: Ikke-infektiøs diaré UNS
Hand foot syndrome	1735.00	DRG 2021, 09MA98: MDC09 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DL271: Lokaliseret dermatitis forårsaget af indtaget lægemiddel
Hypertension	1153.00	DRG 2021, 05MA98: MDC05 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DI109: Essentiel hypertension
ECG QT prolonged	15488.00	DRG 2021, 05MA07: Hjertearytmi og synkope, Diagnosis: DI458: Anden ledningsforstyrrelse i hjertet
Decreased weight	1518.00	DRG 2021, 10MA98: MDC10 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DR634: Abnormt vægttab
Fatigue	3987.00	DRG 2021, 23MA03: Symptomer og fund, u. kompl. bidiag., Diagnosis: DR539A: Udmattelse
Decreased appetite	1518.00	DRG 2021, 10MA98: MDC10 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DR630: Appetitløshed
Rash	1735.00	DRG 2021, 09MA98: MDC09 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DL271: Lokaliseret dermatitis forårsaget af indtaget lægemiddel
Asthenia	3987.00	DRG 2021, 23MA03: Symptomer og fund, u. kompl. bidiag., Diagnosis: DR539A: Udmattelse
Dyspnoea	1732.00	DRG 2021, 04MA98: MDC04 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DR060: Dyspnø
Headache	3987.00	DRG 2021, 23MA03: Symptomer og fund, u. kompl. bidiag., Diagnosis: DR519: Hovedpine UNS
ALT increased	1626.00	DRG 2021, 23MA98: MDC23 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DR740: Transaminase- og laktatdehydrogenaseforhøjelse
AST increased	1626.00	DRG 2021, 23MA98: MDC23 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DR740: Transaminase- og laktatdehydrogenaseforhøjelse
Hyponatraemia	1518.00	DRG 2021, 10MA98: MDC10 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DE871A: Hyponatriæmi
Lymphopenia	3114.00	DRG 2021, 16MA98: MDC16 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DD728: Anden forstyrrelse i hvide blodlegemer

Adverse Event	Cost per Episode (DKK)	Source
Pneumonia	25695.00	DRG 2021, 04MA14: Lungebetændelse og pleurit, pat. 18-59 år, Diagnosis: DJ189: Pneumoni UNS
Hypocalcaemia	1518.00	DRG 2021, 10MA98: MDC10 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DE835D: Hypokalcæmi UNS
Dehydration	1518.00	DRG 2021, 10MA98: MDC10 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DE869A: Dehydrering

AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; ECG = electrocardiogram; NICE = National Institute for Health and Care Excellence.

3.5.3 Resource Use and Costs

Resource use and/or cost estimates for the models were derived from the DRG 2021 tariffs, supplemented by clinical opinion. Drug prices were taken from Danish medicines agency website (Danish Medicines Agency).

3.5.3.1 Diagnostics

An option is included in the model to include the cost of screening to identify patients with *RET*-altered tumours in the selpercatinib arm. Diagnostic costs were not included in the base case analysis results. The impact of including diagnostic costs was explored in scenario analysis.

Estimates of the screen-positive rate in each indication and the cost of the test are presented in Table 31.

Table 31. Diagnostic Test Parameters

Parameter	*RET* Fusion-positive NSCLC	*RET*-Mutant MTC	*RET* Fusion-positive TC
Screen-positive rate	1.5% (Sireci, Morosini et al. 2019)	61.2%[a] Derived from Taccaliti, Silvetti et al. (2011); Wells, Asa et al. (2015)	6.8% (Liu, Gao et al. 2014)
RET test cost		DKK 5,000 (Denmark KOL opinion)	

MTC = medullary thyroid cancer; NSCLC = non–small cell lung cancer; *RET* = REarranged during Transfection; TC = thyroid cancer.

[a] Wells et al. reported that 50% of sporadic MTCs and 95% of hereditary MTCs have *RET* mutations. Taccaliti, Silvetti et al. (2011) reported that 75% of MTC cases are sporadic and 25% are hereditary. 0.5 × 0.75 + 0.95 × 0.25 = 0.612.

3.5.3.2 Drug Acquisition

The price for selpercatinib was provided by Lilly. For the comparators, Denmark list prices were used. Prices for each vial/package size were applied and are presented in Table 33. The body weight and body surface area (BSA) estimates that are used for adjusted-dose interventions are presented in Table 32.

Table 32. Body Weight and Body Surface Area

Parameter	Pre-treated *RET* Fusion-positive NSCLC	*RET*-Mutant MTC and *RET* Fusion-positive TC
Mean weight (kg)	[redacted]	Not applicable
Body surface area (m^2)	[redacted]	Not applicable

BSA = body surface area; MTC = medullary thyroid cancer; NICE = National Institute for Health and Care Excellence; NSCLC = non–small cell lung cancer; *RET* = REarranged during Transfection; SCE = summary of clinical efficacy; TC = thyroid cancer.

Source: Weight, Based on the clinical DMC guideline for metastatic renal cancer https://medicinraadet.dk/media/51yhvker/baggrund-for-medicinr%C3%A5dets-behandlingsvejledning-vedr%C3%B8rende-l%C3%A6gemidler-til-metastatisk-nyrekr%C3%A6ft-vers-1-2_adlegacy.pdf ; BSA, Previous RADS (the predecessor for DMC) assessments of chemotherapy regimens in NSCLC https://rads.dk/media/1873/nsclc-baggrundsnotat-inkl-bilag-1-april-192379_1.pdf

Table 33. Drug Dosage and Cost

Intervention	Dosage	Vial/Package Size	Price (DKK)
Selpercatinib	160 mg twice daily, 4-week cycles	80mg x 60	[redacted]
		40mg x 60	[redacted]
Docetaxel	75 mg/m^2, Day 1 of 3-week cycle, limited to 6 cycles	160 mg	309.00
		80 mg	151.02
Pemetrexed	500 mg/m^2, once every 3 weeks	500 mg	8,809.43
		100 mg	2,114.26
Carboplatin	AUC 5 mg/mL, once every 3 weeks, limited to 6 cycles	450 mg	203.00
		150 mg	84.00
Cabozantinib	140mg once daily	20 mg x 84	40,251.25
Vandetanib	300 mg once daily	300 mg x 30	32,355.61
		100 mg x 30	16,031.62
Sorafenib	400mg once daily	200 mg x 112	21,156.59

In the base case, treatment discontinuation for selpercatinib and comparators was dictated by the PFS curve. The proportion of selpercatinib administrations at each dose level was based on the recorded doses received in the LIBRETTO-001 trial, adjusted to reflect the available tablet sizes (40mg and 80mg). Separate data were applied for the initial dose distribution (applied for the first 4 weeks), and thereafter.

Where dose intensity data for comparators were not available, the relative dose intensity was based on that for selpercatinib as observed in the LIBRETTO-001 trial (Table 34).

Table 34. Relative Dose Intensity

Intervention	*RET* fusion-positive NSCLC	*RET*-mutant MTC	*RET* fusion-positive TC	Source
Selpercatinib[a] (used for comparators where no data are available)	[redacted]	[redacted]	[redacted]	Selpercatinib SCE (Loxo data on file 2020, Loxo data on file 2020)
Vandetanib	NA	NA	94.9%	Derived from NICE TA516
Sorafenib	NA	NA	81.40%	NICE TA535
Other	[redacted]	[redacted]	[redacted]	Assumed same as selpercatinib

MTC = medullary thyroid cancer; NA = not available; NICE = National Institute for Health and Care Excellence; NSCLC = non–small cell lung cancer; *RET* = REarranged during Transfection; SCE = summary of clinical efficacy; TC = thyroid cancer.

[a] Note that these data are not used for selpercatinib in the model. The proportion of patients receiving each selpercatinib dose was based on the recorded doses received in the LIBRETTO-001 trial, adjusted to reflect the available tablet sizes (40mg and 80mg) as described in the text.

In the base case, the cost associated with drug wastage was included. For IV drugs, if wastage is included in the model it is assumed that any unused drug in opened vials is discarded. The weight and BSA distribution of the population is modelled and the lowest cost vial combination is determined according to each weight or BSA category. The cost of each whole vial combination is calculated and the weighted average cost across the population is calculated using the proportion of patients in each weight or BSA category. For oral drugs, the drug wastage scenario assumes the minimum cost of whole tablet combinations to provide the required dose. It is assumed that oral drugs are dispensed as 4-week prescriptions (i.e., patients discontinuing during the 4 weeks after a prescription will be assigned the full cost of that prescription).

3.5.3.3 Drug Administration and Monitoring

Administration costs were based on DRG 2021 tariffs. For selpercatinib and other oral drugs, a cost of DKK 1,732 is assumed to occur only once throughout the model time horizon. For MTC and PTC this cost was DKK 1,543.

Patient time cost and transport costs were also assumed to incur for every time the patient goes for treatment administration. Cost of DKK 100 was taken for every visit and DKK 179 for one hour of patient time.

During treatment, patients were assumed to have one oncologist visit every 3 months (DKK 1,732 for NSCLC and DKK 1,543 for TC and MTC). In addition to this, cost for 7 ECGs were added to Selpercatinib monitoring costs for the first 6 months, in line with the updated label. Detailed per cycle admin cost for different drugs is provided in Table A-1 to Table A-3.

3.5.3.4 Adverse Events

Unit costs for AEs are presented in section 3.5.2. In addition to the AE cost, cost associated with patient time and transport were also included. Cost of DKK 100 was assumed per visit for transport and DKK 179 for 1 hour of patient's time. The number of visits and number of hours of patient's time was derived by summing the AE incidence rate for that particular comparator.

3.5.3.5 Best Supportive Care

Best supportive care was assumed to be monitoring and palliative care, as included in the health state costs (Table 37).

3.5.3.6 Subsequent Systemic Treatment

NSCLC

The cost of subsequent systemic treatment is assumed to be independent of survival postprogression and is applied in the model as a one-off cost at the time of disease progression.

The pattern of subsequent treatments in the pretreated NSCLC analysis was based on KOL opinion. The estimates are presented in Table 35. For BSC no additional cost was assumed. For radiotherapy a one-time cost of DKK 5,383 was applied based on DRG 2021, 27MP10 Stereotaksi, Diagnosis: DC349: Kræft i lunge UNS, Procedure: BWGC2 Stereotaktisk strålebehandling.

Table 35. Subsequent Therapy Distribution Following 2L NSCLC

Therapy	% Patients After Selpercatinib	% Patients After Chemotherapy	Duration
Docetaxel	0.0	60.0	11.64 weeks
Carboplatin	60.0	0.0	13.05 weeks
Best supportive care	20.0	20.0	NA
Radiotherapy	20.0	20.0	NA

Thyroid Cancer

Treatment options for MTC and TC are limited. Consequently, no active systemic therapy will be assumed after progression.

3.5.3.7 Health-State Costs

NSCLC

The types of resource and frequency of use in the progression-free and progressed health states for pretreated NSCLC was based on KOL feedback (Table 36).

Cost associated with patient time and transport was also included in the health state cost. The number of hours of patient's time and frequency of visits for transport cost was assumed to be the maximum of the frequency of resource use for the other components included in the health state cost. This is in line with the assumption that patients use different health care resources simultaneously, for example, when the patient goes for an oncologist visit, they will also get done the blood test, liver function test and CT scan.

Table 36. Resource Use Per Month in Pretreated *RET* Fusion-positive NSCLC, by Health State

Resource	Progression-Free	Progressed	Unit Cost (DKK)	Unit Cost Source
Oncologist visit	[redacted]	[redacted]	1,732.00	DRG 2021, 04MA98: MDC04 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DC349 Kræft i lunge UNS; Resource use based on KOL feedback
Full blood test	[redacted]	[redacted]	101.00	Resource use based on KOL feedback; Unit cost: https://labportal.rh.dk/Labportal.asp
Liver function test	[redacted]	[redacted]	201.00	Resource use based on KOL feedback; Unit cost: https://labportal.rh.dk/Labportal.asp
CT scan (thorax or abdominal)	[redacted]	[redacted]	2433.00	DRG 2021, 36PR07: Klinisk fysiologi/nuklearmedicin grp. G, Diagnosis: DC349: Kræft i lunge UNS Procedure: WMBCSXYXX CT Thorax på SPECT/CT; Resource use based on KOL feedback

CT = computerised tomography; GP = general practitioner; NSCLC = non–small cell lung cancer; *RET* = REarranged during Transfection.

Thyroid Cancer

The types of resource and frequency of use in progression-free and progressed disease state in the MTC and TC analyses were based on KOL feedback (Table 37). For selpercatinib, the health care resource use was estimated separately for the first six months in PF and PD

state by removing the resource use costs associated with ECGs. This was done because costs associated with 7 ECGs are added in selpercatinib monitoring costs for the first 6 months and adding the resource for ECGs again in the health state costs would lead to double counting of this cost.

As for NSCLC, cost associated with patient time and transport was also included in the health state cost. The number of hours of patient's time and frequency of visits for transport cost was assumed to be the maximum of the frequency of resource use for the other components included in the health state cost.

Table 37. Resource Use Per Year in *RET*-mutant Medullary Thyroid Cancer and *RET* fusion-positive Thyroid Cancer

Resource	Progression-Free	Progressed	Unit Cost (DKK)	Unit Cost Source
Consultant-led outpatient visits	[redacted]	[redacted]	1,543.00	DRG 2021, 10MA01: Struma og stofskiftesygdomme, Diagnosis: DC349: Kræft i skjoldbruskkirtel; Resource use based on KOL feedback
ECG	[redacted]	[redacted]	1,543.00	DRG 2021, 10MA01: Struma og stofskiftesygdomme, Diagnosis: DC349: Kræft i skjoldbruskkirtel, Procedure ZZ3925 EKG; Resource use based on KOL feedback
Blood tests	[redacted]	[redacted]	101.00	Resource use based on KOL feedback; Unit cost: https://labportal.rh.dk/Labportal.asp
CT scan	[redacted]	[redacted]	2,433.00	DRG 2021, 36PR07: Klinisk fysiologi/nuklearmedicin grp. G, Diagnosis: DC739 Kræft i skjoldbruskkirtlen Procedure: WMBCSXYXX CT Thorax på SPECT/CT; Resource use based on KOL feedback

CT = computerised tomography; ECG = electrocardiogram; MTC = medullary thyroid cancer; NICE = National Institute of Health and Care Excellence; *RET* = REarranged during Transfection.

3.6 Budget Impact Model Inputs

The budget impact was evaluated for the population of interest (section 3.1.3) by comparing a scenario in which selpercatinib was adopted with the scenario where it is not adopted. All cost components included in the incremental cost analysis except patient time and transport costs were included. Costs associated with different treatment options depend on outcomes (e.g. drug acquisition, drug administration and monitoring are based on the progression-free survival curve, while disease management cost is based on both PFs and OS curves); they are therefore estimated in the economic model, and then used in the BIM for consistency. Year wise undiscounted costs were estimated from the economic model and multiplied by respective market shares and population size to estimate the total cost

associated with the treatment options to estimate the budget impact. The calculations in the economic model use the PFS and OS curves based on parametric survival analysis, so the results change depending on the survival function chosen by the user. This is because the clinical trial data are immature and extrapolation beyond the trial follow-up is required to fully compare the costs of the interventions.

3.6.1 Cost Assignment

All costs were applied in the model in the year in which they occur, in order to estimate how the budget impact of introducing selpercatinib into the market develops over the 5-year period post implementation. This means that costs for the simulated cohort starting treatment in year 1 after the introduction of selpercatinib are included for their first 5 years after treatment initiation, costs for the cohort of patients starting treatment in year 2 are included for their first 4 years, those starting in year 3 for 3 years, those starting in year 4 for 2 years and those starting in year 5 for one year. This approach was taken because a substantial number of patients are expected to receive selpercatinib after one year of treatment. Thus, applying costs in the year in which they are accrued (rather than all costs in year 1 after treatment initiation) gives a more comprehensive overview of the budget impact of introducing selpercatinib into the market.

3.6.2 Analysis Timeframe

Model results show the financial impact on the payer's budget over a period of 5 years following the introduction of selpercatinib. The model is programmed for the calendar years 2021 to 2025.

3.6.3 Population

Patient population details are present in section 3.1.3. Table 38 shows the number of patients for each indication that was used for evaluating the budget impact of introducing Selpercatinib. These numbers were derived from the Danish Medical Council (DMC) protocol and the clinical expert committees estimates of eligible patients, which aligns with the estimates received from the Danish KOLs.

Table 38. Population Inputs

Input Parameter	2021	2022	2023	2024	2025
Pretreated RET fusion positive NSCLC (PD-L1 ≥50%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pretreated RET fusion positive NSCLC (PD-L1 <50%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RET Mutant MTC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pretreated RET fusion-positive TC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

MTC = medullary thyroid cancer; NSCLC = non-small cell lung cancer; *RET* = REarranged during Transfection; TC = thyroid cancer.

3.6.4 Intervention Market Share Estimates

To estimate the overall budget with and without the introduction of selpercatinib to the treatment mix, the market share of each treatment for each year between 2021 and 2025 was estimated. Market share data were based on Denmark KOL feedback. The market shares for each treatment before and after the introduction of selpercatinib are shown below. Separate market shares are shown for the programmed death-ligand 1 positive (PD-L1-positive) and PD-L1-negative populations for NSCLC.

A conservative approach was followed by assuming no costs for best supportive care (BSC) in pre-treated RET fusion positive NSCLC, since PFS and OS data was not available in the economic model for this comparator. In real world, patients on BSC would incur some costs (e.g., cost associated with palliative care), therefore, the budget impact estimated in this analysis was expected to be higher than what it would be in real world setting.

3.6.4.1 Pretreated RET fusion positive NSCLC (PD-L1 ≥50%)

Table 39. Market Shares in Denmark Before the Introduction of Selpercatinib: PD-L1 ≥ 50% Pretreated *RET*-Fusion NSCLC

Treatment	2021	2022	2023	2024	2025
Selpercatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Platinum based chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

BSC = best supportive care; NSCLC = non–small cell lung cancer; PD-L1 = programmed death-ligand 1; *RET* = REarranged during Transfection.

Table 40. Market Shares in Denmark After the Introduction of Selpercatinib: PD-L1 ≥ 50% Pretreated *RET*-Fusion NSCLC

Treatment	2021	2022	2023	2024	2025
Selpercatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Platinum based chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

BSC = best supportive care; NSCLC = non–small cell lung cancer; PD-L1 = programmed death-ligand 1; *RET* = REarranged during Transfection.

3.6.4.2 Pretreated RET fusion positive NSCLC (PD-L1 <50%)

Table 41. Market Shares in Denmark Before the Introduction of Selpercatinib: PD-L1 <50% Pretreated *RET*-Fusion NSCLC

Treatment	2021	2022	2023	2024	2025
Selpercatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pemetrexed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Docetaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

BSC = best supportive care; NSCLC = non–small cell lung cancer; PD-L1 = programmed death-ligand 1; *RET* = REarranged during Transfection.

Table 42. Market Shares in Denmark After the Introduction of Selpercatinib: PD-L1 < 50% Pretreated *RET*-Fusion NSCLC

Treatment	2021	2022	2023	2024	2025
Selpercatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pemetrexed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Docetaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

BSC = best supportive care; NSCLC = non–small cell lung cancer; PD-L1 = programmed death-ligand 1; *RET* = REarranged during Transfection.

3.6.4.3 RET-Mutant MTC

Table 43. Market Shares in Denmark Before the Introduction of Selpercatinib: RET-Mutant MTC

Treatment	2021	2022	2023	2024	2025
Selpercatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cabozantinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

BSC = best supportive care; MTC = medullary thyroid cancer; *RET* = REarranged during Transfection.

Table 44. Market Shares in Denmark After the Introduction of Selpercatinib: RET-Mutant MTC

Treatment	2021	2022	2023	2024	2025
Selpercatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cabozantinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

BSC = best supportive care; MTC = medullary thyroid cancer; *RET* = REarranged during Transfection.

3.6.4.4 Pretreated RET Fusion-positive TC

Table 45. Market Shares in Denmark Before the Introduction of Selpercatinib: Pretreated RET Fusion-positive TC

Treatment	2021	2022	2023	2024	2025
Selpercatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sorafenib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vandetanib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

BSC = best supportive care; TC = thyroid cancer; *RET* = REarranged during Transfection.

