Medicinrådet

Baggrund for Medicinrådets anbefaling vedrørende dacomitinib som mulig standardbehandling til uhelbredelig ikke-småcellet lungekræft med aktiverende EGFR-mutation

Versionsnr.: 1.0

Medicinrådet

Om Medicinrådet

Medicinrådet er et uafhængigt råd, som udarbejder anbefalinger og vejledninger om lægemidler til de fem regioner.

Medicinrådet vurderer, om nye lægemidler og indikationsudvidelser kan anbefales som mulig standardbehandling og udarbejder fælles regionale behandlingsvejledninger.

Nye lægemidler vurderes i forhold til effekt, eksisterende behandling og pris. Det skal give lavere priser og lægemidler, der er til størst mulig gavn for patienterne.

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

Om anbefalingen

Anbefalingen er Medicinrådets vurdering af, om lægemidlets samlede pris er rimelig, når man sammenligner den med lægemidlets værdi for patienterne.

Lægemidlet vurderes efter Håndbog for Medicinrådets proces og metode vedr. nye lægemidler og indikationsudvidelser – version 2. Se Medicinrådets metodehåndbog for yderligere information.

Dokumentoplysninger	
Godkendelsesdato	22. oktober 2019
Ikrafttrædelsesdato	23. oktober 2019
Dokumentnummer	59922
Versionsnummer	1.0

Medicinrådet, Dampfærgevej 27-29, 3. th., 2100 København Ø
www.medicinraadet.dk
Sprog: dansk
Format: pdf
Udgivet af Medicinrådet, 23. oktober 2019

Medicinrådet

Indhold

1 Lægemiddelinformationer

Lægemidlets oplysninger	
Handelsnavn	Vizimpro
Generisk navn	Dacomitinib
Firma	Pfizer
ATC-kode	L01XE47
Virkningsmekanisme	2.-generations epidermal vækstfaktorreceptor (EGFR) tyrosinkinasehæmmer (TKI)
Administration/dosis	Tablet 45 mg én gang dagligt indtil progression eller intolerable bivirkninger. Tabletter fås som 45, 30 og 15 mg.
EMA-indikation	Førstelinjebehandling af voksne patienter med lokalt fremskreden eller metastatisk ikke-småcellet lungecancer (NSCLC) med aktiverende epidermal vækstfaktorreceptor (EGFR)-mutationer.

2 Medicinrådets anbefaling

Medicinrådet **anbefaler ikke** dacomitinib som mulig standardbehandling i første linje til patienter med ikke-småcellet lungekræft og aktiverende Epidermal Growth Factor Receptor (EGFR) mutationer.

Medicinrådet anbefaler ikke lægemidlet, da det har en negativ værdi sammenlignet med osimertinib.

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

Hvilken klinisk merværdi har dacomitinib til patienter med uhelbredelig ikke-småcellet lungekræft med aktiverende EGFR-mutation sammenlignet med osimertinib?

3 Formål

Formålet med Baggrund for Medicinrådets anbefaling vedrørende dacomitinib som mulig standardbehandling til uhelbredelig ikke-småcellet lungekræft med aktiverende EGFR-mutation er at skabe gennemsigtighed om det materiale, der ligger til grund for Medicinrådets anbefaling.

4 Baggrund

Omtrent 4.600 danskere diagnosticeres årligt med lungekræft. Heraf har ca. 140 en aktiverende Epidermal Growth Factor Receptor (EGFR) mutation. Flertallet af disse patienter får progression, og metastaser i centralnervesystemet (CNS) optræder hyppigt.

Yderligere baggrundsinformation findes i "Medicinrådet vurdering af kliniske merværdi af dacomitinib til uhelbredelig ikke-småcellet lungekræft med aktiverende EGFR-mutation" (bilag 4).

4.1 Sagsbehandlingstid og proces for Medicinrådets vurdering

Medicinrådet modtog den foreløbige ansøgning fra Pfizer den 9. januar 2019. Protokollen for vurdering af dacomitinib til uhelbredelig ikke-småcellet lungekræft med aktiverende EGFR-mutation blev godkendt af Medicinrådet den 15. maj 2019, og sekretariatet modtog den endelige ansøgning den 12. juli 2019.

Vurdering af klinisk merværdi blev godkendt af Rådet den 29. september 2019.

Den samlede sagsbehandlingstid var 14 uger og 5 dage fra modtagelse af den kliniske del af ansøgningen.

5 Medicinrådets vurdering af samlet værdi

Medicinrådet vurderer, at dacomitinib til patienter med uhelbredelig ikke-småcellet lungekræft med aktiverende EGFR-mutation giver en **negativ værdi** sammenlignet med osimertinib. Evidensens kvalitet vurderes at være meget lav.

6 Høring

Ansøger har den 1, oktober 2019 indgivet et høringssvar, som ikke opponerer mod kategoriseringen af den kliniske merværdi.

Høringssvaret er vedlagt som bilag 1.

7 Resumé af økonomisk beslutningsgrundlag

Da dacomitinib er vurderet til at give en negativ klinisk merværdi**,** har Amgros **ikke vurderet** forholdet mellem de inkrementelle omkostninger og den kliniske merværdi.

8 Overvejelser omkring alvorlighed/forsigtighed

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

9 Sammensætning af fagudvalg og kontaktinformation til Medicinrådet

Medicinrådets fagudvalg vedrørende lungekræft

Formand	**Indstillet af**
Christa Haugaard Nyhus Overlæge	Lægevidenskabelige Selskaber
Medlemmer	**Udpeget af**
Kan ikke opfylde Medicinrådets habilitetskrav	Region Nordjylland
Halla Skuladottir Overlæge, dr.med.	Region Midtjylland
Stefan Starup Jeppesen Overlæge, ph.d	Region Syddanmark
Jeanette Haar Ehlers Overlæge	Region Sjælland
Lotte Engell-Nørregård Afdelingslæge, ph.d.	Region Hovedstaden
Henrik Hager Overlæge	Inviteret af formanden
Nille Behrendt Overlæge	Dansk Patologiselskab
Peder Fabricius Ledende overlæge	Dansk Selskab for Lungemedicin
Nina Hannover Bjarnason Overlæge, dr.med.	Dansk Selskab for Klinisk Farmakologi
Annie Lorenzen Klinisk farmaceut	Dansk Selskab for Sygehusapoteksledelse
Finn Klausen Patient/patientrepræsentant	Danske Patienter
Lisbeth Søbæk Hansen Patient/patientrepræsentant	Danske Patienter

Medicinrådets sekretariat

Medicinrådet Dampfærgevej 27-29, 3. th. 2100 København Ø + 45 70 10 36 00 medicinraadet@medicinraadet.dk
Sekretariatets arbejdsgruppe: Jane Skov (projekt- og metodeansvarlig) Hjalte Holm Andersen (projektdeltager) Vibe Charlotte Nylander (projektdeltager) Charlotte Wulff Johansen (fagudvalgskoordinator) Jan Odgaard-Jensen (biostatistiker) Tenna Bekker (teamleder)

10 Versionslog

Version	Dato	Ændring
1.0	22. oktober 2019	Godkendt af Medicinrådet.

11 Bilag

Bilagsliste:

- Høringssvar fra ansøger
- Medicinrådets protokol for vurdering af dacomitinib til behandling af ikke-småcellet lungekræft med aktiverende EGFR-mutation – version 1.0
- Ansøgers endelige ansøgning
- Medicinrådets vurdering af dacomitinib til behandling af uhelbredelig ikke-småcellet lungekræft med aktiverende EGFR- mutation – version 1.0

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Pfizer Danmark

Til Medicinrådet

Ballerup den 1. oktober 2019

Vi takker for det tilsendte udkast til Medicinrådets vurdering af klinisk merværdi af dacomitinib til uhelbredelig ikke-småcellet lungekræft med aktiverende EGFR-mutation.

Vi har ikke noget at tilføje på nuværende tidspunkt, men anmoder om, at Medicinrådet vil revurdere deres beslutning, hvis data på fx Overall Survival (OS) og/eller bivirkninger bliver publiceret. Vi erkender, at Medicinrådet ikke medtager abstracts i deres beslutninger, men henleder opmærksomheden på, at der i slutningen af september 2019 blev præsenteret overall survival (OS) data på osimertinib på ESMO konferencen, der i en indirekte sammenligning med dacomitinib viser, at der ikke er forskel på OS med reference til mindste kliniske relevante forskel defineret af fagudvalget i protokollen på dacomitinib. På ESMO konferencen blev der ligeledes præsenteret bivirkningsdata på osimertinib, der viser en øget incidens af grad 3/4 bivirkninger ift. til tidligere vist i FLAURA studiet.

Dacomitinib repræsenterer et vigtigt behandlingsalternativ til osimertinib, der med den rette behandlingstilgang og dosis-modifikation kan reducere bivirkninger uden at gå på kompromis med effekten, som det er beskrevet i artiklen "*Management of common adverse events related to first-line dacomitinib use in EGFR mutation-positive non-small-cell lung cancer: a pooled safety analysis"* af Zhou et al.

https://www-futuremedicine-com.eu1.proxy.openathens.net/doi/full/10.2217/fon-2018-0944?url_ver=Z39.88-2003&rfr_id=ori%3Arid%3Acrossref.org&rfr_dat=cr_pub%3Dpubmed&

På vegne af Pfizer A/S,
Trine Pilgaard
Senior Market Access Manager

Medicinrådet

Medicinrådets protokol for vurdering af dacomitinib til behandling af ikke-småcellet lungekræft med aktiverende EGFR-mutation

Versionsnr. 1.0

Medicinrådet

Om Medicinrådet

Medicinrådet er et uafhængigt råd, som udarbejder anbefalinger og vejledninger om lægemidler til de fem regioner.

Medicinrådet vurderer, om nye lægemidler og nye indikationer kan anbefales som mulig standardbehandling og udarbejder fælles regionale behandlingsvejledninger.

Nye lægemidler vurderes i forhold til effekt, eksisterende behandling og pris. Det skal give lavere priser og lægemidler, der er til størst mulig gavn for patienterne.

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

Om protokollen

Protokollen er grundlaget for Medicinrådets vurdering af et nyt lægemiddel. Den indeholder et eller flere kliniske spørgsmål, som ansøger skal besvare i den endelige ansøgning, og som Medicinrådet skal basere sin vurdering på.

Se Medicinrådets metodehåndbog for yderligere information.