Table 46. Market Shares in Denmark After the Introduction of Selpercatinib: Pretreated RET Fusion-positive TC

Treatment	2021	2022	2023	2024	2025
Selpercatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sorafenib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vandetanib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

BSC = best supportive care; TC = thyroid cancer; *RET* = REarranged during Transfection.

3.7 Model Assumptions

The structure and sources of the economic models include the following key assumptions:

- Outcomes observed in the LIBRETTO-001 trial are representative of routine clinical practice. This also assumes that the pattern of specific *RET* mutations is representative of that in patients in routine practice or that the treatment effect is consistent across different *RET* mutations.
  - No data are available to evaluate whether the LIBRETTO-001 population is similar to the routine clinical practice population in terms of the pattern of specific *RET* mutations. The response rate for different specific *RET*-mutation groups in LIBRETTO-001 are presented in the Summary of Clinical Efficacy documents (Loxo data on file 2019, Loxo data on file 2019).
  - The analyses assume no continuation of the investigational treatment after disease progression (treatment discontinuation is dictated by the PFS curve, capped where relevant at a maximum number of treatment cycles). This is expected to be conservative because treatment with comparator therapies may be continued for some patients. The base case analysis assumes that selpercatinib is discontinued on disease progression.

- The cost of subsequent systemic treatment is assumed to be independent of survival postprogression, and is applied in the model as a one-off cost at the time of progression. For simplicity, the timing was not adjusted in analyses where selpercatinib treatment is continued beyond disease progression. This may result in subsequent treatment costs occurring earlier in the model time horizon than they would in reality. This is expected to be a conservative assumption as less discounting will be applied for the costs of subsequent systemic treatment.

Additional modelling assumptions specific to each indication are presented in Table 47.

Table 47. Modelling Assumptions and Limitations by Indication

Assumption/Limitation	Comment
Pretreated *RET* fusion-positive NSCLC	
Treatment effects for the comparator interventions observed in trials predominantly enrolling patients with *RET* wild-type tumours are generalisable to patients with *RET*-fusion tumours.	A UK clinical expert confirmed that there is no evidence to suggest otherwise and that this is a reasonable assumption that has been accepted in previous NICE appraisals
***RET*-mutant MTC**	
The treatment effects for vandetanib (HRs for PFS and OS in the *RET*-mutation–positive subgroup) continue beyond trial follow-up.	This is a conservative assumption for the incremental cost of selpercatinib.
Pretreated *RET* fusion-positive TC	
RET-fusion is not prognostic.	The prognostic significance of *RET*-fusion in TC appears to be unclear. Some authors have demonstrated *RET*-mutation to be present at a higher frequency in small, slow progressing and less aggressive tumours, while others have reported that *RET* was associated with histologic and clinical short-term aggressiveness in PTC or high-risk groups (Punda et al., 2018). A clinical expert also confirmed that the prognostic significance of *RET*-fusion in TC is unknown (personal communication, 23 June 2020).
Treatment effects for the comparator interventions observed in trials enrolling predominantly patients with *RET* wild-type tumours and mixed histology are generalisable to patients with *RET*-fusion tumours of predominantly papillary histology.	A UK clinical expert confirmed that it is unknown whether *RET*-fusion is a treatment effect modifier in TC, and it is unclear whether outcomes for PTC patients receiving 2L systemic therapy would differ from other patients with DTC receiving 2L therapy (personal communication, 23 June 2020).

Assumption/Limitation	Comment
Differences in patient populations could not be adjusted for due to the lack of patient-level data.	Data for selpercatinib were for pretreated patients, sorafenib, and BSC were predominantly for treatment-naïve patients. This is expected to be conservative because outcomes would be expected to be better for treatment-naïve patients. There is not much data available for Vandetanib in RET fusion positive PTC population since it is not recommended to use for this population as per EMA label. Outcomes for the placebo arms in the SELECT and DECISION trials differed. It was not possible to explore or adjust for this observation.

BSC = best supportive care; DTC = differentiated thyroid cancer; HR = hazard ratio; MTC = medullary thyroid cancer; NICE = National Institute for Health and Care Excellence; NMA = network meta-analysis; NSCLC = non–small cell lung cancer; OS = overall survival; PFS = progression-free survival; PTC = papillary thyroid cancer; *RET* = REarranged during Transfection; TC = thyroid cancer

3.8 Analyses

3.8.1 Deterministic Analysis

Incremental cost per-patient were calculated for each intervention over the time horizon.

Health state traces were calculated for the proportion of the cohort in each health state over time for each comparator.

3.8.2 Univariate Sensitivity and Scenario Analyses

Univariate sensitivity analyses were performed to identify the parameters that have the most influence on the incremental cost. Variation of 10% around the mean value was assumed for lower and upper bound values for parameters to be used in one-way sensitivity analysis.

3.9 Model Validation

Model validation was performed in alignment with best practices (Eddy, Hollingworth et al. 2012).

3.9.1 Face Validity

The model structure, source data and statistical analysis design were reviewed by external experts, including a health economist and UK clinical experts in NSCLC ([redacted]) and TC ([redacted]).

3.9.2 Internal Validity

Quality-control procedures for verification of input data and coding were performed by RTI-HS staff not involved in the model development and in accordance with a prespecified test plan. These procedures included verification of all input data with original sources and programming validation.

Verification of all input data was documented (with the initials of the health economist performing the quality-control procedure and the date the quality-control procedure was performed) in the relevant worksheets of the model. Any discrepancies were discussed, and the model input data was updated where required.

Programming validation included checks of the model results, calculations, data references, model interface, and Visual Basic for Applications code.

In addition, the model was validated by an independent health economist.

3.9.3 Cross Validity

Comparison of results with other models analysing the same problem was to be performed where suitable models were available. Because no economic evaluations have been performed in *RET*-altered NSCLC or TC, cross validation was not possible.

3.9.4 External Validity

Comparisons of model predictions with outcomes in studies used to build the model (i.e., dependent, external validity) and with outcomes in studies not used to build the model (i.e., independent, external validity) was performed. These results are presented in Section 3.4.

3.10 Software and Functionality

The model is programmed in Microsoft Excel for Windows, version 2010, in English.

The model is interactive so that the user can easily enter alternative parameter values. Buttons are provided to restore input parameters to their default values and to navigate within the model. Model calculations are transparent to the user, and model results are presented clearly and concisely in both tabular and graphical format.

The model includes the following elements:

- **Model description and user guide:** These worksheets present a summary of the objective and design of the model, including the decision problem, model structure, key assumptions, and a user guide providing an overview of how to use the Excel model. The model description includes a diagram explaining the data flow between the worksheets in the economic model, to help users to understand the purpose of each worksheet.

- **Input parameter worksheets:** These worksheets contain the input parameters needed by the decision model, together with their base values, sources, and assumptions. User-entry points are available so that the user may modify the input parameter values if desired. Drop-down boxes are provided whenever the user must select a parameter value from a predetermined list. A button is available on each input worksheet, allowing the user to restore the default values on that sheet. Text is included on the input worksheets to provide source information for the input parameters.
- **References worksheet:** A worksheet of full references corresponding to sources cited in the model is incorporated.
- **Results worksheets:** Incremental cost results are displayed in tabular form.
- **One-way sensitivity analysis worksheets:** The results of the one-way sensitivity analysis are summarised in the form of a tornado diagram..
- **Default data sheets:** Default data are held on background sheets that contain source data, any calculations performed to derive model parameters from the source data, and references. Country-specific data are stored together and clearly identified to facilitate adaptation of the model to other countries.
- **Calculations worksheets:** The model calculations are presented on background worksheets of the model so that they do not impede the basic use of the model but are easily accessible to any user who is interested in viewing the calculations. In addition, background Visual Basic for Applications code is documented.

4 RESULTS

Results were generated using the following model versions:

[redacted]

The base case variables and settings are presented in Appendix A. Incremental costs were reported for Selpercatinib versus the comparators. The cost components included drug acquisition cost, administration cost, monitoring cost, adverse event cost, disease management cost, and patient time and transport cost. The budget impact of introducing selpercatinib in the Danish market was also estimated.

4.1 Pretreated *RET* Fusion-positive NSCLC

4.1.1 Incremental Costs

In the base case, the model projected a higher PFS and OS for patients treated with Selpercatinib as compared to all the other treatment options like docetaxel monotherapy, pemetrexed monotherapy and, pemetrexed and carboplatin combination. This can be seen below in Figure 20.

[redacted]

Detailed base case results showing the different cost components and total incremental cost for selpercatinib versus comparators are shown below in Table 48. Selpercatinib was projected to be associated with higher overall costs, mainly driven by drug acquisition costs. Monitoring cost, general disease management cost and patient time and transport costs were also higher for Selpercatinib as compared to other treatment options since patients receiving Selpercatinib live longer and therefore incur more of these costs. Adverse event costs were also slightly higher for selpercatinib as compared to other treatments as selpercatinib is associated with higher adverse event incidence rates as compared to other treatments.

Selpercatinib was associated with cost savings for other cost components like administration cost and subsequent treatment cost. Cost savings for administration was the highest since this cost is incurred only once for oral drugs, while for IV the patients incur administration cost every time they are administered the treatment. When compared with docetaxel the cost-savings from administration cost were lower than when selpercatinib was compared with pemetrexed or pemetrexed plus carboplatin since docetaxel is administered up-to 6 cycles while pemetrexed is given until progression.

Table 48. Incremental Cost Results for Pre-treated *RET* fusion-positive NSCLC: All Non-Squamous Population

Costs (DKK)	Selpercatinib	Docetaxel	Pemetrexed + Carboplatin	Pemetrexed	Incremental Costs (DKK) of Selpercatinib Versus		
					Docetaxel	Pemetrexed + Carboplatin	Pemetrexed
Cost of study treatment							
Acquisition Cost	1,492,643	1,519	188,400	197,142	1,491,124	1,304,243	1,295,501
Administration	1,732	86,019	205,459	216,265	-84,287	-203,727	-214,533
Monitoring	24,225	4,149	4,541	4,787	20,076	19,684	19,438
Adverse Events	4,437	3,532	1,372	1,664	905	3,066	2,773
Total	**1,523,037**	**95,219**	**399,771**	**419,859**	**1,427,819**	**1,123,266**	**1,103,179**
General Disease Management Costs							
Progression-free	35,227	11,174	12,230	12,892	24,053	22,997	22,334
Progressed disease	44,111	28,544	30,246	30,192	15,567	13,865	13,919
Total	**79,338**	**39,717**	**42,475**	**43,084**	**39,621**	**36,863**	**36,254**

Costs (DKK)	Selpercatinib	Docetaxel	Pemetrexed + Carboplatin	Pemetrexed	Incremental Costs (DKK) of Selpercatinib Versus		
					Docetaxel	Pemetrexed + Carboplatin	Pemetrexed
Subsequent Treatment Costs	**5,873**	**42,167**	**42,100**	**42,507**	**-36,294**	**-36,228**	**-36,184**
Patient and Transport Cost							
Transport Cost	5,265	3,133	3,935	4,044	2,131	1,330	1,221
Patient Time Cost	9,424	5,609	7,043	7,238	3,815	2,380	2,185
Total	**14,688**	**8,742**	**10,978**	**11,282**	**5,946**	**3,710**	**3,406**
Total Costs	**1,622,936**	**185,846**	**495,325**	**516,282**	**1,437,091**	**1,127,611**	**1,106,654**

DKK = Danish Kroner; NSCLC = non–small cell lung cancer; *RET* = REarranged during Transfection.
Note: the table presents mean total expected lifetime costs per patient that are discounted at 3.5% per annum.

The impact of including diagnostic cost to identify patients with RET alterations, and impact of excluding drug wastage cost was evaluated in scenario analysis. The results are presented below in Table 49. Including diagnostic test cost increases Selpercatinib cost by DKK 333,334. Excluding drug wastage costs leads to a reduction in the costs of comparators as excluding drug wastage affects the drug acquisition cost of IV drugs only.

Table 49. Scenario Analyses Results for Pretreated *RET* fusion-positive NSCLC: All Non-Squamous Population

Scenarios	Total Costs (DKK)				Incremental Costs of Selpercatinib Versus Comparators (DKK)		
	Selpercatinib	Docetaxel	Pemetrexed + Carboplatin	Pemetrexed	Docetaxel	Pemetrexed + Carboplatin	Pemetrexed
Base case Results	**1,622,936**	**185,846**	**495,325**	**516,282**	**1,437,091**	**1,127,611**	**1,106,654**
Include Diagnostic Test Cost	1,956,270	185,846	495,325	516,282	1,770,424	1,460,945	1,439,988
Exclude Drug Wastage Cost	1,622,936	185,487	476,916	496,917	1,437,450	1,146,021	1,126,019

DKK = Danish Kroner; NSCLC = non–small cell lung cancer; *RET* = REarranged during Transfection.
Note: the table presents mean total expected lifetime costs per patient that are discounted at 3.5% per annum.

4.1.2 Budget Impact

4.1.2.1 PD-L1≥ 50%

The number of patients receiving different treatment options are presented in Table 50 and the year-wise per patient cost for different treatment options are shown below in Table 51. The budget impact of introducing selpercatinib is presented in Table 52. In previously treated RET fusion NSCLC population with PD-L1 ≥ 50%, selpercatinib was associated with an increase in the payer's budget of DKK 1,544,865 in year 1 and DKK 8,356,618 in year 5. These estimates are expected to be conservative (overestimating selpercatinib impact) since no cost was assumed for BSC and therefore, the total cost in the scenario without selpercatinib is underestimated.

Table 50. Number of Patients: Previously Treated RET Fusion-positive NSCLC PD-L1≥ 50%

Treatment	Number of Patients				
	Year 1	Year 2	Year 3	Year 4	Year 5
Without Selpercatinib					
Selpercatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Platin-based chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Best Supportive Care (BSC)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]					
Selpercatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Platin-based chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Best Supportive Care (BSC)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 51. Year-wise Per Patient Costs Associated With Selpercatinib and Comparators: Previously Treated RET Fusion-positive NSCLC PD-L1≥ 50%

Time Period	Drug cost	Administration Cost	Monitoring Cost	AE cost	Disease Management	Subsequent Treatment Cost	Total Costs
Selpercatinib (Costs, DKK)							
Year 1	671,928	1,732	16,991	4,437	17,409	1,894	**714,392**
Year 2	432,521	0	3,827	0	14,660	1,647	**452,654**
Year 3	250,343	0	2,206	0	12,039	1,235	**265,824**
Year 4	123,065	0	1,079	0	9,745	785	**134,673**
Year 5	48,981	0	426	0	7,805	403	**57,615**
Platinum Based Chemotherapy (Costs, DKK)							
Year 1	159,194	173,031	3,774	1,372	16,022	32,642	**386,036**
Year 2	27,061	30,046	714	0	10,922	8,498	**77,241**
Year 3	3,100	3,442	79	0	7,036	1,247	**14,904**
Year 4	180	200	4	0	4,386	90	**4,861**
Year 5	3	4	0	0	2,671	3	**2,680**
BSC (Costs, DKK)	Assumed to be DKK 0						

DKK = Danish Kroner; NSCLC = non–small cell lung cancer; *RET* = REarranged during Transfection.
Note: the table presents mean undiscounted costs per patient

Table 52. Budget Impact Results: Previously Treated RET Fusion-positive NSCLC PD-L1≥ 50%

Treatment	Costs (DKK)				
	Year 1	Year 2	Year 3	Year 4	Year 5
Without Selpercatinib					
Selpercatinib	0	0	0	0	0
Platin-based chemotherapy	1,852,971	2,223,728	2,295,269	2,318,601	2,331,466
Best Supportive Care (BSC)	0	0	0	0	0
Total	**1,852,971**	**2,223,728**	**2,295,269**	**2,318,601**	**2,331,466**
With Selpercatinib					
Selpercatinib	2,286,054	6,020,601	8,319,731	9,601,322	10,216,645
Platin-based chemotherapy	1,111,783	593,048	487,670	473,053	471,439
Best Supportive Care (BSC)	0	0	0	0	0
Total	**3,397,837**	**6,613,650**	**8,807,401**	**10,074,375**	**10,688,084**
Budget Impact	**1,544,865**	**4,389,922**	**6,512,132**	**7,755,774**	**8,356,618**

DKK = Danish Kroner; NSCLC = non–small cell lung cancer; *RET* = REarranged during Transfection.

4.1.2.2 PD-L1<50%

The number of patients receiving different treatment options are presented in Table 53 and the year-wise per patient cost for different treatment options are shown below in Table 54. The budget impact of introducing selpercatinib is presented in Table 55. In previously treated RET fusion NSCLC population with PD-L1 < 50%, selpercatinib was associated with an increase in the payer's budget of DKK 3,276,537 in year 1 and DKK 17,708,260 in year 5. These estimates are expected to be conservative since no cost was assumed for BSC and therefore, the total cost in the scenario without selpercatinib is underestimated.

Table 53. Number of Patients: Previously Treated RET Fusion-positive NSCLC PD-L1< 50%

Treatment	Number of Patients				
	Year 1	Year 2	Year 3	Year 4	Year 5
Without Selpercatinib					
Selpercatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Docetaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pemetrexed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Best Supportive Care (BSC)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]					
Selpercatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Docetaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pemetrexed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Best Supportive Care (BSC)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 54. Year-wise Per Patient Costs Associated With Selpercatinib and Comparators: Previously Treated RET Fusion-positive NSCLC PD-L1< 50%

Time Period	Drug cost	Administration Cost	Monitoring Cost	AE cost	Disease Management	Subsequent Treatment Cost	Total Costs
Selpercatinib (Costs, DKK)							
Year 1	671,928	1,732	16,991	4,437	17,409	1,894	**714,392**
Year 2	432,521	0	3,827	0	14,660	1,647	**452,654**
Year 3	250,343	0	2,206	0	12,039	1,235	**265,824**
Year 4	123,065	0	1,079	0	9,745	785	**134,673**
Year 5	48,981	0	426	0	7,805	403	**57,615**
Docetaxel (Costs, DKK)							
Year 1	1,519	86,019	3,559	3,532	15,818	34,153	**144,600**
Year 2	0	0	561	0	10,430	7,423	**18,415**
Year 3	0	0	49	0	6,467	857	**7,373**
Year 4	0	0	2	0	3,869	45	**3,916**
Year 5	0	0	0	0	2,256	1	**2,257**
Pemetrexed (Costs, DKK)							
Year 1	163,248	178,633	3,899	1,664	16,064	31,713	**395,221**
Year 2	30,924	34,335	815	0	11,024	9,108	**86,206**
Year 3	4,028	4,472	102	0	7,157	1,523	**17,282**
Year 4	277	308	7	0	4,499	130	**5,221**
Year 5	6	7	0	0	2,763	5	**2,781**
BSC (Costs, DKK)	Assumed to be DKK 0						

DKK = Danish Kroner; NSCLC = non–small cell lung cancer; *RET* = REarranged during Transfection.
Note: the table presents mean undiscounted costs per patient

Table 55. Budget Impact Results: Previously Treated RET Fusion-positive NSCLC PD-L1< 50%

Treatment	Costs (DKK)				
	Year 1	Year 2	Year 3	Year 4	Year 5
Without Selpercatinib					
Selpercatinib	0	0	0	0	0
Docetaxel	694,081	782,474	817,864	836,662	847,495
Pemetrexed	1,897,060	2,310,850	2,393,804	2,418,864	2,432,215
Best Supportive Care (BSC)	0	0	0	0	0
Total	**2,591,141**	**3,093,324**	**3,211,668**	**3,255,526**	**3,279,710**
With Selpercatinib					
Selpercatinib	4,572,108	12,041,203	16,639,462	19,202,644	20,433,290
Docetaxel	347,041	159,876	148,107	145,710	144,860
Pemetrexed	948,530	523,072	426,619	411,497	409,820
Best Supportive Care (BSC)	0	0	0	0	0
Total	**5,867,678**	**12,724,151**	**17,214,188**	**19,759,851**	**20,987,970**
Budget Impact	**3,276,537**	**9,630,827**	**14,002,521**	**16,504,325**	**17,708,260**

DKK = Danish Kroner; NSCLC = non–small cell lung cancer; *RET* = REarranged during Transfection.