Dokumentoplysninger	
Godkendelsesdato	15.05.2019
Ikrafttrædelsesdato	15.05.2019
Dokumentnummer	49103
Versionsnummer	1.0

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

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

1 Lægemiddelinformationer

Lægemidlets oplysninger	
Handelsnavn	Vizimpro
Generisk navn	Dacomitinib
Firma	Pfizer
ATC-kode	L01XE47
Virkningsmekanisme	2. generations epidermal vækstfaktorreceptor (EGFR)-tyrosinkinasehæmmer (TKI)
Administration/dosis	Tablet 45 mg én gang dagligt indtil progression eller intolerable bivirkninger. Tabletter fås som 45, 30 og 15 mg.
Forventet EMA-indikation	Førstelinjebehandling af voksne patienter med lokalt fremskreden eller metastatisk ikke-småcellet lungecancer (NSCLC) med aktiverende epidermal vækstfaktorreceptor (EGFR)-mutationer.

2 Forkortelser

ARR:	Absolut risikoreduktion
CI:	Konfidensinterval (Confidence Interval)
CNS:	Centralnervesystemet
CHMP	*Committee for Medicinal Products for Human Use*
DOR:	Responsvarighed (*Duration Of Response*)
EGFR:	Epidermal vækstfaktorreceptor (*Epidermal Growth Factor Receptor*)
EMA:	Det Europæiske Lægemiddelagentur (*European Medicines Agency)*
EORTC – CTAE:	*European Organisation for Research and Treatment of Cancer – Common Terminology Criteria for Adverse Events*
EORTC QLQ-C30:	*European Organisation for Research and Treatment of Cancer Quality-of-life Questionnaire-Core 30*
EPAR:	*European public assessment report*
GRADE:	System til evidensvurdering (*Grading of Recommendations Assessment, Development and Evaluation*)
HR:	*Hazard Ratio*
IALSC:	*International Association for the Study of Lung Cancer*
ITT:	*Intention to treat*
NSCLC:	Ikke små-cellet lungekræft (*Non-small-cell lung cancer*)
OR:	*Odds Ratio*
ORR:	Objektiv responsrate / *overall response rate*
OS:	Overlevelse (O*verall survival)*
PFS:	Progressionsfri overlevelse (P*rogression-free survival)*
PICO:	*Population, Intervention, Comparator, Outcome*
RECIST	*Response Evaluation Criteria in Solid Tumors*
RR:	Relativ Risiko
SAE:	Alvorlig uønsket hændelse (*Serious Adverse Event*)
SMD:	*Standardized Mean Difference*
TKI:	Tyrosinkinasehæmmer (*Tyrosine kinase inhibitor)*

3 Formål

Protokollen har til formål at definere de kliniske spørgsmål, der ønskes belyst i vurderingen af dacomitinib som mulig standardbehandling i første linje af patienter med lokalt fremskreden eller metastatisk ikke-småcellet lungekræft (NSCLC) med aktiverende epidermal vækstfaktorreceptor (EGFR)-mutationer. I protokollen angives en definition af populationer, komparator og effektmål, der skal præsenteres i den endelige ansøgning, samt de metoder der ønskes anvendt til den komparative analyse. Arbejdet med protokollen er igangsat på baggrund af den foreløbige ansøgning vedrørende dacomitinib modtaget d. 09/01-2019.

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

4 Baggrund

I 2017 blev 4.856 danskere diagnosticeret med lungekræft [1], og dermed er lungekræft en af de hyppigst forekommende kræftsygdomme i Danmark [2]. Lungekræft inddeles i fire stadier (I-IV) afhængigt af udbredelsesgrad [3]. Stadieinddelingen foretages jævnfør *Tumor, Node, Metastasis* (TNM)-klassifikation for lungekræft. De epidemiologiske data i dette afsnit stammer fra Tumor Node Metastasis (TNM) version 7 klassifikationen. TNM 8 efterfølgende er indført i Danmark [3]. Stadie III betyder, at tumor enten har en vis størrelse, indvækst i nærliggende struktur eller spredning til regionale lymfeknuder. Metastatisk lungekræft betegnes som stadie IV, og er uhelbredelig. Nogle patienter med NSCLC i stadie III betragtes også som havende uhelbredelig lungekræft og behandles som patienter i stadie IV.

I 2017 var 417 danskere med lungekræft registreret med stadium IIIB sygdom og 2.098 med stadium IV sygdom [1]. Ca. 25 % af patienter med stadium IIIB/IV sygdom har tumor af planocellulær histologi og ca. 75 % af ikke-planocellulær histologi. Langt de fleste tumorer af ikke-planocellulær histologi er adenokarcinomer, og denne patologitype er også samlet set den hyppigste (42% af alle lungekræfttilfælde) [1]. I 2017 var 1-års overlevelsesraten for patienter med lungekræft stadie IIIB på 51 % og for stadie IV på 27,7 %, mens den observerede overlevelse for patienter diagnosticeret 5 år forinden var 6,5 % ved stadie IIIB og 2,5 % ved stadie IV [1].