4.2 *RET*-Mutant Medullary Thyroid Cancer

4.2.1 Incremental Costs

In the base case, the model projected a higher PFS and OS for patients treated with Selpercatinib as compared to all the other treatment options like cabozantinib and BSC. This can be seen below in Figure 21.

[redacted]

[redacted]

Detailed base case results showing the different cost components and total incremental cost for selpercatinib versus comparators are shown below in Table 56. Selpercatinib was also projected to be associated with higher overall costs, mainly driven by drug acquisition costs. Monitoring cost, general disease management cost, and patient time and transport costs were also higher for Selpercatinib as compared to other treatment options since patients receiving Selpercatinib live longer and therefore incur more of these costs.

Table 56. Incremental Cost Results for *RET*-Mutant MTC

Costs (DKK)	Selpercatinib	Cabozantinib	BSC (Placebo)	Incremental Costs (DKK) of Selpercatinib Versus	
				Cabozantinib	BSC (Placebo)
Cost of study treatment					
Acquisition Cost	2,136,213	1,393,599	0	742,614	2,136,213
Administration	1,543	1,543	0	0	1,543
Monitoring	28,348	7,861	0	20,487	28,348
Adverse Events	2,367	3,714	1,210	-1,347	1,157
Total	**2,168,471**	**1,406,717**	**1,210**	**761,754**	**2,167,261**
General Disease Management Costs					
Progression-free	75,022	34,795	14,485	40,228	60,537
Progressed disease	99,375	47,639	48,904	51,736	50,472
Total	**174,398**	**82,434**	**63,389**	**91,964**	**111,009**
Patient and Transport Cost					
Transport Cost	3,927	1,962	1,274	1,965	2,653
Patient Time Cost	7,029	3,512	2,280	3,518	4,749
Total	**10,956**	**5,474**	**3,554**	**5,483**	**7,402**
Total Costs	**2,353,825**	**1,494,625**	**68,154**	**859,200**	**2,285,671**

BSC = best supportive care; MTC = medullary thyroid cancer; *RET* = REarranged during Transfection.

Note: the table presents mean total expected lifetime costs per patient that are discounted at 3.5% per annum.

The impact of including diagnostic test cost for Selpercatinib was evaluated in a scenario analysis. The results are shown below in Table 57.

Table 57. Scenario Analyses Results for RET-Mutant MTC

Scenarios	Total Costs (DKK)			Incremental Costs (DKK) of Selpercatinib Versus	
	Selpercatinib	Cabozantinib	BSC (Placebo)	Cabozantinib	BSC (Placebo)
Base case Results	**2,353,825**	**1,494,625**	**68,154**	**859,200**	**2,285,671**
Include Diagnostic Test Cost	2,361,988	1,494,625	68,154	867,364	2,293,835

BSC = best supportive care; MTC = medullary thyroid cancer; *RET* = Rearranged during Transfection.

Note: the table presents mean total expected lifetime costs per patient that are discounted at 3.5% per annum.

4.2.2 Budget Impact

The number of patients receiving different treatment options are presented in Table 58 and the year-wise per patient cost for different treatment options are shown below in Table 59. The budget impact of introducing selpercatinib is presented in Table 60. In RET mutant MTC population, selpercatinib was associated with an increase in the payer's budget of DKK 979,490 in year 1 and DKK 8,084,725 in year 5.

Table 58. Number of Patients: RET-Mutant MTC

Treatment	Number of Patients				
	Year 1	Year 2	Year 3	Year 4	Year 5
Without Selpercatinib					
Selpercatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cabozantinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Best Supportive Care (BSC)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]					
Selpercatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cabozantinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Best Supportive Care (BSC)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 59. Year-wise Per Patient Costs Associated With Selpercatinib and Comparators: RET Mutant MTC

Time Period	Drug cost	Administration Cost	Monitoring Cost	AE cost	Disease Management	Total Costs
Selpercatinib (Costs, DKK)						
Year 1	721,817	1,543	16,647	2,367	23,763	**766,136**
Year 2	546,318	0	4,522	0	24,373	**575,213**
Year 3	341,173	0	2,815	0	21,114	**365,102**
Year 4	205,041	0	1,693	0	18,154	**224,888**
Year 5	128,505	0	1,063	0	15,655	**145,222**
Cabozantinib (Costs, DKK)						
Year 1	864,795	1,543	4,867	3,714	23,153	**898,072**
Year 2	310,842	0	1,749	0	15,938	**328,529**
Year 3	110,311	0	626	0	11,670	**122,606**
Year 4	51,402	0	293	0	8,888	**60,583**
Year 5	28,640	0	164	0	6,874	**35,678**
BSC (Costs, DKK)						
Year 1	0	0	0	1,210	20,808	**22,018**
Year 2	0	0	0	0	13,205	**13,205**
Year 3	0	0	0	0	9,357	**9,357**
Year 4	0	0	0	0	6,755	**6,755**
Year 5	0	0	0	0	4,921	**4,921**

BSC = best supportive care; DKK = Danish Kroner; MTC = medullary thyroid cancer; *RET* = REarranged during Transfection.
Note: the table presents mean undiscounted costs per patient

Table 60. Budget Impact Results: RET Mutant MTC

Treatment	Costs (DKK)				
	Year 1	Year 2	Year 3	Year 4	Year 5
Without Selpercatinib					
Selpercatinib	0	0	0	0	0
Cabozantinib	3,592,288	4,906,406	5,396,829	5,639,162	5,781,875
Best Supportive Care (BSC)	88,073	140,895	178,322	205,341	225,023
Total	**3,680,361**	**5,047,301**	**5,575,150**	**5,844,502**	**6,006,899**
With Selpercatinib					
Selpercatinib	2,451,635	6,743,951	9,752,961	11,640,932	12,825,286
Cabozantinib	2,155,373	1,506,928	1,275,535	1,224,765	1,213,460
Best Supportive Care (BSC)	52,844	49,308	50,635	51,876	52,878
Total	**4,659,852**	**8,300,187**	**11,079,131**	**12,917,573**	**14,091,624**
Budget Impact	**979,490**	**3,252,886**	**5,503,981**	**7,073,071**	**8,084,725**

BSC = best supportive care; DKK = Danish Kroner; MTC = medullary thyroid cancer; *RET* = REarranged during Transfection.

4.3 Pretreated *RET* Fusion-positive Thyroid Cancer

4.3.1 Incremental Costs

In the base case, the model projected a higher PFS for patients treated with Selpercatinib as compared to all the other treatment options like sorafenib (vandetanib PFS assumed same as sorafenib), and BSC. Higher OS was projected for sorafenib (vandetanib OS assumed same as sorafenib) as compared to selpercatinib mainly because of differences in patient population in the DECISION and LIBRETTO-001 trial (e.g., DECISION trial population consisted mainly of first line patients while in LIBRETTO -001 majority of patients were previously treated). The OS and PFS curves can be seen below in Figure 22.

[redacted]

[redacted]

Detailed base case results showing the different cost components and total incremental cost for selpercatinib versus comparators are shown below in Table 61. Selpercatinib was also projected to be associated with higher overall costs, mainly driven by drug acquisition costs. Monitoring cost, general disease management cost in progression-free state was higher for Selpercatinib as compared other treatment options since higher PFS was projected for patients receiving selpercatinib. The disease management cost in the progressed disease state and patient time and transport cost was lower for selpercatinib as compared to sorafenib and vandetanib because of lower OS projections for selpercatinib compared to these comparators.

Table 61. Incremental Cost Results for *RET* fusion-positive TC

Costs (DKK)	Selpercatinib	Vandetanib	Sorafenib	BSC	Incremental Costs (DKK) of Selpercatinib Versus		
					Vandetanib	Sorafenib	BSC
Cost of study treatment							
Acquisition Cost	1,311,660	460,465	139,844	0	851,195	1,171,815	1,311,660
Administration	1,543	1,543	1,543	0	0	0	1,543
Monitoring	21,082	7,428	7,428	0	13,654	13,654	21,082
Adverse Events	2,228	2,317	1,402	204	-88	826	2,025
Total	**1,336,513**	**471,753**	**150,218**	**204**	**864,761**	**1,186,296**	**1,336,310**
General Disease Management Costs							
Progression-free	44,527	32,876	32,876	21,217	11,650	11,650	23,309
Progressed disease	56,448	92,424	92,424	32,633	-35,976	-35,976	23,814
Total	**100,974**	**125,300**	**125,300**	**53,851**	**-24,326**	**-24,326**	**47,123**
Patient and Transport Cost							
Transport Cost	2,380	2,627	2,653	1,132	-248	-273	1,247
Patient Time Cost	4,259	4,703	4,748	2,026	-444	-489	2,233
Total	**6,639**	**7,330**	**7,401**	**3,158**	**-691**	**-762**	**3,481**
Total Costs	**1,444,126**	**604,383**	**282,918**	**57,213**	**839,744**	**1,161,208**	**1,386,914**

BSC = best supportive care; OS = overall survival; PFS = progression-free survival; *RET* = Rearranged during Transfection; TC = thyroid cancer.

Note: the table presents mean total expected lifetime costs per patient that are discounted at 3.5% per annum.

The impact of including diagnostic test cost for Selpercatinib was evaluated in a scenario analysis. The results are shown below in Table 62.

Table 62. Scenario Analyses Results for Pretreated RET-Fusion-positive TC

Scenarios	Total Costs (DKK)				Incremental Costs (DKK) of Selpercatinib Versus		
	Selpercatinib	Vandetanib	Sorafenib	BSC	Vandetanib	Sorafenib	BSC
Base case Results	**1,444,126**	**604,383**	**282,918**	**57,213**	**839,744**	**1,161,208**	**1,386,914**
Include Diagnostic Test Cost	1,517,460	604,383	282,918	57,213	913,077	1,234,541	1,460,247

BSC = best supportive care; TC = thyroid cancer; *RET* = Rearranged during Transfection.

Note: the table presents mean total expected lifetime costs per patient that are discounted at 3.5% per annum.

4.3.2 Budget Impact

The number of patients receiving different treatment options are presented in Table 63 and the year-wise per patient cost for different treatment options are shown below in Table 64. The budget impact of introducing selpercatinib is presented in Table 65. In RET mutant MTC population, selpercatinib was associated with an increase in the payer's budget of DKK 426,095 in year 1 and DKK 1,776,823 in year 5.

Table 63. Number of Patients: Pretreated RET-Fusion-positive TC

Treatment	Number of Patients				
	Year 1	Year 2	Year 3	Year 4	Year 5
Without Selpercatinib					
Selpercatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vandetanib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sorafenib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Best Supportive Care (BSC)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]					
Selpercatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vandetanib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sorafenib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Best Supportive Care (BSC)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 64. Year-wise Per Patient Costs Associated With Selpercatinib and Comparators: Pretreated RET-Fusion-positive TC

Time Period	Drug cost	Administration Cost	Monitoring Cost	AE cost	Disease Management	Total Costs
Selpercatinib (Costs, DKK)						
Year 1	669,822	1,543	15,829	2,228	23,058	**712,480**
Year 2	401,949	0	3,302	0	20,453	**425,704**
Year 3	183,331	0	1,496	0	15,337	**200,164**
Year 4	66,498	0	539	0	11,657	**78,694**
Year 5	19,762	0	159	0	9,038	**28,960**
Vandetanib (Costs, DKK)						
Year 1	280,631	1,543	4,530	2,317	24,577	**313,597**
Year 2	120,663	0	1,946	0	19,529	**142,139**
Year 3	45,509	0	732	0	15,939	**62,181**
Year 4	15,855	0	255	0	13,319	**29,428**
Year 5	5,209	0	84	0	11,270	**16,562**
Sorafenib (Costs, DKK)						
Year 1	85,816	1,543	4,530	1,402	24,577	**117,869**
Year 2	36,251	0	1,946	0	19,529	**57,726**
Year 3	13,672	0	732	0	15,939	**30,344**
Year 4	4,763	0	255	0	13,319	**18,337**
Year 5	1,565	0	84	0	11,270	**12,918**
BSC (Costs, DKK)						
Year 1	0	0	0	204	22,006	**22,210**
Year 2	0	0	0	0	13,148	**13,148**
Year 3	0	0	0	0	8,034	**8,034**
Year 4	0	0	0	0	5,021	**5,021**
Year 5	0	0	0	0	3,167	**3,167**

BSC = best supportive care; DKK = Danish Kroner; TC = thyroid cancer; *RET* = REarranged during Transfection.
Note: the table presents mean undiscounted costs per patient

Table 65. Budget Impact Results: Pretreated RET-Fusion-positive TC

Treatment	Costs (DKK)				
	Year 1	Year 2	Year 3	Year 4	Year 5
Without Selpercatinib					
Selpercatinib	0	0	0	0	0
Vandetanib	313,597	455,736	517,917	547,345	563,907
Sorafenib	23,574	35,119	41,188	44,855	47,439
Best Supportive Care (BSC)	17,768	28,286	34,714	38,731	41,264
Total	**354,939**	**519,141**	**593,818**	**630,931**	**652,610**
With Selpercatinib					
Selpercatinib	569,984	1,480,531	1,981,226	2,204,312	2,290,435
Vandetanib	188,158	148,003	128,456	121,240	119,406
Sorafenib	11,787	10,487	10,058	10,071	10,263
Best Supportive Care (BSC)	11,105	10,128	9,674	9,453	9,330
Total	**781,034**	**1,649,149**	**2,129,414**	**2,345,077**	**2,429,433**
Budget Impact	**426,095**	**1,130,008**	**1,535,596**	**1,714,146**	**1,776,823**

BSC = best supportive care; DKK = Danish Kroner; TC = thyroid cancer; *RET* = REarranged during Transfection.

4.4 Univariate Sensitivity Analysis Results

4.4.1 *Pretreated* RET *Fusion-positive NSCLC*

The tornado diagram depicted below in shows the impact of parameter variation on the incremental cost as derived from the one-way deterministic sensitivity analyses. The variables that had the most impact on the incremental cost were discount rate for costs, drug administration cost for IV drugs, subsequent treatment cost for docetaxel and health state costs in the progression free and progressed disease state.

Figure 23. Tornado Diagram: Pre-treated *RET* Fusion-positive NSCLC, All Non-Squamous Population, Selpercatinib vs. Docetaxel

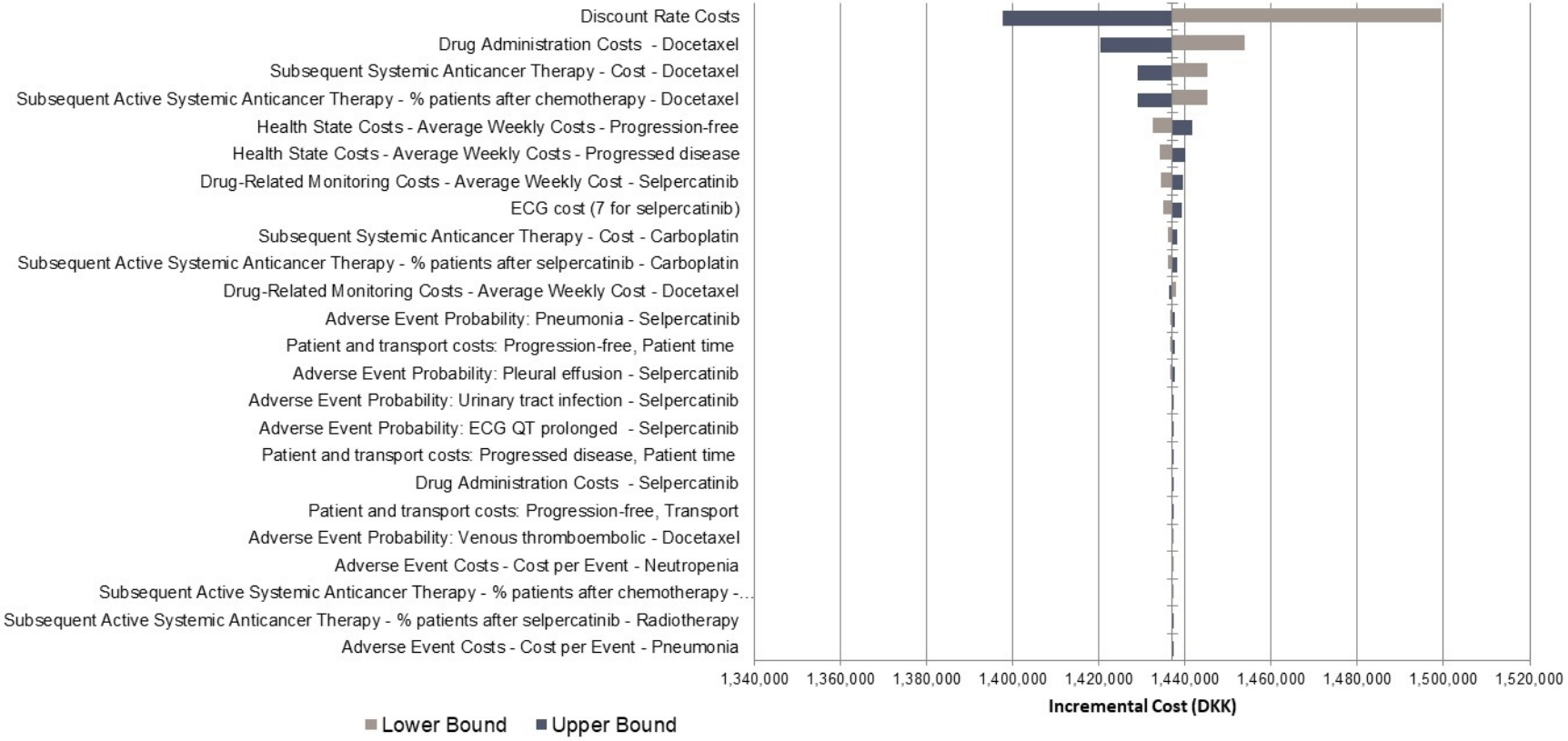


Figure 24. Tornado Diagram: Pre-treated *RET* Fusion-positive NSCLC, All Non-Squamous Population, Selpercatinib vs. Pemetrexed + Carboplatin