Der kendes flere biomarkører for NSCLC, hvoraf enkelte har betydning for behandlingen. En undergruppe af disse er aktiverende EGFR-mutationer, der findes hos ca. 8 % af de testede patienter med adenokarcinomer [1,4–6]. Ifølge Dansk Lunge Cancer Gruppe årsrapport var der registreret 161 patienter i Danmark i 2017, som havde en aktiverende EGFR-mutation. Det reelle antal af lungekræftpatienter med en aktiverende EGFR-mutation er formodentlig omkring 200, da EGFR-status ikke var registreret for 18,7 % af patienter med adenokarcinom, hvor mutationsfrekvensen er højest [1].

Ca. 1/3 af patienter med NSCLC og en aktiverende EGFR-mutation vil i deres sygdomsforløb progrediere med metastaser til centralnervesystemet (CNS) i deres sygdomsforløb [7,8]. Patienter med hjernemetastaser oplever betydelig morbiditet og reduceret livskvalitet, ofte med neurologiske symptomer og kognitive ændringer.

4.1 Nuværende behandling

For uhelbredelig NSCLC er behandlingsmålet symptomlindring og levetidsforlængelse. Behandlingen er systemisk i form af kemoterapi, immunterapi eller targeteret behandling [1,6,9]. Patienter med en aktiverende EGFR-mutation får i første linje targeteret behandling, i form af en EGFR-tyrosinkinasehæmmer (EGFR-TKI).

Osimertinib blev d. 10.04.2019, anbefalet af Medicinrådet som mulig standardbehandling i første linje til patienter med uhelbredelig NSCLC og aktiverende EGFR-mutation. Gefitinib, afatinib og erlotinib er tidligere ligestillet til førstelinjebehandling. Fagudvalget vurderer, at man i dansk klinisk praksis fremover fortrinsvist vil anvende osimertinib grundet dets større effekt [10].

Fagudvalget vurderer, at omkring 140 patienter (ud af estimatet på ca. 200 patienter, som har en EGFR-aktiverende mutation) årligt, er kandidater til denne type behandling [1]. Behandlingen gives indtil sygdomsprogression eller intolerable bivirkninger. Patienter, der progredierer under førstelinjebehandling, tilbydes typisk behandling jævnfør retningslinjerne for ikke-planocellulær NSCLC [13].

Den mediane progressionsfrie overlevelse ved førstelinjebehandling med osimertinib er ca. 19 måneder [10]. Der mangler modne data for den samlede mediane overlevelse ved førstelinjebehandling med osimertinib.

4.2 Dacomitinib

Dacomitinib er en 2. generations EGFR-TKI, der virker gennem hæmning af EGFR-signalering. Ved at blokere EGFR mindsker dacomitinib tumors vækst samt spredning i NSCLC med EGFR-aktiverende mutationer (exon 19 deletion eller exon 21 L858R substitutionsmutation).

Dacomitinib opnåede *'positive opinion'* fra det Europæiske Lægemiddelagenturs (EMA) *Committee for Medicinal Products for Human Use* (CHMP) d. 31-01/2019, for indikationen: førstelinjebehandling af voksne patienter med lokalt fremskreden eller metastatisk NSCLC med aktiverende epidermal vækstfaktorreceptor (EGFR)-mutationer.

Dacomitinib administreres peroralt af patienten selv. Standarddosis er 45 mg én gang dagligt.

5 Kliniske spørgsmål

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

5.1 Klinisk spørgsmål 1

Hvilken klinisk merværdi tilbyder dacomitinib til patienter med NSCLC-stadie IIIB-IV med aktiverende EGFR-mutation sammenlignet med osimertinib?

Population

Voksne patienter med lokalt fremskreden eller metastatisk NSCLC (stadie IIIB-IV) og aktiverende EGFR-mutation, som ikke tidligere har modtaget systemisk behandling for deres fremskredne sygdom (1. linje).

Intervention

Dacomitinib tablet 45 mg én gang dagligt.

Komparator

Osimertinib som tablet 80 mg én dagligt. Osimertinib er valgt som komparator da fagudvalget vurderer, at det vil være den foretrukne førstelinjebehandling efter Medicinrådets anbefaling d. 10.04.2019.

Effektmål

Se tabel 1.

5.2 Valg af effektmål

Tabel 1 opsummerer de valgte effektmål, deres vigtighed, den retningsgivende mindste klinisk relevante forskel, en evt. justeret mindste klinisk relevant forskel og kategori. I forbindelse med justeringen af Medicinrådets metodehåndbog, som trådte i kraft pr. 1. januar 2019, vil absolutte effektforskelle fremover blive kategoriseret ud fra konfidensintervaller (tabel 3, side 29 i metodehåndbogen). Det er derfor nødvendigt at foretage en justering af den mindste klinisk relevante forskel. Den *retningsgivende* mindste klinisk relevante forskel er fremkommet på samme måde som under den gamle metode og afspejler den mindste forskel, som fagudvalget vurderer, er klinisk relevant. Når lægemidlets værdi for det enkelte effektmål skal kategoriseres, vil grænsen for konfidensintervallet blive sammenholdt med den *justerede* mindste klinisk relevante forskel. Den justerede værdi, vil være det halve af den retningsgivende værdi, i de tilfælde hvor et konfidensinterval forventes at være tilgængeligt. Rationalet for denne tilgang er at sikre, at alle værdier i konfidensintervallet ligger tættere på den *retningsgivende MKRF* end på 'ingen forskel' (absolut effektforskel på 0). Eller sagt på en anden måde – alle de sandsynlige værdier for effekten er tættere på en klinisk relevant effekt end på 'ingen effekt'.