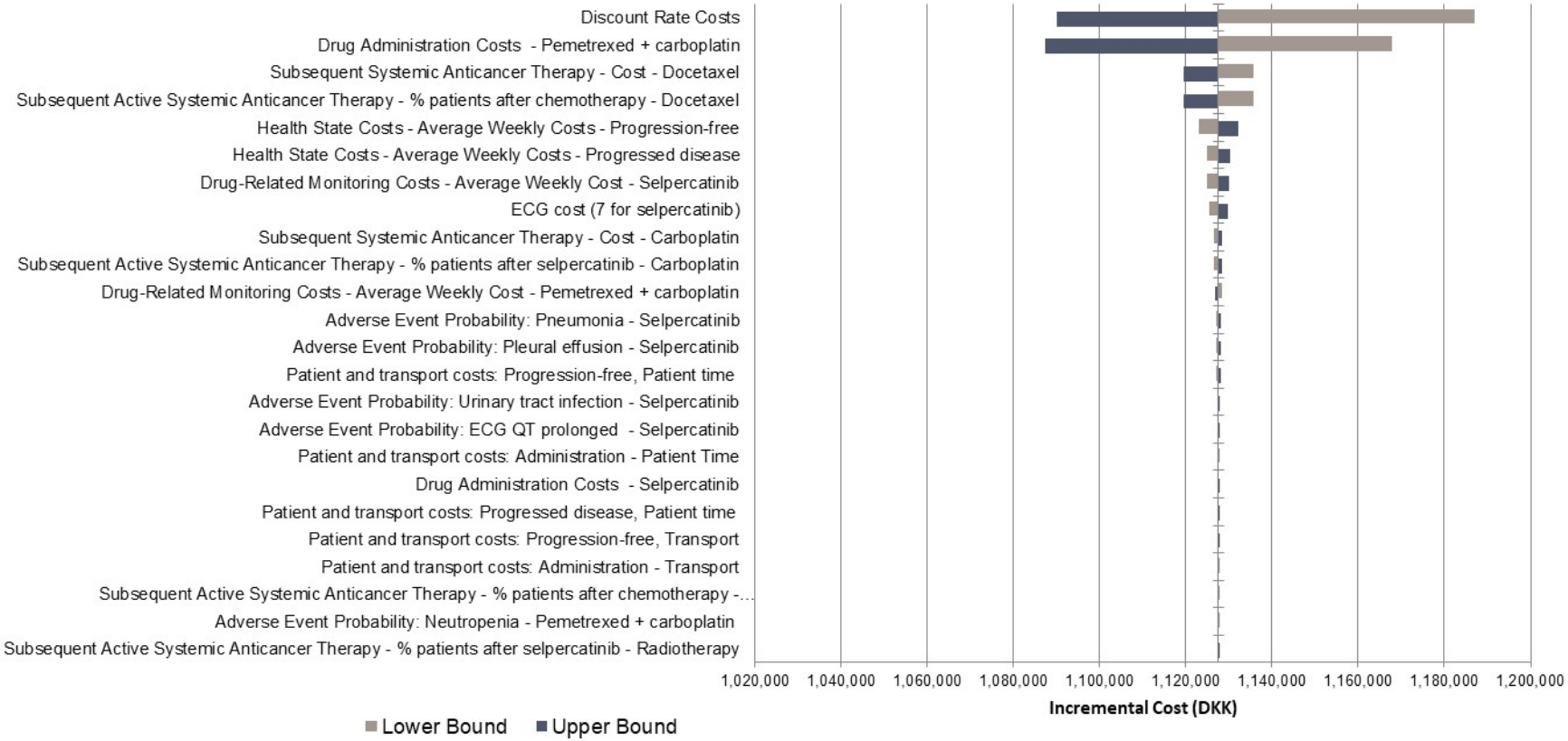
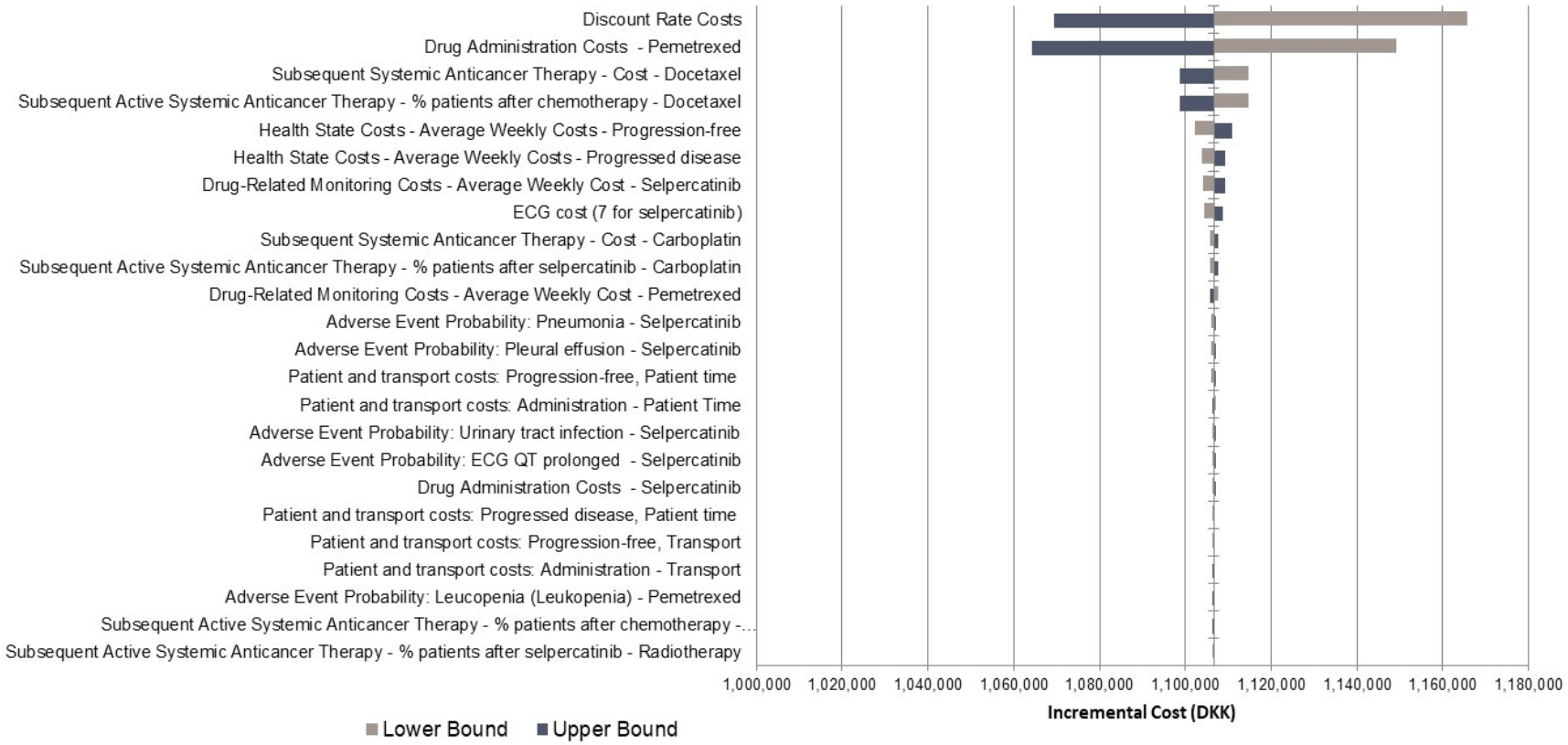


Figure 25. Tornado Diagram: Pre-treated *RET* Fusion-positive NSCLC, All Non-Squamous Population, Selpercatinib vs. Pemetrexed



4.4.2 RET-*Mutant Medullary Thyroid Cancer*

As for pretreated RET fusion-positive NSCLC, the variables that had the most impact on the incremental cost were discount rate for costs, health state costs in the progression free and progressed disease state, drug-related monitoring cost and ECG cost. When selpercatinib was compared with cabozantinib, the hazard ratio for cabozantinib OS was also an impactful parameter.

Figure 26. Tornado Diagrams: RET Mutant MTC Population, Selpercatinib vs. Cabozantinib

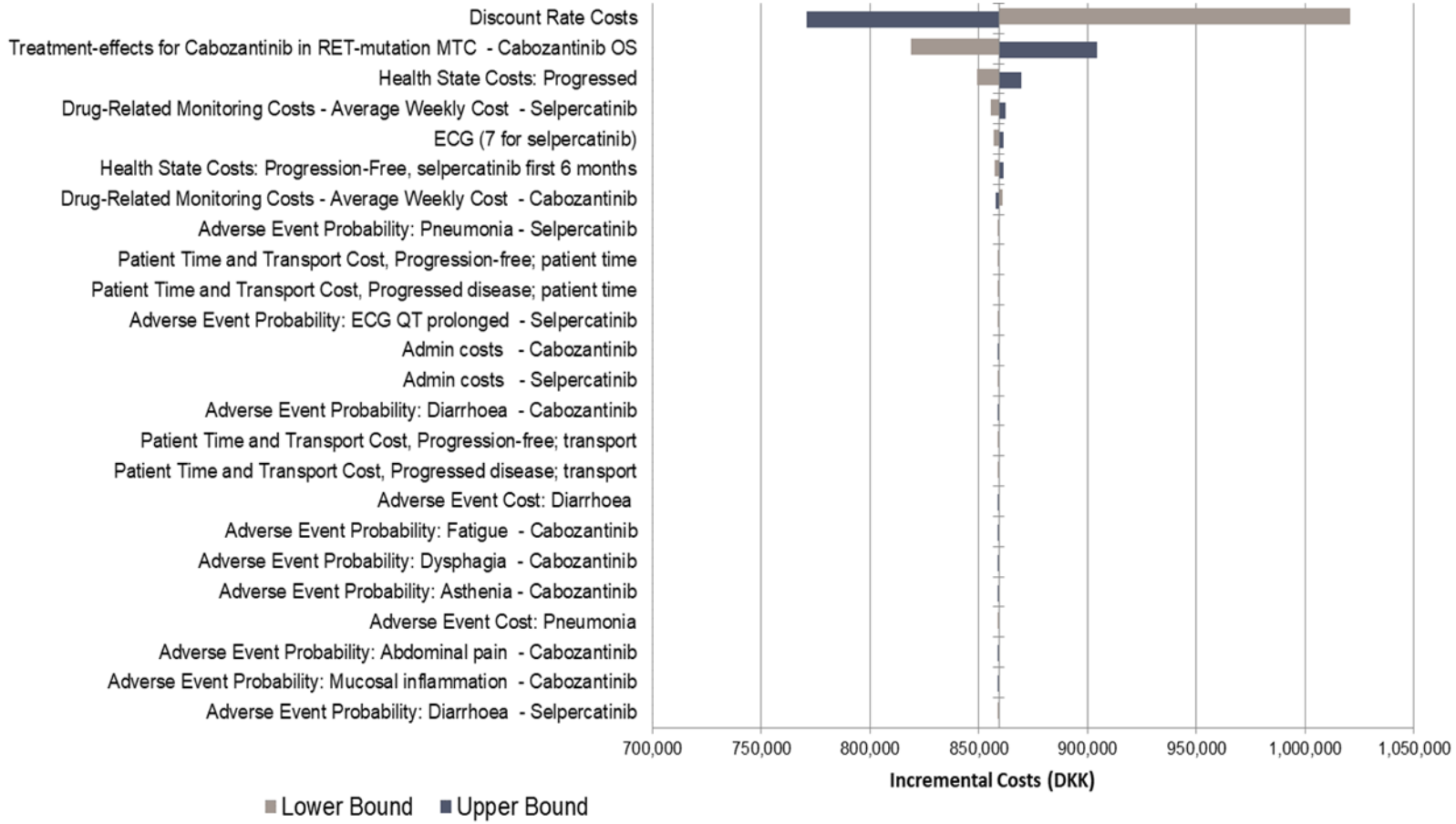
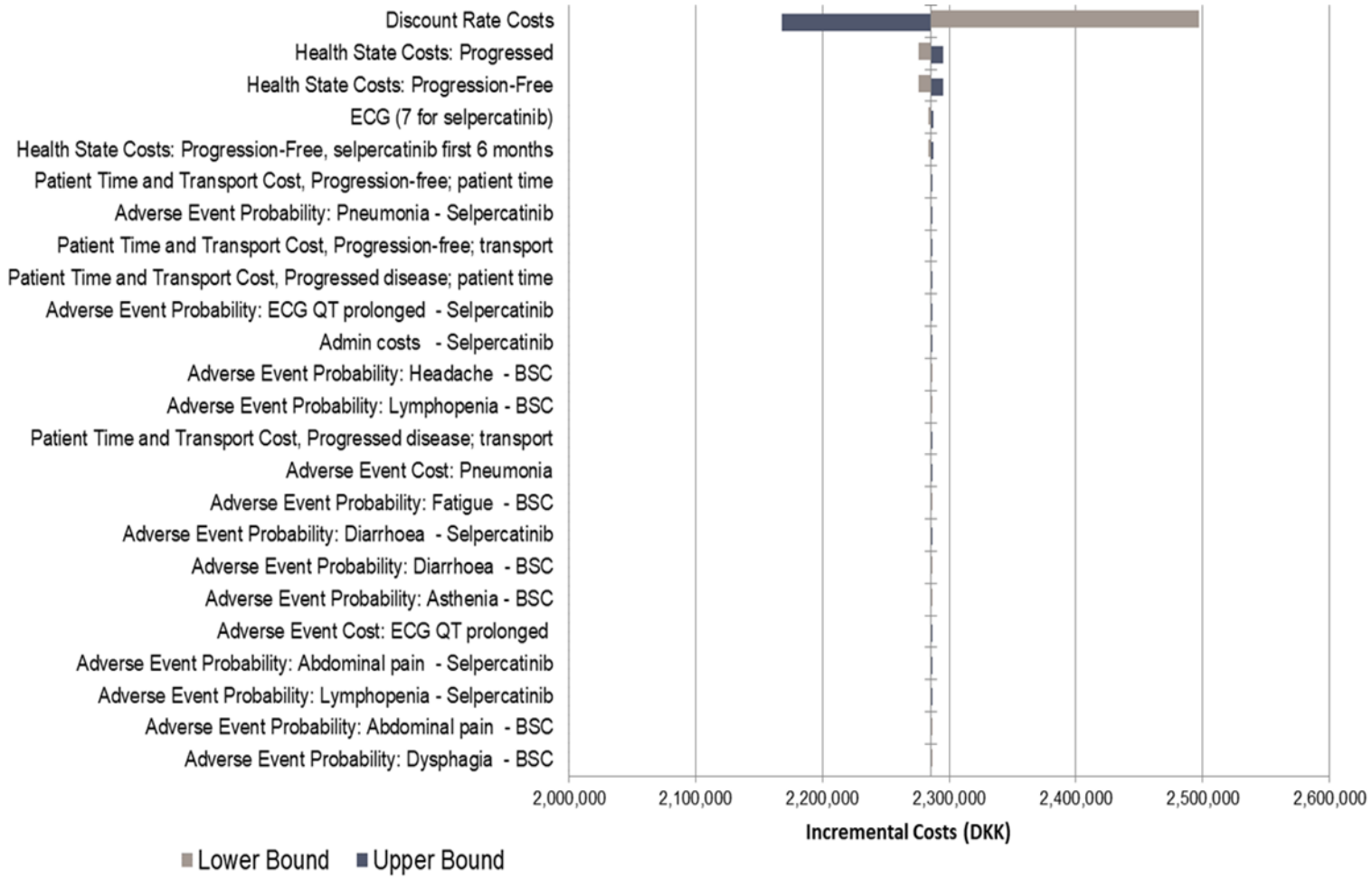


Figure 27. Tornado Diagrams: RET Mutant MTC Population, Selpercatinib vs. BSC



4.4.3 *Pretreated* RET *Fusion-positive Thyroid Cancer*

As for RET mutant MTC, the variables that had the most impact on the incremental cost were discount rate for costs, health state costs in the progression free and progressed disease state, drug-related monitoring cost and ECG cost.

Figure 28. Tornado Diagrams: Pre-treated *RET* Fusion-positive Thyroid Cancer, Selpercatinib vs. Vandetanib

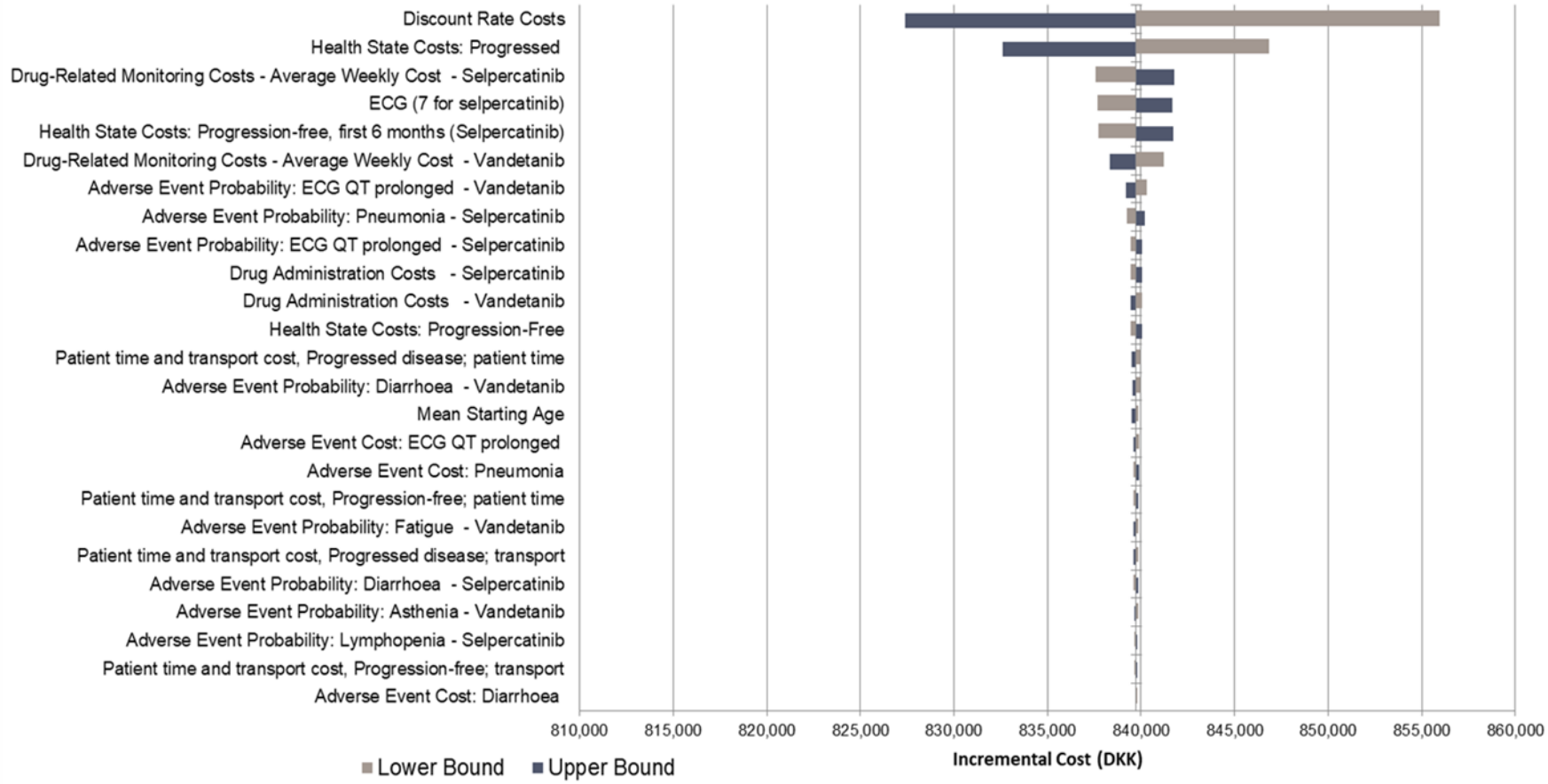


Figure 29. Tornado Diagrams: Pre-treated *RET* Fusion-positive Thyroid Cancer, Selpercatinib vs. Sorafenib