For alle effektmål ønskes både absolutte og relative værdier, jf. ansøgningsskemaet. Der ønskes både punktestimater og konfidensintervaller (for de absolutte værdier ønskes dog ikke konfidensintervaller, hvor metoderne til beregning af disse ikke er veldefinerede). For de absolutte værdier, hvor der kan beregnes konfidensintervaller efter veldefinerede metoder, vurderes den kliniske relevans (værdi), jf. tabel 3 i Medicinrådets håndbog for vurdering af nye lægemidler. For de relative værdier vurderes den kliniske relevans (værdi), jf. væsentlighedskriterierne beskrevet i Medicinrådets håndbog. De relative effektestimater skal angives i relativ risiko (RR) eller hazard ratio (HR). Hvis studierne resulterer i en odds ratio (OR), skal denne transformeres til relativ risiko, jf. appendiks 2 i Medicinrådets håndbog. Det skal begrundes i ansøgningen, hvis der afviges fra de ønskede effektmål.

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

Effektmål*	**Vigtighed**	**Kategori**	**Måleenhed**	**Retningsgivende mindste klinisk relevante forskel**	**Justeret mindste klinisk relevante forskel**
Overlevelse	Kritisk	Overlevelse	Median forskel og andel patienter	3 måneder *eller* 5 % ARR efter 12 måneder	*Ikke relevant og* ≥ 2,5 %-point
CNS-progression	Kritisk	Alvorlige symptomer og bivirkninger	Median forskel	3 måneder *eller* 5 % ARR efter 12 måneder	*Ikke relevant og* ≥ 2,5 %-point
Bivirkninger	Kritisk	Alvorlige symptomer og bivirkninger	Andel patienter der ophører behandlingen pga. bivirkninger.	5 % ARR	≥ 2,5 %-point.
			Andel patienter, der oplever en eller flere grad 3-4 bivirkninger.	5 % ARR	≥ 2,5 %-point
			Gennemgang af bivirkningsprofil.	Narrativ vurdering.	*Ikke relevant.*
Progressionsfri overlevelse	Vigtig	Alvorlige symptomer og bivirkninger	Median forskel (blindet PFS-evaluering foretrækkes)	3 måneder *eller* 5 % ARR efter 12 måneder	*Ikke relevant og* ≥ 2,5 %-point
Livskvalitet EORTC QLQ-C30	Vigtig	Helbredsrelateret livskvalitet	Forskel i gennemsnitlig ændring i EORTC-QLQ-C30	10 point	≥ 5 point
Objektiv responsrate	Mindre vigtig	Alvorlige symptomer og bivirkninger			

For alle effektmål, både for intervention og komparator, ønskes data med længst mulig opfølgningstid. For bivirkninger ønskes den længst mulig opfølgningstid, også hvis der foreligger data, som rækker ud over perioden af de kliniske studier.

Kritiske effektmål

Overlevelse (OS)

Da lokal fremskredet og metastatisk NSCLC er uhelbredelig, vurderes forbedret samlet overlevelse med mindst mulig toksicitet som afgørende. Derfor vurderer fagudvalget, at OS er et kritisk effektmål. Der findes mange relevante effektmål for overlevelse, heriblandt 1-års overlevelse, men i denne sammenhæng er median OS vurderet som det mest relevante effektmål.
Der mangler data på den samlede mediane overlevelse ved anvendelse af osimertinib i første linje [10]. Ved behandling med afatinib, erlotinib eller gefitinib i første linje er den mediane overlevelse ca. 25 måneder [11]. Fagudvalget vurderer, at 3 måneder er den mindste klinisk relevante forskel. Såfremt der ikke er data med tilstrækkelig opfølgningstid til at give et sikkert estimat, anser fagudvalget en ARR på 5 % for 1 års overlevelse som klinisk relevant.

CNS-progression

Da EGFR-positiv NSCLC metastaserer til CNS hos 1/3 af patienterne hvilket medfører betydelig morbiditet og reduceret livskvalitet, anser fagudvalget CNS-progression som et kritisk effektmål.
Fagudvalget vurderer, at 3 måneder er den mindste klinisk relevante forskel. Hvis median data endnu ikke er modne, anser fagudvalget en ARR på 5 % for 1 års data som klinisk relevant.

Bivirkninger

Forekomst af alvorlige bivirkninger grad 3-4 er et udtryk for alvorlig toksicitet af lægemidlet [12]. Fagudvalget finder, at ophør med en effektiv behandling grundet bivirkninger er kritisk for patienterne. På den baggrund vurderes det, at bivirkninger er et kritisk effektmål. Fagudvalget ønsker data på nedenstående måleenheder.

Behandlingsophør på grund af bivirkninger
Fagudvalget ønsker en opgørelse over forskellen i andelen af patienter, som ophører behandlingen grundet bivirkninger. Fagudvalget vurderer, at en forskel på 5 %-point i andelen af patienter, der ophører behandlingen på grund af bivirkninger, er klinisk relevant.