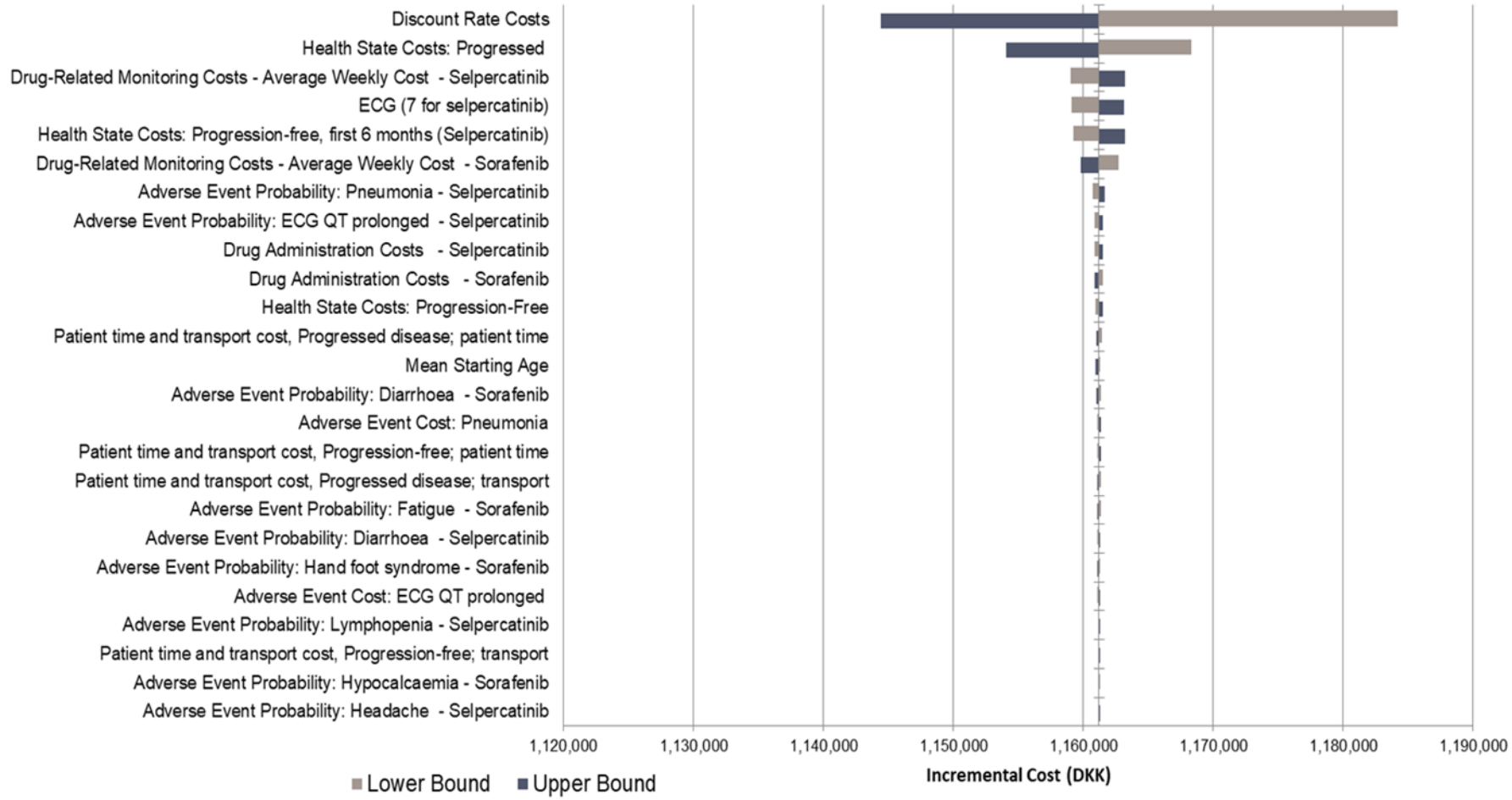
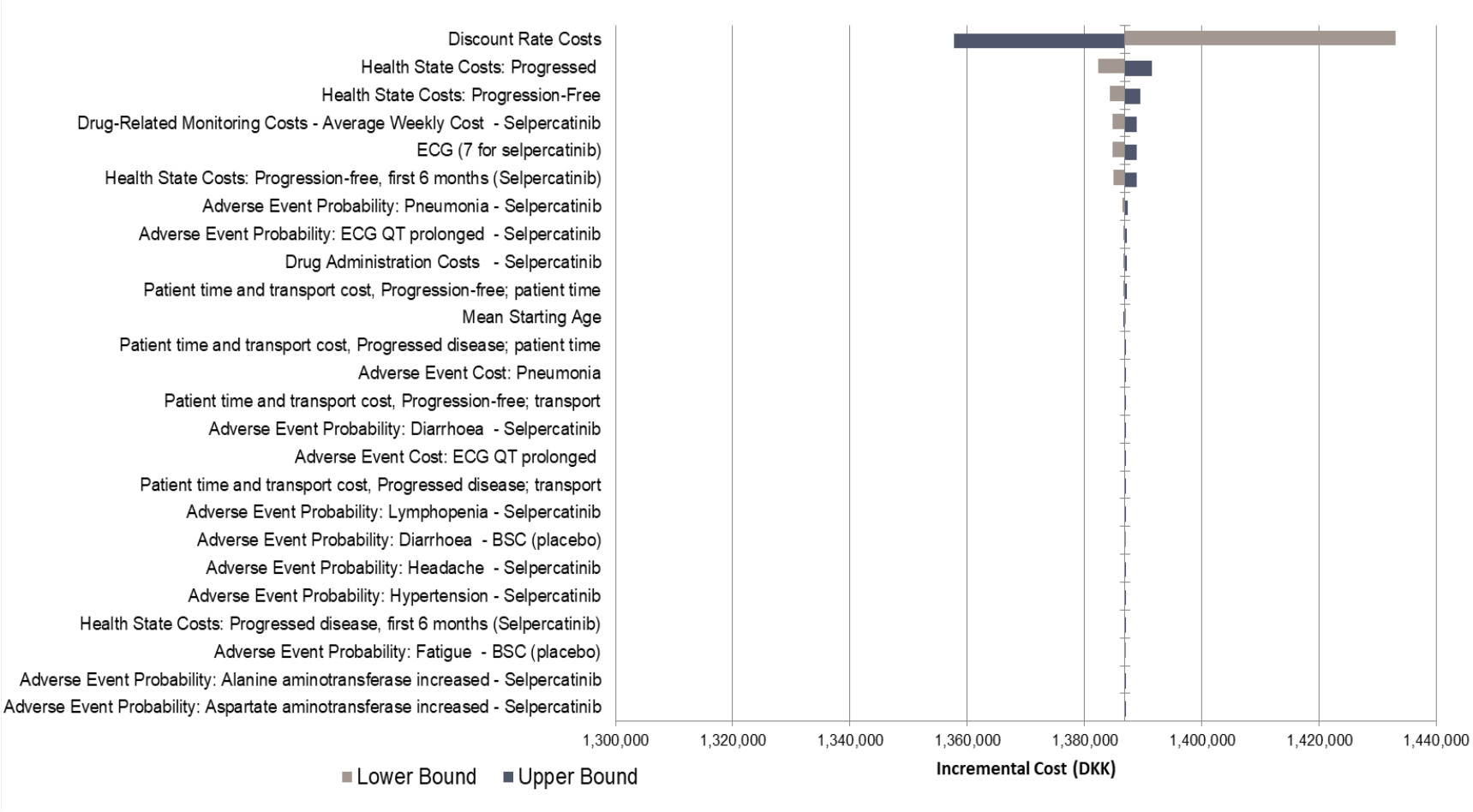


Figure 30. Tornado Diagrams: Pre-treated *RET* Fusion-positive Thyroid Cancer, Selpercatinib vs. BSC



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Appendix A. Base Case Variables and Settings

Table A-1. Pretreated *RET* Fusion-positive NSCLC

Parameter	Value	SE	Source
Time horizon	Lifetime (25-year)	NA	Assumption
Mean Starting Age	[redacted]	1.1	Selpercatinib SCE
Percentage Female	[redacted]	3.6%	Selpercatinib SCE
Mean weight (Kg)	80	1.3	clinical DMC guideline for metastatic renal cancer
Mean BSA (mg/m^2)	1.89	0.1	Previous RADS (the predecessor for DMC) assessments of chemotherapy regimens in NSCLC
Discount Rate Costs	3.5%	NA	https://fm.dk/media/18371/dokumentationsnotat-for-den-samfundsoekonomiske-diskonteringsrente_7-januar-2021.pdf
Survival approach	Trial survival extrapolation	NA	NA
NMA HRs	PSM	NA	NA
PFS function: Selpercatinib	Stratified Gompertz	VCVM	Lilly data on file
Estimated control (docetaxel)	Stratified Gompertz	VCVM	Lilly data on file
Estimated control arm for NMA	Stratified Gompertz	VCVM	Lilly data on file
TTD function: Selpercatinib	Use PFS curve	VCVM	Lilly data on file
OS function: Selpercatinib	Spline/Knot 1	VCVM	Lilly data on file
Estimated control (docetaxel)	Spline/Knot 1	VCVM	Lilly data on file
Estimated control arm for NMA	Spline/Knot 1	VCVM	Lilly data on file
Mortality ratio	1.00	0.10	Assumption
Costs (DKK)			
Selpercatinib price: 60 x 80 mg tabs	[redacted]	NA	
Selpercatinib price: 60 x 40 mg tabs	[redacted]	NA	
Include drug wastage	Yes	NA	Assumption
Oral treatment cycle length (weeks)	4	NA	NICE TA630
Selpercatinib	[redacted]	NA	

Parameter	Value	SE	Source
Pemetrexed + carboplatin	18,381.98	NA	www.Medicinpriser.dk
Pemetrexed	18,171.98	Varies with BSA	www.Medicinpriser.dk
Docetaxel	341.23	Varies with BSA	www.Medicinpriser.dk
Pemetrexed + carboplatin	1,542.76	Varies with BSA	www.Medicinpriser.dk
Dose intensity: selpercatinib	[redacted]	1.9%	LOXO Safety Tables Data cut March 11, 2020
Dose intensity: comparators	[redacted]	1.9%	Assumed same as selpercatinib
Drug administration costs (per treatment cycle)			
Selpercatinib	1,732.00	173.2	DRG 2021, 04MA98: MDC04 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DC349: Kræft i lunge UNS Procedure: BTPD5 Indøvning af administration af egen medicin
Pemetrexed	17,556.00	175.56	DRG 2021, 27MP21: Kemoterapi, kompleks, Diagnosis: DC349: Kræft i lunge UNS Procedure: BWHA239 Behandling med pemetrexed
Docetaxel	17,556.00	175.56	DRG 2021, 27MP21: Kemoterapi, kompleks, Diagnosis: DC349: Kræft i lunge UNS Procedure: BWHA208 Behandling med docetaxel
Pemetrexed + carboplatin	17,556.00	175.56	DRG 2021, 27MP21: Kemoterapi, kompleks, Diagnosis: DC349: Kræft i lunge UNS Procedure: BWHA239 Behandling med pemetrexed, BWHA109 Behandling med carboplatin
Monitoring cost (per week)	133.23	13.32	DRG 2021, 04MA98: MDC04 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DC349 Kræft i lunge UNS
Subsequent active systemic therapy (total)			
Selpercatinib	6,174.05	617.41	KOL Feedback
Chemotherapy	42,479.59	424.79	KOL Feedback
Health state costs (per week)			
Progression-free	358.80	35.88	Resources: KOL Feedback; Unit costs: DRG 2021
Progressed	358.80	35.88	Resources: KOL Feedback; Unit costs: DRG 2021
Diagnostic test (per test)	[redacted]	0.00	KOL Feedback
Screen positive rate	1.50%	0.003%	Sereci, 2019 (abstract text)

BSA = body surface area; NA = not applicable; NHSRC = NHS Reference costs 2018/19; SCE = summary of clinical efficacy; TMLE = targeted minimum loss-based estimation; VCVM = variance covariance matrix for survival function parameters.

Table A-2. RET-Mutant MTC

Parameter	Value	SE	Source
Time horizon	Lifetime (25-year)	NA	Assumption
Mean Starting Age	[redacted]	1.2	Selpercatinib SCE
Percentage Female	[redacted]	4.0%	Selpercatinib SCE
Discount Rate Costs	3.5%	NA	https://fm.dk/media/18371/dokumentationsnotat-for-den-samfundsoekonomiske-diskonteringsrente_7-januar-2021.pdf
Survival approach	Trial survival extrapolation	NA	NA
PFS function: Selpercatinib	Loglogistic	VCVM	Lilly data on file
Cabozantinib	Loglogistic	VCVM	Lilly data on file
BSC	Loglogistic	VCVM	Lilly data on file
TTD function: Selpercatinib	Use PFS curve	VCVM	Lilly data on file
OS function: Selpercatinib	Stratified Loglogistic	VCVM	Lilly data on file
BSC	Stratified Weibull	VCVM	Lilly data on file
Cabozantinib HR	0.79	0.16	EXAM (Schlumberger et al., 2017)
Mortality ratio	1.00	0.10	Assumption
Costs (DKK)			
Selpercatinib price: 60 x 80 mg tabs	[redacted]	NA	Placeholder
Selpercatinib price: 60 x 40 mg tabs	[redacted]	NA	Placeholder
Drug cost per treatment cycle (planned dose)			
Oral treatment cycle length (weeks)	4	NA	NICE TA630
Selpercatinib	[redacted]	NA	Placeholder
Cabozantinib	93,919.58	NA	www.Medicinpriser.dk
BSC	0.00	NA	Assumption
Dose intensity: selpercatinib	[redacted]	1.1%	Dose intensity = LIBRETTO-001
Cabozantinib	[redacted]	1.1%	Dose intensity assumed same as selpercatinib (TA516 data redacted)
Vandetanib	94.9%	See DI Table	Dose intensity = NICE TA516
Drug administration costs (per treatment cycle)			
Selpercatinib	1,532.00	153.20	DRG 2021, 10MA01: Struma og stofskiftesygdomme, Diagnosis: DC349: Kræft i skjoldbruskkirtel Procedure: BVDY02 Oplæring af patient i manuel færdighed

Parameter	Value	SE	Source
Cabozantinib	1,532.00	153.20	DRG 2021, 10MA01: Struma og stofskiftesygdomme, Diagnosis: DC349: Kræft i skjoldbruskkirtel Procedure: BVDY02 Oplæring af patient i manuel færdighed
Monitoring cost (per week)	117.85	11.78	DRG 2021, 10MA01: Struma og stofskiftesygdomme, Diagnosis: DC349: Kræft i skjoldbruskkirtel
Subsequent active systemic therapy (total)	0.00	NA	TA516
Health state costs (per week)			
Progression-free	525.35	52.53	DRG 2021; KOL Feedback
Progressed	430.83	43.08	DRG 2021; KOL Feedback
Diagnostic test (per test)	[redacted]	NA	KOL Feedback
Screen positive rate	61.25%	6.13%	Taccaliti et al., 2011; Wells et al., 2015

BSA = body surface area; NA = not applicable; NHSRC = NHS Reference costs 2018/19; SCE = summary of clinical efficacy; VCVM = variance covariance matrix for survival function parameters.

Table A-3. Pretreated *RET* Fusion-positive TC

Parameter	Value	SE	Source
Time horizon	Lifetime (25-year)	NA	Assumption
Mean Starting Age	[redacted]	4.3	Selpercatinib SCE
Percentage Female	[redacted]	11.5%	Selpercatinib SCE
Discount Rate Costs	3.5%	NA	https://fm.dk/media/18371/dokumentationsnotat-for-den-samfundsoekonomiske-diskonteringsrente_7-januar-2021.pdf
Survival approach	Trial survival extrapolation	NA	NA
PFS function	Stratified Weibull	VCVM	Lilly data on file
TTD function: Selpercatinib	Use PFS curve	VCVM	Lilly data on file
OS function	Piecewise exponential	VCVM	Lilly data on file
Mortality ratio	1.00	0.10	Assumption
Costs (DKK)			
Selpercatinib price: 60 x 80 mg tabs	[redacted]	NA	Placeholder
Selpercatinib price: 60 x 40 mg tabs	[redacted]	NA	Placeholder
Drug cost per treatment cycle (planned dose)			
Oral treatment cycle length (weeks)	4	NA	NICE TA630

Parameter	Value	SE	Source
Selpercatinib	[redacted]	NA	Placeholder
Vandetanib	30,198.57	NA	www.Medicinpriser.dk
Sorafenib	10,578.30	NA	www.Medicinpriser.dk
BSC	0.00	NA	Assumption
Dose intensity: selpercatinib	[redacted]	1.1%	Dose intensity = LIBRETTO-001
Vandetanib	94.9%	See DI Table	Dose intensity = NICE TA516
Sorafenib	81.4%	8.1%	Dose intensity = NICE TA535, AG model
Drug administration costs (per treatment cycle)			
Selpercatinib	1,532.00	153.20	DRG 2021, 10MA01: Struma og stofskiftesygdomme, Diagnosis: DC349: Kræft i skjoldbruskkirtel Procedure: BVDY02 Oplæring af patient i manuel færdighed
Vandetanib	1,532.00	153.20	DRG 2021, 10MA01: Struma og stofskiftesygdomme, Diagnosis: DC349: Kræft i skjoldbruskkirtel Procedure: BVDY02 Oplæring af patient i manuel færdighed
Sorafenib	1,532.00	153.20	DRG 2021, 10MA01: Struma og stofskiftesygdomme, Diagnosis: DC349: Kræft i skjoldbruskkirtel Procedure: BVDY02 Oplæring af patient i manuel færdighed
Monitoring cost (per week)	117.85	11.78	DRG 2021, 10MA01: Struma og stofskiftesygdomme, Diagnosis: DC349: Kræft i skjoldbruskkirtel
Subsequent active systemic therapy (total)	0.00	NA	TA516
Health state costs (per week)			
Progression-free	525.35	52.53	DRG 2021; KOL Feedback
Progressed	430.83	43.08	DRG 2021; KOL Feedback
Diagnostic test (per test)	5,000.00	0.00	KOL Feedback
Screen positive rate	6.82%	1.15%	Liu et al., 2014

BSA = body surface area; NA = not applicable; NHSRC = NHS Reference costs 2018/19; SCE = summary of clinical efficacy; VCVM = variance covariance matrix for survival function parameters.

Appendix B. The rationale for the selection of statistical distributions to extrapolate OS for comparators in RET-Mutant MTC

Ideally, all comparators should be extrapolated using the same statistical distribution fitted to the individual patient level data. Since the (reconstructed) patient level OS data was only available for selpercatinib and placebo/BSC, the cabozantinib extrapolation had be based on applying hazard ratio (HR) to extrapolated BSC curve. Using this approach, the selected baseline (BSC) distribution has to be consistent with proportional hazard assumption (PHA), which limits available selection when cabozantinib is included in the model as comparator.

Due to relatively immature OS data from LIBRETTO-001 trial, the selection of survival distributions was heavily relying on the feedback from a UK based external clinical expert. The clinical expert preferred Stratified Loglogistic due to longer tail to capture a (very) small proportion of likely long-term survivors. However, he also said that predicted proportion of surviving patients at 25 years, in the BSC arm specifically, was too high (3.4%) if applied to BSC arm. Stratified Gamma and Stratified Weibull were also representing clinically plausible alternatives although the proportion of survivors, in BSC arm, at 25 years was 0.0% which was not in line with the expert's experience in clinical practice. Stratified Weibull predicted 0.0% survival at 25 years for selpercatinib which was not considered clinically plausible.

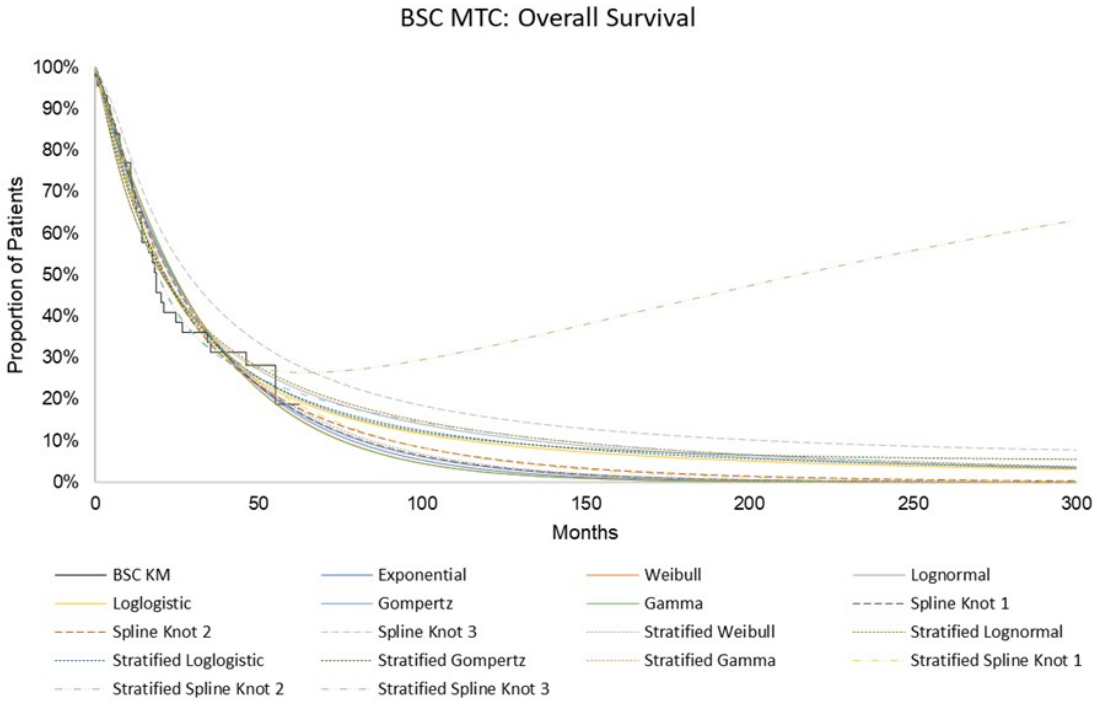
Hence, in the base-case, the selection of statistical distribution for selpercatinib was based on the best AIC/BIC among the clinically plausible (Stratified Loglogistic/Stratified Gamma) alternatives. For the BSC and cabozantinib it was considered more appropriate to select same parametric distribution. The statistically sound approach would require cabozantinib HR to be applied to the baseline curve (BSC) which conforms with the proportional hazard assumption (PHA). The only distribution among these three was Stratified Weibull. The use of distributions which are not consistent with PHA has not been implemented in the model. Stratified Weibull can be selected for selpercatinib extrapolation in the model if it is required that all extrapolations are based on the same distribution. However, based on clinical expert's opinion it would be too conservative for selpercatinib. The best alternative distribution for selpercatinib OS would be Stratified Gamma, which was also preferred by clinical expert in Sweden.