Bivirkninger grad 3-4
Fagudvalget finder, at forskellen i andelen af patienter, som i løbet af opfølgningstiden oplever en eller flere bivirkninger af grad 3 eller 4, er relevant for vurderingen. Bivirkninger af grad 3-4 er defineret i henhold til National Cancer Institute CTCAE version 4.03 [13].

Fagudvalget vurderer, at en forskel på 5 %-point i andelen af patienter, der får bivirkninger af grad 3-4, er klinisk relevant.

Kvalitativ gennemgang af bivirkningsprofil
Fagudvalget ønsker en gennemgang af osimertinib og dacomitinib bivirkningsprofiler med henblik på at vurdere bivirkningernes type, håndterbarhed og reversibilitet. Der ønskes desuden en liste med alle bivirkninger som fører til behandlingsophør, og deres frekvens i både komparator- og interventionsgruppen. Der skal specielt fokuseres på de bivirkninger, som adskiller sig mellem de to grupper.

Vigtige effektmål

Progressionsfri overlevelse (PFS) bliver anvendt til at vurdere, hvor lang tid der går, inden patienternes sygdom udvikler sig. PFS er defineret som tiden fra randomisering til første dokumentation af progression i henhold til Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 [14] eller dødsfald.

Patienter tåler generelt behandling med en EGFR-TKI godt i sammenligning med kemoterapi. Behandling efter progression består i skrivende stund for ca. halvdelen af patienterne typisk af platinbaseret kemoterapi. Fagudvalget vurderer derfor, at det har stor betydning for patienterne at forblive i behandling med en EGFR-TKI længst muligt, pga. den favorable bivirkningsprofil. Derfor vurderer fagudvalget, at PFS er et vigtigt effektmål.

Ved førstelinjebehandling med osimertinib er patienterne progressionsfri i ca. 19 måneder (median PFS) [10]. Baseret på dette finder fagudvalget, at en forskel på mindst 3 måneder i median PFS mellem osimertinib og dacomitinib er klinisk relevant.

Livskvalitet

Livskvalitet kan for NSCLC patienter måles med flere forskellige instrumenter. I dette tilfælde vil vurdering af livskvalitet blive baseret på følgende: European Organisation for Research and Treatment of Cancer Quality-of-life Questionnaire-Core 30 (EORTC QLQ-C30) [15,16].

EORTC QLQ-C30 består af 30 spørgsmål omhandlende funktionsniveau, symptomer samt selvevalueret globalt helbred og livskvalitet. Data fra hvert domæne konverteres til en scoringsskala fra 0-100 [17]. Fagudvalget vil i deres vurdering tage udgangspunkt i resultater for global livskvalitet. Den mindste klinisk relevante forskel baserer sig på en lille ændring, defineret som 5-10 point på den globale skala [18]. En moderat ændring er 10-20 point, og en stor ændring er > 20 point. Fagudvalget har defineret den mindste klinisk relevante forskel som ≥ 10 point, da dette vil overstige mindstegrænsen for en lille ændring.

Mindre vigtige effektmål

Objektiv responsrate eller 'overall response rate' (ORR)

ORR anvendes til belysning af behandlingsrespons. 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). Såfremt der opnås et godt respons på behandlingen, vil patientens symptomer på kræftsygdommen aftage i en periode og således medføre bedre livskvalitet. På den baggrund vurderer fagudvalget at ORR er et mindre vigtigt effektmål.

6 Litteratursøgning

Vurderingen af klinisk merværdi baseres som udgangspunkt på data fra peer-reviewed publicerede fuldtekstartikler og data fra EMAs EPAR – public assessment report(s). Data skal derudover stemme overens med protokollens beskrivelser.

Sekretariatet har ikke fundet artikler, som kan anvendes til direkte sammenligning af dacomitinib og osimertinib.

Virksomheden skal derfor søge efter studier, der kan anvendes til en indirekte sammenligning af dacomitinib og osimertinib. Det betyder, at der både skal søges efter primærstudier af dacomitinibs effekt og efter primærstudier af effekten af osimertinib. Til det formål har sekretariatet udarbejdet søgestrenge, som skal anvendes i MEDLINE (via PubMed) og CENTRAL (via Cochrane Library). Søgestrengene kan findes i bilag 1. Derudover skal EMAs European public assessment reports (EPAR) konsulteres for både det aktuelle lægemiddel og dets komparator(er).

Kriterier for udvælgelse af litteratur

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

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

Inklusions- og eksklusionskriterier: designs der ikke er randomiserede, kontrollerede studier såvel som fase-I og IIa studier ekskluderes.

7 Databehandling og analyse

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

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

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

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

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

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

For effektmål, hvor forskellige måleinstrumenter er brugt på tværs af de inkluderede studier, vil eventuelle metaanalyser blive baseret på standardized mean difference (SMD). Den estimerede SMD vil blive omregnet til den foretrukne skala for effektmålet. Til dette formål anvendes medianen af de observerede standardafvigelser i de inkluderede studier.

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

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

8 Andre overvejelser

Patienter med CNS-metastaser ved studiestart er ekskluderet fra ARCHER 1050-studie [19]. Da CNS-metastaser er hyppigt forekommende i den pågældende patientpopulation bedes ansøger redegøre for overvejelserne bag dette eksklusionskriterium. Ansøger bedes ligeledes kommentere på, om tilstedeværelse af CNS-metastaser også bør være en kontraindikation for anvendelse af dacomitinib, samt redegøre kvantitativt for eventuelle forskelle i tilkomst af CNS-metastaser mellem de to grupper i ARCHER 1050-studiet.

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10 Sammensætning af fagudvalg og kontaktinformation til Medicinrådet

Medicinrådets fagudvalg vedrørende lungekræft

Formand	**Indstillet af**
Christa Haugaard Nyhus Overlæge	Lægevidenskabelige Selskaber
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11 Versionslog

Version	Dato	Ændring
1.0	15. maj 2019	Godkendt af Medicinrådet.

12 Bilag

12.1 Bilag 1

Søgestrategi, PubMed https://www.ncbi.nlm.nih.gov/pubmed

#	Søgetermer	Kommentar
1	carcinoma, non-small-cell lung[mh]	Søgeord for indikation. De søges som MeSH termer, og som fritekst i titel og abstract
2	nsclc[tiab]	
3	nonsmall cell[tiab] or non-small cell[tiab] or squamous cell[tiab] or large cell[tiab]	
4	lung*[tiab]	
5	neoplasm* or cancer[tiab] or cancers[tiab] or carcinoma*[tiab] or adenocarcinoma*[tiab]	
6	#3 and #4 and #5	
7	adenocarcinoma of lung[mh]	
8	(adenocarcinoma[tiab]) and (lung*[tiab])	
9	#1 or #2 or #6 or #7 or #8	
10	PF 00299804[nm]	Søgeord for ansøgers lægemiddel og komparator. De søges som Supplementary Concept/Substance, og som fritekst i titel og abstract
11	dacomitinib[tiab] or vizimpro*[tiab] or PF00299804[tiab] or PF-00299804[tiab]	
12	osimertinib[nm]	
13	osimertinib[tiab] or Tagrisso*[tiab] or AZD-9291[tiab] or AZD9291[tiab]	
14	#10 or #11 or #12 or #13	
15	**#9 and #14**	**Indikation og lægemidler kombineres**
16	animals[mh] not humans[mh]	Eksklusion af (indekserede) dyreforsøg
17	#15 not #16	
18	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]	Afgrænsning til randomiserede, kontrollerede forsøg
19	**#17 and #18**	**Endeligt resultat**

Feltkoder

mh = MeSH Term

nm = Supplementary Concept/Substance (dette er en indekseret term, der pt ikke (endnu) er en MeSH term)

tiab = title/abstract, inkl. forfatterkeywords

pt = publication type

Søgestrategi, CENTRAL https://www.cochranelibrary.com/advanced-search/search-manager

#	Søgetermer	Kommentar
1	[mh "carcinoma, non-small-cell lung"]	Søgeord for indikation. De søges som MeSH termer, og som fritekst i titel og abstract **Indikation og lægemidler kombineres** Eksklusion af (indekserede) dyreforsøg Afgrænsning til randomiserede, kontrollerede forsøg
2	("non small cell lung cancer" or "large cell lung carcinoma" or "adenocarcinoma of lung" or "lung adenocarcinoma" or "squamous cell lung carcinoma"):kw	
3	nsclc:ti,ab	
4	(("non small cell" or "nonsmall cell" or "squamous cell" or "large cell") near/4 lung near/4 (cancer* or carcinoma* or neoplasm* or adenocarcinoma*)):ti,ab	
5	#1 or #2 or #3 or #4	
6	(PF00299804 or "PF 00299804" or dacomitinib or vizimpro*):ti,ab,kw	Søgeord for ansøgers lægemiddel og komparator. De søges som Supplementary Concept/Substance, og som fritekst i titel og abstract
7	(osimertinib or AZD-9291 or AZD9291 or Tagrisso*):ti,ab,kw	
8	#6 or #7	
9	**#5 and #8**	**Indikation og lægemidler kombineres**
10	("conference abstract" or review):pt	Afgrænsning (eksklusion) på publikationstype samt (en del) af de resultater, der kommer fra clinicaltrials.gov.
11	NCT*:au	
12	clinicaltrials gov:so	
13	#10 OR #11 OR #12	
14	**#9 NOT #13**	**Endeligt resultat**

Feltkoder

ti: title

ab: abstract

kw: keywords, her kontrollerede/indekserede termer fra databaserne Medline og/eller Embase

pt = publication type

Medicinrådet

Clinical application for the assessment of Dacomitinib for EGRF-positive non-small cell lung cancer

Contents

1 Basic information

TABLE 1 CONTACT INFORMATION

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TABLE 2 OVERVIEW OF THE PHARMACEUTICAL

Proprietary name	Vizimpro®
Generic name	Dacomitinib
Marketing authorisation holder in Denmark	Pfizer, Europe MA EEIG, Boulevard de la Plaine 17, 1050 Bruxelles, Belgium
ATC code	L01XE47
Pharmacotherapeutic group	Anti-neoplastic agents, protein kinase inhibitors
Active substance	Dacomitinib monohydrate
Pharmaceutical form	Tablets
Mechanism of action	Dacomitinib is a pan-human epidermal growth factor receptor (HER) (EGFR/HER1, HER2, and HER4) inhibitor, with activity against mutated EGFR with deletions in exon 19 or the L858R substitution in exon 21. Dacomitinib binds selectively and irreversibly to its HER family targets thereby providing prolonged inhibition.
Dosage regimen	The starting dose for dacomitinib is 45 mg administered orally once daily in 28-day cycles. Dacomitinib dose reductions for a maximum of 2 dose levels (30 mg and 15 mg) should be initiated for treatment-related toxicity in case of grade 3 or worse toxicity, or prolonged grade 2 adverse events lasting more than 1 cycle.
Therapeutic indication relevant for assessment (as defined by the European Medicines Agency, EMA)	Vizimpro, as monotherapy, is indicated for the first-line treatment of adult patients with locally advanced or metastatic non-small-cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) activating mutations.
Other approved therapeutic indications	None