Violating another assumption would not improve any comparisons. Due to immature OS data from LIBRETTO-001 the extrapolations are subject to significant uncertainty. Figure A- 1 clearly shows that there are only 4 statistical distributions (circled) which can be considered as clinically plausible, and of these only two of these would be consistent with clinical expert's view of non-zero proportion of OS at 25 years.

The clinical experts' opinion is important to consider seriously, even if it would imply using different distributions for comparator therapies. Also, while for BSC any distribution can be selected it should be one of those plausible for selpercatinib too. Strat Loglogistic results in too high percentage of long-term survivors. Stratified Gamma is potentially the only plausible common distribution for selpercatinib and BSC – and as can be seen from the BSC curve extrapolation the difference to Stratified Weibull is very small. Using the HR approach same would apply to the extrapolated cabozantinib curve.

Just looking at the OS extrapolations for selpercatinib and BSC, the set of common distributions that would be clinically plausible for both is very limited. Using HR for cabozantinib would in practice provide the same set of plausible curves than for BSC. Therefore, adding extrapolation options (by violating PHA) for cabozantinib would be of very limited value to the evaluation.

[redacted]


BSC MTC: Overall Survival
Proportion of Patients
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
0
50
100
150
200
250
300
Months
BSC KM
Exponential
Weibull
Lognormal
Loglogistic
Gompertz
Gamma
Spline Knot 1
Spline Knot 2
Spline Knot 3
Stratified Weibull
Stratified Lognormal
Stratified Loglogistic
Stratified Gompertz
Stratified Gamma
Stratified Spline Knot 1
Stratified Spline Knot 2
Stratified Spline Knot 3

Medicinrådet

Medicinrådets protokol for vurdering vedrørende selpercatinib til behandling af RET-forandret kræft i skjoldbruskkirtlen eller ikke-småcellet lungekræft

Version 1.0

Om Medicinrådet

Medicinrådet er et uafhængigt råd etableret af Danske Regioner.

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

Om protokollen

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

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

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

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1. Begreber og forkortelser

ALK: Anaplastisk lymfomkinase

CNS: Centralnervesystemet

CR: Komplet respons (*Complete response*)

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

EPAR: *European Public Assessment Report*

EGFR: *Epidermal growth factor receptor*

EORTC-QLQ C30: *European Organisation for Research and Treatment of Cancer Quality-of-life Questionnaire-Core 30*

EUnetHTA: *European Network for Health Technology Assessment*

FDA: *The Food and Drug Administration*

FINOSE: Finland, Norge og Sveriges samarbejde om medicinske teknologivurderinger

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

HTA: Medicinsk teknologivurdering (*Health Technology Assessment)*

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

ITT: *Intention to treat*

MKRF: Mindste klinisk relevante forskel

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

NSCLC: Ikke-småcellet lungekræft *(Non-small-cell lung cancer)*

ORR: Objektiv responsrate

OS: Samlet overlevelse (*Overall survival*)

PR: Partielt respons (*Partial response*)

PD-L1: *Programmed death-ligand 1*

PFS: Progressionsfri overlevelse

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

PP: *Per Protocol*

RECIST: *Response Evaluation Criteria in Solid Tumors*

RET: *Rearranged during transfection*

ROS1: *ROS proto-onkogene 1 receptor tyrosinkinase*

RR: Relativ risiko

SMD: *Standardized Mean Difference*

2. Introduktion

Protokollen er udarbejdet, fordi Medicinrådet har modtaget en foreløbig ansøgning fra Eli Lilly, som ønsker, at Medicinrådet vurderer selpercatinib (Retsevmo) til avanceret RET-muteret medullær kræft i skjoldbruskkirtlen, avanceret RET-fusion-positiv kræft i skjoldbruskkirtlen og uhelbredelig RET-fusion-positiv ikke-småcellet lungekræft (NSCLC). Medicinrådet modtog den foreløbige ansøgning den 16. november 2020. Eli Lilly fik forhåndsgodkendelse (positive opinion) i EMA den 11. december 2020.

2.1 RET-mutation og -fusioner samt kræft i skjoldbruskkirtlen og ikke-småcellet lungekræft

RET-mutationer og -fusioner

Forandringer i genet *Rearranged during transfection* (RET) ses i forskellige kræftformer bl.a. i skjoldbruskkirtel og lunger. RET-genet koder for en tyrosinkinasereceptor, som har en vigtig rolle i udviklingen i flere væv [1]. RET-mutationer og RET-fusioner repræsenterer to forskellige mekanismer for forandringer i og medfølgende overaktivering af RET-proteinet. Begge kan medføre en overekspression af RET-onkoproteiner, der kan virke som onkogen driver [1].

RET-mutationer er hyppigst i medullær kræft i skjoldbruskkirtlen, mens RET-fusioner er hyppigst ved papillær kræft i skjoldbruskkirtlen og forskellige former for lungekræft [2]. Samlet set ses RET-forandringer i ca. 0,5-2 % af tumorvæv på tværs af kræftformer [2–4], og i disse tumorer repræsenterer det overaktive RET-protein en genetisk forandring, man kan målrette behandling imod.

Kræft i skjoldbruskkirtlen

Antallet af nye tilfælde af kræft i skjoldbruskkirtlen i Danmark var i 2019 ca. 420. Omkring en tredjedel havde kræft i stadie III-IV [5]. Generelt er prognosen god med 5-årsoverlevelser omkring 80-95 %. Dette er dog meget afhængigt af den histologiske (mikroskopisk anatomi) undertype og stadie på diagnosetidspunktet [6].

Fokus i denne protokol er på papillære og medullære karcinomer, da langt størstedelen af patienter med RET-forandring har en af disse tumorer. Den hyppigst forekommende histologi er papillært karcinom, der udgår fra follikelepitelcellerne og udgør omkring to tredjedele af alle tilfælde. Papillært karcinom udgør, sammen med follikulært karcinom, de differentierede former for kræft i skjoldbruskkirtlen (ca. 85-90 % af alle tilfælde). Derudover udgør udifferentierede og anaplastiske karcinomer omkring 5 % af tilfældene, mens de resterende ca. 7 % udgår fra de parafollikulære celler (C-celler) og betegnes medullært karcinom [6]. RET-forandringer er hyppigt forekommende i sporadisk medullært karcinom (ca. 60 %) og familiært medullært karcinom (100 %) [7], mindre hyppigt i differentieret skjoldbruskkirtel karcinom (10 %) og meget sjældent i andre histologier [1,2]. Det anslås, at der i Danmark vil være omkring 10 – 20 nydiagnosticerede patienter årligt med RET-forandret kræft i skjoldbruskkirtlen.

De generelt gode prognoser for kræft i skjoldbruskkirtlen skyldes til dels, at patienterne kun udvikler fjernmetastaser i 4-15 % af tilfældene [8]. Ved lokalt avanceret eller metastatisk sygdom ses en 5-årsoverlevelse omkring 40 – 80 % afhængig af den underliggende histologi. Prognosen kan dog være påvirket yderligere i negativ retning ved medullært karcinom ved den ikke-arvelige form for RET-forandring [7,9]. Det vides ikke, om udviklingen af fjernmetastaser er mere hyppig ved RET-forandrede tumorer i skjoldbruskkirtlen. Det totale antal patienter om året vil dog, uanset hvad, være lavt. Fagudvalget forventer, at omkring henholdsvis 1 patient (differentieret) og 7 patienter (medullært) om året vil udvikle RET-forandret lokalt avanceret eller metastatisk kræft i skjoldbruskkirtlen.

Ikke-småcellet lungekræft
Omtrent 4.600 danskere diagnosticeres årligt med lungekræft, og dermed er lungekræft en af de hyppigst forekommende kræftsygdomme i Danmark [10,11]. I slutningen af 2016 levede knap 11.151 personer med lungekræft, mens cirka 3.700 personer årligt dør af lungekræft [11]. Af de diagnosticerede har ca. 80 – 85 % ikke-småcellet lungekræft (NSCLC) [12]. NSCLC inddeles i planocellulære (ca. 25 %) og ikke-planocellulære tumorer (ca. 75 %).

Omkring 55 % af alle patienter har spredning til ikke-regionale lymfeknuder og/eller fjernmetastaser ved diagnosetidspunktet, hvilket betegnes uhelbredelig NSCLC [12]. Den seneste årsrapport fra Dansk Lunge Cancer Register viser, at 1-årsoverlevelsesraten for patienter med lungekræft udredt i 2017 uanset stadie var 51,4 %, mens 5-årsoverlevelsen for patienter udredt i 2013 var 15,9 % [12].

NSCLC kan drives af forskellige onkogene mutationer, bl.a. aktiverende *epidermal growth factor receptor* (EGFR)-mutationer samt anaplastisk lymfomkinase (ALK)-translokationer [13]. En tredje mutation, som er fundet hos 0,9-2 % af patienter med lungekræft, er translokationer, som involverer genet ROS proto-onkogene 1 receptor tyrosinkinase (ROS1) [14]. RET-forandringer er hovedsageligt fundet i ikke-planocellulær NSCLC (ca. 1-5 %), men findes også i andre histologier [2,15,16]. Både EGFR- og ALK-ændringer kan co-eksistere med RET-forandringer i NSCLC, dog begge med lav sandsynlighed (1-3 % af RET-forandrede) [2]. Derfor vil hovedparten af patienter med diagnosticeret RET-forandring ikke samtidig have targeterbare EGFR- eller ALK-ændringer. Det er et fællestræk for forandringerne, at de hyppigt er årsag til NSCLC i patienter, der hverken er tidligere eller nuværende rygere [17,18] Fagudvalget forventer, at 20-30 patienter årligt vil udvikle uhelbredelig RET-forandret NSCLC, og langt størstedelen af disse vil have ikke-planocellulær-NSCLC.

2.2 Selpercatinib

Selpercatinib (Retsevmo) er en selektiv hæmmer af RET-proteinet. Selpercatinib hæmmer derved tyrosinkinaseaktiviteten i væv, der udtrykker RET-protein, hvilket forårsager en hæmning af cellevækst i det targeterede væv. Der ansøges aktuelt hos EMA og Medicinrådet om indikationerne:

- Voksne med avanceret RET-fusion-positiv kræft i skjoldbruskkirtlen, der kræver systemisk behandling, og som er progredieret efter behandling med en multikinasehæmmer.
- Voksne og børn ≥ 12 år med avanceret RET-muteret medullær kræft i skjoldbruskkirtlen, som kræver systemisk behandling, og som tidligere er behandlet med cabozantinib og/eller vandetanib.
- Voksne med avanceret RET-fusion-positiv ikke-småcellet lungekræft, som kræver systemisk behandling efter tidligere behandling med immunterapi og/eller platinbaseret kemoterapi.

Dosering af selpercatinib forventes at være ens for de tre indikationer og er afhængig af, om patienten vejer over eller under 50 kg. Ved vægt under 50 kg er dosis 120 mg oralt to gange dagligt. Ved vægt over 50 kg er dosis 160 mg oralt to gange dagligt. Selpercatinib er hovedsageligt undersøgt i voksne patienter. Dog er det vist, at den systemiske eksponering i børn over 12 år ikke afviger fra eksponeringen i voksne [19].

2.3 Nuværende behandling

Den nuværende behandling for henholdsvis papillær skjoldbruskkirtelkræft, medullær skjoldbruskkirtelkræft og ikke-småcellet lungekræft er beskrevet i de følgende afsnit.

Papillær skjoldbruskkirtelkræft
Standardbehandlingen for papillær skjoldbruskkirtelkræft er kirurgisk resektion (total thyroidektomi). Dette efterfølges af behandling med radioaktivt jod til patienter med et mere fremskredent stadie (vævsinfiltration, residual tumor efter operation eller bestemte aggressive tumortyper) [6]. Patienterne behandles efterfølgende med skjoldbruskkirtelhormon (T4 og T3) for at erstatte den normale produktion af disse, typisk i en højere dosis for at undertrykke stimulation af eventuelt tilbageværende tumorceller, hvilket kan reducere risikoen for tilbagefald.

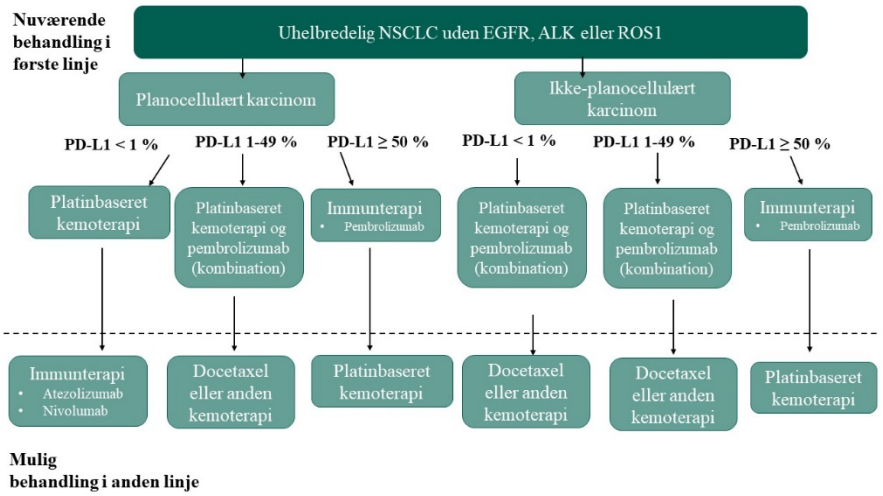
En lille del af patienterne udvikler jod-refraktær metastatisk sygdom, som betragtes som uhelbredelig. Hos disse vurderes behovet for systemisk antineoplastisk behandling med tyrosinkinasehæmmere. Ifølge DATHYRCA-gruppens behandlingsvejledning behandles disse med lenvatinib i første linje, og efter progression behandles med sorafenib eller vandetanib [6]. Alle tre lægemidler har vist at kunne forlænge den progressionsfri overlevelse med 5-12 måneder [20-22]. De patienter, der tilbydes dette, har progredierende metastatisk sygdom, som er symptomatisk og/eller med truende metastatiske manifestationer, der ikke kan kontrolleres med lokal behandling.

Medullær skjoldbruskkirtelkræft
Standardbehandlingen for medullær skjoldbruskkirtelkræft afviger fra behandlingen for differentieret skjoldbruskkirtelkræft [6]. Der bliver altid udført komplet thyroidektomi, og ofte fjernes også lymfeknuder, da der er stor risiko for lymfeknudemetastaser. I nogle tilfælde gives postoperativ strålebehandling, afhængig af operationsresultatet.
En del af patienterne oplever dog tilbagefald af sygdommen med risiko for at udvikle uhelbredelig metastaserende medullær skjoldbruskkirtelkræft. Behandlingen af disse er

afhængig af patientens symptomer, samt i hvilket væv metastaserne er lokaliseret. De fleste af disse patienter modtager i dansk klinisk praksis systemisk antineoplastisk behandling med tyrosinkinasehæmmere, vandetanib i første linje efterfulgt af cabozantinib i anden linje [6]. Disse har begge vist at kunne forlænge den progressionsfri overlevelse med 7-10 måneder [23,24].

Ikke-småcellet lungekræft

Behandlingsmålet for patienter med uhelbredelig NSCLC er symptomlindring og levetidsforlængelse. Patienter med uhelbredelig NSCLC kan få forskellige typer behandling afhængig af tumorkarakteristika. Targeteret behandling er første prioritet for patienter med aktiverende EGFR-mutation eller ALK-translokation. Patienter uden en targeterbar mutation behandles i første linje enten med platinbaseret kemoterapi eller pembrolizumab, der hæmmer bindingen mellem *programmed death-ligand 1* (PD-L1) og dets receptor (check-point inhibitor immunterapi) eller med en kombination af de to modaliteter. Valget af behandling er afhængigt af PD-L1-ekspression og histologisk type af tumoren (planocellulær eller ikke-planocellulær). Patienter med PD-L1-ekspression ≥ 50 % behandles med pembrolizumab monoterapi, uanset histologi. Patienter med PD-L1-ekspression på 1-49 % (uanset histologi) behandles med enten pembrolizumab i kombination med kemoterapi eller platinbaseret kemoterapi, hvis de har for dårlig almen tilstand eller kontraindikationer til kombinationsbehandlingen. Patienter med planocellulær NSCLC og PD-L1-ekspression < 1 % behandles med platinbaseret kemoterapi, mens patienter med ikke-planocellulær NSCLC og PD-L1 ekspression < 1 % kan behandles med pembrolizumab i kombination med platin-baseret kemoterapi. Behandlingen i anden linje er afhængig af, hvad patienten har modtaget i første linje. De mulige behandlinger for uhelbredelig NSCLC er skitseret i figuren nedenfor.



Figur 2-1- Oversigt over anbefalede førstelinjebehandlinger for uhelbredelig ikke-småcellet lungekræft (NSCLC) uden aktiverende EGFR-, ALK- eller ROS1-forandringer samt mulige behandlinger efter progression fra første linje. Figuren er modificeret fra Medicinrådets behandlingsvejledning for uhelbredelig ikke-småcellet lungekræft [13]. Behandlingsalgoritmerne er udtryk for Medicinrådets anbefalinger efter Rådsmødet 27. januar 2021 og kan ændres.

3. Kliniske spørgsmål

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

Fagudvalget har formuleret fire kliniske spørgsmål. Dette skyldes, at selpercatinib har tre forskellige indikationer, samt at indikationen vedr. NSCLC opdeles i to spørgsmål. Da langt størstedelen af patienterne med RET-forandret NSCLC vil have ikke-planocellulær histologi, bliver der kun stillet kliniske spørgsmål til disse. Førstelinjebehandlingen af ikke-planocellulær NSCLC er afhængig af PD-L1-ekspression, hvilket har betydning for behandlingsmulighederne i anden linje og dermed valget af relevante komparatorer.

3.1 Klinisk spørgsmål 1

Hvilken værdi har selpercatinib sammenlignet med sorafenib eller vandetanib for voksne med avanceret RET-forandret jodrefraktær kræft i skjoldbruskkirtlen, der tidligere er progredieret efter behandling med en multikinasehæmmer?

Population
Voksne med avanceret RET-forandret jod-refraktær kræft i skjoldbruskkirtlen, som kræver systemisk behandling, og som tidligere er progredieret efter behandling med en multikinasehæmmer.

Intervention
Selpercatinib.

Komparator
Sorafenib og vandetanib.

Fagudvalget ønsker at sammenligne interventionen med både sorafenib og vandetanib. Dette skyldes, at sorafenib er den eneste af de to stoffer, der er indiceret af EMA til sygdommen, men at vandetanib anvendes som standard i dansk klinisk praksis. Vandetanib er, i lighed med sorafenib, en multikinasehæmmer, som i øvrigt er indiceret til behandling af medullær kræft i skjoldbruskkirtlen. Vandetanib udviser sammenlignelig effekt og lavere toksicitet i sammenligning med sorafenib, og derfor anvendes vandetanib som standardbehandling efter progression på lenvatinibbehandling.

Effektmål
De valgte effektmål fremgår af tabel 1.

3.2 Klinisk spørgsmål 2

Hvilken værdi har selpercatinib sammenlignet med cabozantinib for voksne og børn ≥ 12 år med avanceret RET-forandret medullær kræft i skjoldbruskkirtlen, der tidligere er progredieret efter behandling med en multikinasehæmmer?

Population
Voksne og børn ≥ 12 år med avanceret RET-forandret medullær kræft i skjoldbruskkirtlen, som kræver systemisk behandling, og som tidligere er progredieret efter behandling med en multikinasehæmmer.

Intervention
Selpercatinib.

Komparator
Cabozantinib.

Effektmål
De valgte effektmål fremgår af tabel 1.

3.3 Klinisk spørgsmål 3

Hvilken værdi har selpercatinib sammenlignet med platinbaseret kemoterapi for voksne med avanceret RET-forandret NSCLC, der er progredieret efter behandling med check point-inhibitor immunterapi.

Population
Voksne med uhelbredelig RET-forandret ikke-planocellulær, ikke-småcellet lungekræft med PD-L1-ekspression ≥ 50 %, som tidligere er progredieret efter behandling med check point-inhibitor immunterapi.

Intervention
Selpercatinib.

Komparator
Platinbaseret kemoterapi.

Effektmål
De valgte effektmål fremgår af tabel 1.

3.4 Klinisk spørgsmål 4

Hvilken værdi har selpercatinib sammenlignet med docetaxel eller pemetrexed for voksne med avanceret RET-forandret ikke-småcellet lungekræft, der er progredieret efter behandling med check point-inhibitor immunterapi og platinbaseret kemoterapi.

Population
Voksne med uhelbredelig RET-forandret ikke-planocellulær, ikke-småcellet lungekræft med PD-L1-ekspression < 50 %, som tidligere er progredieret efter behandling med check point-inhibitor immunterapi og platinbaseret kemoterapi.

Intervention
Selpercatinib.

Komparator
Docetaxel eller pemetrexed afhængig af tidligere behandling.

Effektmål
De valgte effektmål fremgår af tabel 1.

3.5 Effektmål

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

Tabel 1 Oversigt over valgte effektmål

Effektmål*	Vigtighed	Effektmålsgruppe**	Måleenhed	Mindste klinisk relevante forskel	
				Skjoldbruskkirtel	NCSLC
Samlet overlevelse (OS)	Kritisk	Dødelighed	Median OS	3 måneder	3 måneder
			OS-rate ved 24 måneder	5 procentpoint	5 procentpoint
Livskvalitet	Kritisk	Livskvalitet og alvorlige symptomer og bivirkninger	EORTC-QLQ-C30. Gennemsnitlig ændring i post-basislinje relativt til basislinjen	10 point	10 point
Objektiv responsrate	Vigtig	Livskvalitet og alvorlige symptomer og bivirkninger	Andel, der opnår komplet eller partielt respons	15 %	15 %
Progressionsfri overlevelse (PFS)	Vigtig	Livskvalitet og alvorlige symptomer og bivirkninger	Median PFS	3 måneder	3 måneder

Effektmål*	Vigtighed	Effektmålsgruppe**	Måleenhed	Mindste klinisk relevante forskel	
				Skjoldbruskkirtel	NCSLC
Uønskede hændelser	Vigtig	Livskvalitet og alvorlige symptomer og bivirkninger	Andel af patienter, der oplever en grad 3-4 uønsket hændelse	5 procentpoint	5 procentpoint
			Gennemgang af uønskede hændelser	Kvalitativ gennemgang	Kvalitativ gennemgang
CNS-progression	Vigtig	Livskvalitet og alvorlige symptomer og bivirkninger	Median tid til CNS-progression	Ikke relevant	3 måneder

*For alle effektmål ønsker Medicinrådet data med længst mulig opfølgningstid, medmindre andet er angivet.
** Effektmålsgruppe refererer til de væsentlighedskriterier, som Medicinrådet lægger til grund for kategoriseringen af de relative forskelle i effekt, bivirkninger eller livskvalitet.

3.5.1 Kritiske effektmål

Samlet overlevelse (OS)
Der er tale om uhelbredelig sygdom ved både avanceret NSCLC og avanceret kræft i skjoldbruskkirtlen. Derfor er forbedret samlet overlevelse (OS) med mindst mulig toksicitet kritisk. For patienter med uhelbredelig RET-forandret NSCLC forventes en median OS omkring 20-24 måneder fra start af førstelinjebehandling [18,25,26]. For avanceret skjoldbruskkirtelkræft (uden kendskab til RET-status) er prognoserne for OS typisk bedre, og studier af førstelinjebehandlinger viser 24 måneders OS-rater mellem 60 % og 85 % (median OS ikke nået) [21,24]. Det er dog ofte vanskeligt at opnå modne OS-data for behandling af skjoldbruskkirtelkræft grundet den generelt gode prognose. Selv for metastatisk sygdom. Derudover vil mange patienter i de randomiserede, placebokontrollerede kliniske studier krydses over til den aktive behandling efter progression på kontrolbehandlingen, hvorved den samlede OS-effekt af den aktive behandling overfor kontrolbehandlingen vil mindskes.

I denne protokol vurderes selpercatinib som andenlinjebehandling, og der må forventes kortere overlevelser end anført ovenfor. Derfor vurderer fagudvalget, at en forskel på 3 måneder for median OS og 5 procentpoint for 24 måneders OS-rate er klinisk relevant. Hvis der findes data for median OS, vil denne blive vægtet højere end OS-raten.

Livskvalitet
Livskvalitet er et afgørende helbredsrelateret mål for den enkelte patient. Hos kræftpatienter kan livskvalitet måles med en række forskellige instrumenter, som omfatter både sygdomsspecifikke og generiske værktøjer. I dette tilfælde vil vurdering af livskvalitet hos voksne blive baseret på *European Organisation for Research and Treatment of Cancer Quality-of-life Questionnaire-Core 30* (EORTC QLQ-C30) [27,28]. EORTC QLQ-C30 er et hyppigt anvendt generisk måleredskab, som 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 en lille ændring, defineret som 10 point på tværs af domæner [29]. Ved opgørelsen ønsker fagudvalget at se, hvorledes livskvaliteten ændres igennem behandlingsforløbet, og den endelige værdi skal opgives som gennemsnittet af alle post-basislinje-målinger fratrukket den gennemsnitlige basislinje-måling.

3.5.2 Vigtige effektmål

Objektiv responsrate (ORR)
Objektiv responsrate (ORR) anvendes til belysning af behandlingsrespons og afspejler interventionens umiddelbare antineoplastiske potentiale. Ved vurdering af ORR kategoriserer man ændringer af tumors størrelse efter påbegyndt behandling, jævnfør standardiserede guidelines (*Response Evaluation Criteria in Solid Tumors* (RECIST) version 1.1 [30]. Fagudvalget vurderer, at et væsentligt tumorsvind ofte vil medføre en reduktion i patientens sygdomsbyrde.

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.

Fagudvalget vil vurdere den samlede andel af patienter, som opnår objektivt respons, samt andelen af patienter, som opnår CR eller PR. Ved RET-forandret NSCLC er der rapporteret ORR omkring 50 % ved kemoterapi [18]. ORR med tyrosinkinasehæmmerbehandling for kræft i skjoldbruskkirtlen varierer meget, hvor de fleste studier har vist ORR fra 8-30 % [20,21,23], mens et studie har vist ORR på 45 % for vandetanib til lokalt avanceret eller metastatisk medullær skjoldbruskkirtelkræft [24]. Fagudvalget vurderer, at en forskel fra komparator på 15 procentpoint er klinisk relevant. Den høje grænse afspejler, at det er svært at overføre ORR til et direkte patientrelevant effektmål.

Progressionsfri overlevelse (PFS)
Progressionsfri overlevelse (PFS) bliver anvendt til at vurdere, hvor lang tid der går, inden sygdommen udvikler sig under den aktuelle behandling. PFS er defineret som tiden fra randomisering til første dokumentation af progression i henhold til Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 [30] eller dødsfald.

PFS påvirkes ikke af akkumulerede effekter af efterfølgende behandlinger på samme måde som OS, hvilket medfører sikrere estimater. Dette er især relevant ved skjoldbruskkirtelkræft, hvor OS er relativt lang, og patienterne i studierne ofte krydses over til den aktive behandling efter progression. Fagudvalget er dog opmærksomme på, at der ikke er demonstreret sammenhæng mellem OS og PFS ved behandling af skjoldbruskkirtelkræft.

Fagudvalget vurderer, at PFS er et vigtigt effektmål, som afspejler symptombyrde, og som giver et direkte indblik i behandlingens antineoplastiske effekt uden påvirkninger af senere behandlingslinjer eller overkrydsning til aktiv behandling i kliniske studier. Derudover bemærker fagudvalget, at patienter generelt tåler behandling med en tyrosinkinasehæmmer godt i sammenligning med kemoterapi, og at det derfor har stor betydning for patienterne med skjoldbruskkirtelkræft at forblive i behandling med en tyrosinkinasehæmmer længst muligt.

For patienter med RET-forandret NSCLC er PFS for førstelinjebehandling omkring 6-8 måneder med platinbaseret kemoterapi [18]. For patienter med papillær eller medullær kræft i skjoldbruskkirtlen findes der meget varierende PFS-medianer i litteraturen, men generelt er der rapporteret om forlængelse af median PFS på omkring 10 måneder med cabozantinib eller vandetanib overfor placebo for medullær skjoldbruskkirtelkræft [31] og 5-15 måneder med sorafenib, lenvatinib eller vandetanib for jod-refraktær papillær kræft i skjoldbruskkirtlen [20–22]. De ovennævnte studier rapporterer dog hovedsageligt PFS fra førstelinjebehandlinger. Det er fagudvalgets erfaring, at andenlinjebehandling medfører kortere PFS. Derfor vurderer fagudvalget, at en mindste klinisk relevant forskel på median PFS er 3 måneder.

Uønskede hændelser
Forekomst af uønskede hændelser af grad 3-4 er et udtryk for alvorlig toksicitet af lægemidlet [32]. På den baggrund vurderer fagudvalget, at uønskede hændelser er et vigtigt effektmål. Fagudvalget ønsker data for:

- Andelen af patienter, der oplever minimum 1 uønsket hændelse af grad 3 eller 4.

Uønskede hændelser af grad 3-4 er defineret i henhold til National Cancer Institute CTCAE version 4.03 [32]. Fagudvalget vurderer, at en forskel på 5 procentpoint er klinisk relevant.

- Kvalitativ gennemgang af de uønskede hændelser.

Ansøger skal indsende en opgørelse for frekvensen af alle uønskede hændelser. Fagudvalget ønsker at foretage en gennemgang af alle uønskede hændelser, der opstår ved behandling med selpercatinib versus komparator med henblik på at vurdere

hændelsernes type, håndterbarhed og reversibilitet, samt i hvor høj grad uønskede hændelser medfører behandlingsstop.

CNS-progression
Patienter med RET-forandret NSCLC har ofte spredning til hjernen [33], hvilket medfører betydelig morbiditet og kortere overlevelse [34]. Derfor anser fagudvalget udvikling af sygdom i centralnervesystemet (CNS-progression) som et vigtigt effektmål. Effektmålet omfatter både CNS-progression hos patienter med hjernemetastaser på inklusionstidspunktet, samt patienter der får hjernemetastaser under behandlingen. Fagudvalget vurderer, at 3 måneder er den mindste klinisk relevante forskel, når CNS-progression opgøres som et time-to-event effektmål, hvilket foretrækkes. Dette svarer til den mindste klinisk relevante forskel defineret i tidligere vurderinger af targeteret behandling til uhelbredelig NSCLC. Patienter med kræft i skjoldbruskkirtlen oplever sjældent CNS-metastaser [6]. Derfor er effektmålet ikke relevant for klinisk spørgsmål 1 og 2.

4. Litteratursøgning

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

Ansøger har oplyst, at der ikke foreligger data fra randomiserede eller kontrollerede studier, hvor selpercatinib er sammenlignet med andre lægemidler. Der er igangværende randomiserede kliniske studier, der sammenligner selpercatinib med hhv. platinbaseret kemoterapi og/eller pembrolizumab i patienter med NSCLC (LIBRETTO-431, NCT04194944) og med cabozantinib og vandetanib i patienter med medullær skjoldbruskkirtelkræft (LIBRETTO-531, NCT04211337). Resultater herfra foreligger tidligst i 2023-24. Derfor skal ansøger søge efter studier til en indirekte sammenligning.

Fagudvalget har kendskab til, at der findes kohortestudier for patienter med RET-forandret NSCLC, som er behandlet med kemoterapi, og efterspørger derfor en naiv sammenstilling af data for selpercatinib med data herfra. Derudover kan det være relevant at foretage en naiv sammenstilling med data fra patienter uden påvist RET-forandring, da dette vil give et større datagrundlag at vurdere komparatorerne ud fra.

[1] For yderligere detaljer se Medicinrådets kriteriepapir om anvendelse af upublicerede data

Ved søgninger vedrørende patienter uden RET-forandring, skal der så vidt muligt fokuseres på randomiserede kliniske studier. For komparatoren, platin-baseret kemoterapi, vil dette dog hovedsageligt vise data fra førstelinjebehandlinger. Derfor bør søgningen til dette deles op, så der dels søges efter randomiserede kliniske studier, der undersøger effekten af platin-baseret kemoterapi i førstelinje, og dels søges efter studier, der undersøger effekten af platin-baseret kemoterapi i patienter, der tidligere er behandlet med immunterapi. Dette er specificeret i de vedlagte søgestrenge.

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

Baselinekarakteristika skal så vidt muligt fremgå, herunder særligt patienternes rygehistorik i de studier, der vedrører patienter med NSCLC, da RET-forandret NSCLC ofte opstår i patienter, der ikke tidligere har røget [18].

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

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

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

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

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

5. Den endelige ansøgning

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

Studier og resultater

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

Statistiske analyser

- Begrund valget af syntesemetode (metaanalyse eller narrativ beskrivelse), og lad specifikke analysevalg fremgå tydeligt.
- Udfør en komparativ analyse for hvert enkelt effektmål på baggrund af de ekstraherede data.
- Hvis data for et effektmål ikke er baseret på alle deltagere i et studie, skal ansøger ikke gøre forsøg på at erstatte manglende data med en meningsfuld værdi.
- Angiv for hvert effektmål og studie, hvilken analysepopulation (fx intention to treat (ITT), per-protocol) der er anvendt.
- Angiv en sensitivitetsanalyse baseret på ITT-populationen, hvis den komparative analyse ikke er baseret herpå.
- Angiv for hvert effektmål og studie, hvilken statistisk analysemetode der er anvendt.
- Basér de statistiske analyser for dikotome effektmål på den relative forskel.
- Beregn den absolutte forskel med udgangspunkt i den estimerede relative forskel for et antaget niveau på hændelsesraten i komparatorgruppen (jf. appendiks 5 i Håndbog for Medicinrådets proces og metode vedr. nye lægemidler og indikationsudvidelser).
- Foretag eventuelt en indirekte analyse, hvis der ikke foreligger direkte sammenlignende studier, og hvis intervention og komparator er sammenlignet med samme alternative komparator i separate studier. Anvend eventuelt Buchers metode for indirekte justeret sammenligning.

Metaanalyser

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

Narrative analyser

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

Særlige forhold i denne protokol

- Fagudvalget efterspørger, at oversigter over basislinjekarakteristika for alle studier, der bruges til naive sammenstillinger, indeholder en opgørelse over andelen af patienter med RET-forandring og patienternes rygehistorik (ved NSCLC).
- Fagudvalget ønsker at vurdere data for komparatorer fra patienter uden påvist RET-forandring i de tilfælde, hvor der ikke forefindes data fra randomiserede kliniske studier, hvor patienternes RET-status er kendt.
- Fagudvalget er bekendt med, at de fleste randomiserede kliniske studier omhandlende komparatorerne for skjoldbruskkirtelkræft er udført som første behandlingslinje. Derfor ønsker fagudvalget, at data fra førstelinjestudier bliver inkluderet i datagrundlagene til at besvare klinisk spørgsmål 1 og 2.

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

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

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

- Beskriv den valgte modelstruktur grundigt.
- Beskriv, hvis der er anvendt en indirekte analyse, hvordan den vil blive håndteret i den sundhedsøkonomiske analyse.
- Begrund og beskriv samtlige antagelser i modellen, og lad specifikke analysevalg fremgå tydeligt.
- Beskriv alle de inkluderede studier, argumentér for deres relevans, og beskriv, hvor og hvordan data anvendes i modellen.
- Begrund både de inkluderede og ekskluderede omkostninger.
- Beskriv, hvad der driver modellen, fx behandlingslængde eller lægemiddelomkostninger.
- Ekstrapoleret data skal beskrives.
- Udfør følsomhedsanalyser, som belyser, hvilke parametre i modellen der har størst indflydelse på resultatet.
- Argumentér for eventuelle afvigelser fra protokollen og den kliniske ansøgning.
- Budgetkonsekvensanalysen skal være dynamisk med omkostningsanalysen, uden diskontering og patientomkostninger.
- Inddrag omkostninger for diagnostik af RET-forandringer, da der ikke undersøges for disse i dansk klinisk praksis, bortset fra ved familiær medullær kræft i skjoldbruskkirtlen.

6. Evidensens kvalitet

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

7. Andre overvejelser

Fagudvalget ønsker informationer, der kan belyse en vurdering af, hvorvidt og hvordan indførelsen af entrectinib i dansk klinisk praksis vil påvirke efterfølgende behandlinger, hvad angår type, varighed og forventet effekt.

Fagudvalget er bekendt med, at RET-forandringer også kan forekomme ved planocellulær NSCLC. Disse indgår ikke i protokollens kliniske spørgsmål, da datagrundlaget vil være for småt til at kunne vurdere effekten. Fagudvalget vil i stedet, under andre overvejelser, lave en klinisk vurdering af, om effekterne ved ikke-planocellulær NSCLC også kan dække patienter med planocellulær NSCLC.

8. Relation til behandlingsvejledning

Der findes ikke en relevant behandlingsvejledning.

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10. Sammensætning af fagudvalg og kontaktinformation til Medicinrådet

Medicinrådets fagudvalg vedrørende tværgående kræftlægemidler

Sammensætning af fagudvalg	
Formand	**Indstillet af**
Lars Henrik Jensen *Overlæge*	Lægevidenskabelige Selskaber
Medlemmer	**Udpeget af**
Morten Ladekarl *Professor, overlæge, dr.med.*	Region Nordjylland
Deltager ikke	Region Nordjylland
Anni Ravnsbæk Jensen *Ledende overlæge*	Region Midtjylland
Pernille Wendtland *Overlæge*	Region Midtjylland
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Eckhard Schomerus *Overlæge (pædiatri)*	Region Syddanmark
Karen Julie Gehl *Professor, overlæge, dr.med.*	Region Sjælland
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Lisa Sengeløv *Ledende overlæge, dr.med.*	Region Hovedstaden
Troels K. Bergmann *Overlæge, klinisk lektor (speciallæge i klinisk farmakologi)*	DSKF
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Sammensætning af fagudvalg	
Karsten Nielsen *Overlæge, lektor, dr.med.*	Dansk Patologiselskab
Simone Møller Hede *Patient/patientrepræsentant*	Danske Patienter
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11. Versionslog

Versionslog		
Version	**Dato**	**Ændring**
1.0	3. februar 2021	Godkendt af Medicinrådet.

12. Bilag

Bilag 1: Søgestrenge

Klinisk spørgsmål 1 og 2
Søgestreng til PubMed:

#	Søgetermer	Kommentar
1	Thyroid Cancer, Papillary[mh] OR Thyroid cancer, medullary[nm]	Søgetermer for population (begge kræfttyper)
2	(thyroid[ti] AND (cancer[ti] OR cancers[tiab] OR adenocarcinoma[ti] OR carcinoma[ti])) OR Thyroid Neoplasms[mh:noexp]	
3	papillary[tw] OR differentiated[tiab] OR nonmedullary[tiab] OR "non medullary"[tiab] OR medullary[tw] OR Carcinoma, Neuroendocrine[mh:noexp] OR Carcinoma, Medullary[mh]	
4	#2 AND #3	
5	#1 OR #4	
6	selpercatinib[nm] OR selpercatinib[tiab] OR LOXO-292[tiab] OR Retevmo*[tiab]	Søgetermer for interventioner
7	Sorafenib[mh] OR sorafenib[tiab] OR Nexavar*[tiab]	
8	N-(4-bromo-2-fluorophenyl)-6-methoxy-7-((1-methylpiperidin-4-yl)methoxy)quinazolin-4-amine[nm] OR vandetanib[tiab] OR Caprelsa*[tiab] OR Zactima*[tiab]	
9	cabozantinib[nm] OR cabozantinib[tiab] OR Cometriq*[tiab]	
10	#6 OR #7 OR #8 OR #9	
11	#5 AND #10	Kombination af population og lægemidler
12	Case Reports[pt] OR Comment[pt] OR Editorial[pt] OR Guideline[pt] OR Letter[pt] OR News[pt] OR Review[pt] OR Systematic Review[pt] OR case report[ti] OR review[ti]	Publikationstyper til eksklusion
13	#11 NOT #12	

14	Proto-Oncogene Proteins c-ret[mh]	Søgetermer til RET-forandring
15	(RET[tiab] OR "rearranged during transfection"[tiab]) AND (alteration*[tiab] OR altered[tiab] OR aberration*[tiab] OR aberrant[tiab] OR rearrange*[tiab] OR re-arrange*[tiab] OR fusion*[tiab] OR fused[tiab] OR mutant*[tiab] OR mutat*[tiab])	
16	#13 AND (#14 OR #15)	
17	("Randomized Controlled Trial"[pt] OR "Controlled Clinical Trial"[pt] OR randomized[tiab] OR randomised[tiab] OR placebo[tiab] OR "Clinical Trials as Topic"[mh:noexp] OR randomly[tiab] OR trial[ti]) NOT ("Animals"[mh] NOT "Humans"[mh])	Filter til identifikation af RCT (population og lægemidler)
18	#13 AND #17	
19	**#16 OR #18**	**Samlet sæt af RET-forandring og RCT**

Søgestreng til CENTRAL:

#	Søgetermer	Kommentar
#1	[mh "Thyroid Cancer, Papillary"] or "thyroid papillary carcinoma":kw	Søgetermer for population (begge kræfttyper)
#2	("thyroid medullary carcinoma"):kw	
#3	(thyroid near/4 (cancer or adenocarcinoma or carcinoma)):ti,ab OR [mh ^"Thyroid Neoplasms"]	
#4	(papillary or differentiated or nonmedullary or "non medullary" or medullary):ti,ab	
#5	[mh ^"Carcinoma, Neuroendocrine"] or [mh "Carcinoma, Medullary"]	
#6	#3 AND (#4 OR #5)	
#7	#1 or #2 or #6	
#8	(selpercatinib or LOXO-292 or Retevmo*):ti,ab,kw	Søgetermer for interventioner
#9	(sorafenib OR Nexavar*):ti,ab,kw	

#10	(vandetanib or Caprelsa* or Zactima*):ti,ab,kw	
#11	(cabozantinib or Cometriq*):ti,ab,kw	
#12	#8 or #9 or #10 or #11	
#13	#7 and #12	Kombination af population og lægemidler
#14	[mh "Proto-Oncogene Proteins c-ret"]	Søgetermer til RET forandring
#15	protein next Ret:kw	
#16	((RET OR "rearranged during transfection") near/5 (alteration* or altered or aberration* or aberrant or rearrange* or re-arrange* or fusion* or fused or mutant* or mutat*)):ti,ab	
#17	#14 or #15 or #16	
#18	#13 and #17	
#19	("conference abstract" or review):pt	Publikationstyper til eksklusion
#20	(abstract or review):ti	
#21	NCT*:au	
#22	(clinicaltrials.gov or trialsearch):so	
#23	(abstract or conference or meeting or proceeding*):so	
#24	annual meeting:ab	
#25	{or #19-#24}	
#26	#18 not #25	**RET**
#27	(#13 not #18) not #25	**Population og lægemidler** (ikke RET)

Klinisk spørgsmål 3 og 4

RET forandringer, med/uden lægemidler

Søgestreng til PubMed:

#	Søgetermer	Kommentar
1	nsclc[ti]	Søgetermer for population
2	(non-small-cell-lung[ti] OR nonsmall-cell-lung[ti]) AND (cancer[ti] OR cancers[ti] OR carcinoma[ti] OR adenocarcinoma[ti])	
3	Carcinoma, Non-Small-Cell Lung[mh] AND drug therapy[sh]	
4	(nonsquamous[ti] OR non-squamous[ti]) AND lung[ti] AND (cancer[ti] OR carcinoma[ti])	
5	lung[ti] AND adenocarcinoma[ti]	
6	Adenocarcinoma of Lung[mh] AND drug therapy[sh]	
7	#1 OR #2 OR #3 OR #4 OR #5 OR #6	
8	selpercatinib[nm] OR selpercatinib[tiab] OR LOXO-292[tiab] OR Retevmo*[tiab]	Søgetermer for interventioner
9	Platinum[mh] OR Platinum Compounds[mh] OR Cisplatin[mh] OR Organoplatinum Compounds[mh] OR Carboplatin[mh] OR platin*[tiab] OR cisplatin[tiab] OR cis-platin[tiab] OR carboplatin[tiab]	
10	Docetaxel[mh] OR docetaxel[tiab]	
11	Pemetrexed[mh] OR pemetrexed[tiab]	
12	#8 OR #9 OR #10 OR #11	
13	Proto-Oncogene Proteins c-ret[mh]	Søgetermer for RET forandring
14	(RET[tiab] OR "rearranged during transfection"[tiab]) AND (alteration*[tiab] OR altered[tiab] OR aberration*[tiab] OR aberrant[tiab] OR rearrange*[tiab] OR re-arrange*[tiab] OR fusion*[tiab] OR fused[tiab] OR mutant*[tiab] OR mutat*[tiab])	
15	#13 OR #14	
16	Case Reports[pt] OR Comment[pt] OR Editorial[pt] OR Letter[pt] OR News[pt] OR case report[ti]	Publikationstyper til eksklusion

17	#15 NOT #16	
18	#7 AND #12 AND #17	Kombination af population, lægemidler og RET
19	Clinical Trial[pt] OR Comparative Study[pt] OR Multicenter Study[pt] OR Observational Study[pt]	Søgefilter til identifikation af øvrige studier i populationen (uden lægemidler) med RET forandring
20	Cohort Studies[mh] OR Prospective Studies[mh] OR Retrospective Studies[mh]	
21	clinical trial[tiab] OR controlled trial[tiab]	
22	randomized[tiab] OR randomised[tiab] OR randomly[tiab] OR controlled[tiab] OR placebo[tiab]	
23	(phase 1[tiab] OR phase I[tiab] OR phase 2[tiab] OR phase II[tiab] OR phase 3[tiab] OR phase III[tiab]) AND (trial*[tiab] OR study[tiab])	
24	(comparative[tiab] OR multicent*[tiab] OR multi-cent* OR single-cent*[tiab] OR single-arm[tiab]) AND (trial*[tiab] OR study[tiab])	
25	(observational[tiab] OR cohort[tiab] OR prospective[tiab] OR retrospective*[tiab]) AND (study[tiab] OR analy*[tiab])	
26	Registries[mh] OR registry[tiab] OR nation-wide[tiab] OR nationwide[tiab] OR real-worl[tiab] OR real-life[tiab]	
27	#19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26	
28	#7 AND #17 AND #27	
29	**#18 OR #28**	**Samlet sæt, RET forandring**

Søgestreng til CENTRAL:

#	Søgetermer	Kommentar
#1	nsclc:ti	Søgetermer for population
#2	((non-small-cell-lung or nonsmall-cell-lung) and (cancer or carcinoma or adenocarcinoma)):ti	
#3	[mh "Carcinoma, Non-Small-Cell Lung"] or "non small cell lung cancer":kw	
#4	[mh "Adenocarcinoma of Lung"] or (lung next adenocarcinoma):ti,kw	
#5	#1 or #2 or #3 or #4	
#6	(selpercatinib or LOXO-292 or Retevmo*):ti,ab,kw	Søgetermer for interventioner
#7	(organoplatinum or carboplatin or platin* or cisplatin or cis-platin):ti,kw	
#8	(docetaxel or pemetrexed):ti,ab,kw	
#9	#6 or #7 or #8	
#10	[mh "Proto-Oncogene Proteins c-ret"]	Søgetermer for RET forandring
#11	protein next Ret:kw	
#12	((RET OR "rearranged during transfection") near/5 (alteration* or altered or aberration* or aberrant or rearrange* or re-arrange* or fusion* or fused or mutant* or mutat*)):ti,ab	
#13	#10 or #11 or #12	
#14	NCT*:au	Publikationstyper til eksklusion
#15	(clinicaltrials.gov or trialsearch):so	
#16	(abstract or conference or meeting or proceeding*):so	
#17	#14 or #15 or #16	
#18	**(#5 and #9 and #13) not #17**	**Kombination af population, lægemidler og RET**
#19	**((#5 and #13) not #17) not #18**	**Kombination af population og RET**

Søgestrenge til scenarier uden RET-forandring

Klinisk spørgsmål 3:

Observationelle studier for platinbaseret kemoterapi efter tidl. behandling med immunterapi.

Søgestreng til PubMed:

#	Søgetermer	Kommentar
1	NSCLC[ti]	Søgetermer for population
2	(non-small-cell-lung[ti] OR nonsmall-cell-lung[ti]) AND (cancer*[ti] OR carcinoma[ti] OR adenocarcinoma[ti])	
3	Carcinoma, Non-Small-Cell Lung[mh] AND drug therapy[sh]	
4	(nonsquamous[ti] OR non-squamous[ti]) AND lung[ti] AND (cancer[ti] OR carcinoma[ti] OR adenocarcinoma[ti])	
5	lung[ti] AND adenocarcinoma[ti]	
6	Adenocarcinoma of Lung[mh] AND drug therapy[sh]	
7	#1 OR #2 OR #3 OR #4 OR #5 OR #6	
8	advanced[tiab] OR metasta*[tw] OR stage III*[tiab] OR stage IV[tiab]	
9	2L[tiab] OR second-line[tiab] OR late* line[tiab] OR salvage[tiab] OR palliative[tiab] OR progressed[tiab] OR relapsed[tiab] OR Salvage Therapy[mh]	
10	#7 AND #8 AND #9	
11	Platinum[mh] OR Platinum Compounds[mh] OR Cisplatin[mh] OR Organoplatinum Compounds[mh] OR Carboplatin[mh] OR platin*[tiab] OR cisplatin[tiab] OR cis-platin[tiab] OR carboplatin[tiab] OR chemotherapy[ti]	Søgetermer for platin og immunterapi
12	#10 AND #11	
13	immunotherapy[ti] OR prior immunotherapy[tiab]	
14	checkpoint[ti] AND inhibit*[ti]	
15	PD-L1[ti] OR PDL1[ti] OR PD-1[ti] OR PD1[ti]	

16	programmed cell death[ti] OR programmed death ligand[ti]	
17	#13 OR #14 OR #15 OR #16	
18	#12 AND #17	
19	Observational Study[pt] OR Multicenter Study[pt] OR Cohort Studies[mh] OR Prospective Studies[mh] OR Retrospective Studies[mh]	Søgefilter til identifikation af observationelle studier
20	(observational[tiab] OR cohort[tiab] OR prospective[tiab] OR retrospective[tiab]) AND (study[tiab] OR analysis[tiab])	
21	Registries[mh] OR registry[tiab] OR database[tiab] OR nation-wide[tiab] OR nationwide[tiab] OR real-world[tiab]	
22	#19 OR #20 OR #21	
23	**#18 AND #22**	

Søgestreng til CENTRAL:
Ingen søgestreng, da CENTRAL hovedsageligt består af randomiserede studier.

Platinbaseret kemoterapi i første linje – RCT.

Søgestreng til PubMed:

#	Søgetermer	Kommentar
1	NSCLC[ti]	Søgetermer for population
2	(non-small-cell-lung[ti] OR nonsmall-cell-lung[ti]) AND (cancer*[ti] OR carcinoma[ti] OR adenocarcinoma[ti])	
3	Carcinoma, Non-Small-Cell Lung[mh] AND drug therapy[sh]	
4	nonsquamous[tiab] OR non-squamous[tiab] OR adenocarcinoma*[tw]	
5	(#1 OR #2 OR #3) AND #4	
6	(nonsquamous[ti] OR non-squamous[ti]) AND lung[ti] AND (cancer[ti] OR carcinoma[ti] OR adenocarcinoma[ti])	
7	lung[ti] AND adenocarcinoma[ti]	

8	Adenocarcinoma of Lung[mh] AND drug therapy[sh]	
9	#5 OR #6 OR #7 OR #8	
10	advanced[tiab] OR metasta*[tw] OR stage* III*[tiab] OR stage* IV[tiab] OR unresectable[tiab] OR inoperable[tiab] OR aNSCLC[tiab] OR mNSCLC[tiab]	
11	#9 AND #10	
12	Platinum[mh] OR Platinum Compounds[mh] OR Cisplatin[mh] OR Organoplatinum Compounds[mh] OR Carboplatin[mh] OR platin*[ti] OR cisplatin[ti] OR cis-platin[ti] OR carboplatin[ti]	Søgetermer for platin
13	#11 AND #12	
14	("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])	Søgefilter til identifikation af RCT
15	#13 AND #14	
16	Case Reports[pt] OR Comment[pt] OR Editorial[pt] OR Guideline[pt] OR Letter[pt] OR News[pt] OR Review[pt] OR case report[ti]	Publikationstyper til eksklusion
17	#15 NOT #16	
18	resectable[ti] OR resected[ti] OR neoadjuvant[ti] OR adjuvant[ti]	Eksklusion af termer for irrelevant behandling/population
19	2L[ti] OR second-line[ti] OR late* line[ti] OR salvage[ti] OR palliative[ti] OR Salvage Therapy[mh]	
20	pre-treated[tiab] OR pretreated[tiab] OR previously treated[tiab] OR heavily treated[tiab]	
21	#18 OR #19 OR #20	
22	#17 NOT #21	
23	**1st[ti] OR 1L[tiab] OR first-line[tiab] OR firstline[tiab] frontline[tiab] OR front-line[tiab] OR induction[tiab]**	**Termer for første linje behandling**
24	naive[tiab] OR untreated[tiab] OR non-treated[tiab] OR nontreated[tiab]	

25	#23 OR #24	
26	**#22 AND #25**	

Søgestreng til CENTRAL:

#	Søgetermer	Kommentar
#1	nsclc:ti	Søgetermer for population
#2	((non-small-cell-lung or nonsmall-cell-lung) and (cancer or carcinoma or adenocarcinoma)):ti	
#3	[mh "Carcinoma, Non-Small-Cell Lung"] or "non small cell lung cancer":kw	
#4	(nonsquamous or "non squamous" or adenocarcinoma):ti,ab	
#5	(#1 or #2 or #3) and #4	
#6	[mh "Adenocarcinoma of Lung"] or (lung next adenocarcinoma):ti,kw	
#7	#5 or #6	
#8	(advanced or metasta* or stage* next III* or stage* next IV or unresectable or inoperable or aNSCLC or mNSCLC):ti,ab,kw	
#9	#7 and #8	
#10	(organoplatinum or carboplatin or platin* or cisplatin or cis-platin):ti,kw	Søgetermer for intervention
#11	#9 and #10	
#12	(resectable or resected or neoadjuvant or adjuvant or 2L or second-line or late* next line or salvage or palliative):ti	Eksklusion af irrelevant behandling/population
#13	(pre-treated or pretreated or previously next treated or heavily next treated):ti,ab	
#14	#12 or #13	
#15	#11 not #14	

#16	(1st or 1L or first-line or firstline or frontline or front-line or induction or naive or untreated or non-treated or nontreated):ti,ab	Termer for første linje behandling
#17	#15 and #16	
#18	("conference abstract" or review):pt	Publikationstyper til eksklusion
#19	(abstract or review):ti	
#20	NCT*:au	
#21	(clinicaltrials.gov or trialsearch):so	
#22	(abstract or conference or meeting or proceeding*):so	
#23	annual meeting:ab	
#24	{or #18-#23}	
#25	#17 not #24	
#26	**#25 not pubmed:an**	**Eksklusion af referencer, der kommer fra PubMed**

Klinisk spørgsmål 4:

Docetaxel eller pemetrexed i anden linje - RCT

Søgestreng til PubMed:

#	Søgetermer	Kommentar
1	NSCLC[ti]	Søgetermer for population
2	(non-small-cell-lung[ti] OR nonsmall-cell-lung[ti]) AND (cancer*[ti] OR carcinoma[ti] OR adenocarcinoma[ti])	
3	Carcinoma, Non-Small-Cell Lung[mh] AND drug therapy[sh]	
4	nonsquamous[tiab] OR non-squamous[tiab] OR adenocarcinoma*[tw]	
5	(#1 OR #2 OR #3) AND #4	

6	(nonsquamous[ti] OR non-squamous[ti]) AND lung[ti] AND (cancer[ti] OR carcinoma[ti] OR adenocarcinoma[ti])	
7	lung[ti] AND adenocarcinoma[ti]	
8	Adenocarcinoma of Lung[mh] AND drug therapy[sh]	
9	#5 OR #6 OR #7 OR #8	
10	advanced[tiab] OR metasta*[tw] OR stage* III*[tiab] OR stage* IV[tiab] OR unresectable[tiab] OR inoperable[tiab] OR aNSCLC[tiab] OR mNSCLC[tiab]	
11	#9 AND #10	
12	Docetaxel[mh] OR docetaxel[tiab] OR Pemetrexed[mh] OR pemetrexed[tiab]	Søgetermer for intervention
13	#11 AND #12	
14	("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])	Søgefilter til identifikation af RCT
15	#13 AND #14	
16	Case Reports[pt] OR Comment[pt] OR Editorial[pt] OR Guideline[pt] OR Letter[pt] OR News[pt] OR Review[pt] OR case report[ti]	Publikationstyper til eksklusion
17	#15 NOT #16	
18	treatment-naive[tiab] OR untreated[tiab] OR non-treated[tiab] OR nontreated[tiab]	Eksklusion af irrelevant behandling/population
19	resectable[ti] OR resected[ti] OR neoadjuvant[ti] OR adjuvant[ti]	
20	#18 OR #19	
21	#17 NOT #20	
22	2L[tiab] OR second-line[tiab] OR salvage[tiab] OR palliative[tiab] OR Salvage Therapy[mh]	Termer for anden linje behandling
23	pre-treated[tiab] OR pretreated[tiab] OR previously treated[tiab]	

24	#22 OR #23	
25	**#21 AND #24**	

Søgestreng til CENTRAL:

#	Søgetermer	Kommentar
#1	nsclc:ti	Termer for population
#2	((non-small-cell-lung or nonsmall-cell-lung) and (cancer or carcinoma or adenocarcinoma)):ti	
#3	[mh "Carcinoma, Non-Small-Cell Lung"] or "non small cell lung cancer":kw	
#4	(nonsquamous or "non squamous" or adenocarcinoma):ti,ab	
#5	(#1 or #2 or #3) and #4	
#6	[mh "Adenocarcinoma of Lung"] or (lung next adenocarcinoma):ti,kw	
#7	#5 or #6	
#8	(advanced or metasta* or stage* next III* or stage* next IV or unresectable or inoperable or aNSCLC or mNSCLC):ti,ab,kw	
#9	#7 and #8	
#10	(docetaxel or pemetrexed):ti,ab,kw	Termer for intervention
#11	#9 and #10	
#12	(treatment-naive or untreated or non-treated or nontreated):ti,ab	Eksklusion af irrelevant behandling/population
#13	(resectable or resected or neoadjuvant or adjuvant):ti,ab,kw	
#14	#11 not (#12 or #13)	
#15	(2L or second-line or salvage or palliative):ti,ab,kw	Termer for anden linje behandling
#16	(pre-treated or pretreated or previously next treated):ti,ab	
#17	#14 and (#15 or #16)	

#18	("conference abstract" or review):pt	Publikationstyper til eksklusion
#19	(abstract or review):ti	
#20	NCT*:au	
#21	(clinicaltrials.gov or trialsearch):so	
#22	(abstract or conference or meeting or proceeding*):so	
#23	annual meeting:ab	
#24	{or #18-#23}	
#25	#17 not #24	
#26	**#25 not pubmed:an**	**Eksklusion af referencer, der kommer fra PubMed**