Will dispensing be restricted to hospitals?	Yes
Combination therapy and/or co-medication	Monotherapy
Packaging – types, sizes/number of units, and concentrations	Vizimpro® is available as 15, 30 and 45 mg tablets for oral administration
Orphan drug designation	No

2 Abbreviations

AE	Adverse event
ACR	Absolute cumulative risk
ARR	Absolute risk reduction
CI	Confidence interval
CTCAE	Common Terminology Criteria for Adverse Events
ECG	Electrocardiogram
EGFR	Epidermal growth factor receptor
EORTC QLQ-LC13	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaires - Lung Cancer 13
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 Items
HER	Human epidermal growth factor receptor
IRC	Independent Review Committee
ILD	Interstitial lung disease
ITT	Intention-to-treat
NCI	National Cancer Institute
NSCLC	Non-small-cell lung cancer
ORR	Objective response rate
OS	Overall survival
PFS	Progression-free survival
PRO	Patient reported outcome
QoL	Quality of life
QTcF	QT interval corrected for heart rate using Fridericia's formula
RECIST	Response Evaluation Criteria in Solid Tumors
RD	Relative difference
RR	Relative risk
TKI	Tyrosine kinase inhibitor
Vs	Versus

3 Summary

Vizimpro® (dacomitinib) is an epidermal growth factor receptor (EGFR) inhibitor approved by EMA in April 2019 as monotherapy for the first-line treatment of adult patients with locally advanced or metastatic non-small-cell lung cancer (NSCLC) with EGFR activating mutations.

The ARCHER 1050 trial was a randomised, controlled, open-label phase 3 study comparing the efficacy and safety of dacomitinib with gefitinib in patients with locally advanced or metastatic NSCLC with EGFR activating mutations.

The comparator, Tagrisso® (osimertinib), was investigated in the FLAURA trial, a randomised, controlled, double-blind phase 3 study comparing the efficacy and safety of osimertinib with a standard oral EGFR-tyrosine kinase inhibitor (TKI) (gefitinib or erlotinib) in patients with locally advanced or metastatic NSCLC.

In the ARCHER 1050 trial, dacomitinib demonstrated improved overall survival (OS) with a median OS of 34.1 months [95% CI 29.5; 37.7]. Due to immaturity, median OS data was not available for the comparator osimertinib, and consequently, median OS data could not be compared. There was no statistically significant difference in OS at 12 months between dacomitinib and osimertinib (HR: 1.20 [95% CI 0.79; 1.85], p=0.3911). The relative difference (RD) for overall survival at 12 months was estimated to be 2.1%.

In the ARCHER 1050 study, where patients with CNS metastases at study entry were excluded, only a single patient (0.4%) in the dacomitinib group had CNS progression during the study. In the FLAURA study, the corresponding number was 7 patients (3.1%) in the subgroup of patients with no known/treated CNS metastases at baseline. An indirect comparison analysis showed that the risk for CNS progression was numerically lower for dacomitinib as compared to osimertinib (RR 0.20 [95% CI 0.02; 1.88], p=0.1603), albeit, the difference was not statistical significant. Data for time to CNS progression was not available for dacomitinib due to study design and for osimertinib, it was only available for the subgroup of patients with confirmed CNS metastases at study entry.

Safety profiles for dacomitinib and osimertinib demonstrated some essential differences. Whereas treatment with osimertinib involved changes in cardiac contractility and implied a risk of potentially life-threatening cardiac events (QT prolongation was among the most common grade 3-4 events, and four patients (1%) discontinued treatment due to a prolonged QT interval), this was not an issue for dacomitinib. Rather, patients treated with dacomitinib were at risk of developing dermatitis acneiform, which can affect quality of life, but is a reversible condition susceptible to treatment (dermatitis acneiform was the third most prevalent adverse event for dacomitinib and the most frequent grade 3 event).

Indirect comparison analyses showed, that the risk of experiencing grade 3-4 events was significantly higher (RR: 2.14 [95% CI 1.56; 2.94], p<0.001) for dacomitinib compared to osimertinib. The frequency of discontinuations was the same for dacomitinib and for osimertinib (9.7%) and the indirect comparison analysis showed, that the risk of discontinuing treatment due to adverse events was not statistically significant different (RR: 2.05 [95% CI 0.94 ; 4.49], p=0.0719).

An indirect analysis of median PFS could not be performed, but an indirect comparison of proportion of patients with PFS at 12 months showed that there was no statistical significant difference between the two treatments: the risk of progression at 12 months for dacomitinib compared to osimertinib by independent review was HR: 1.31 [95% CI 0.95; 1.81], p=0.1026.

4 Literature search

4.1 Databases and search strategy

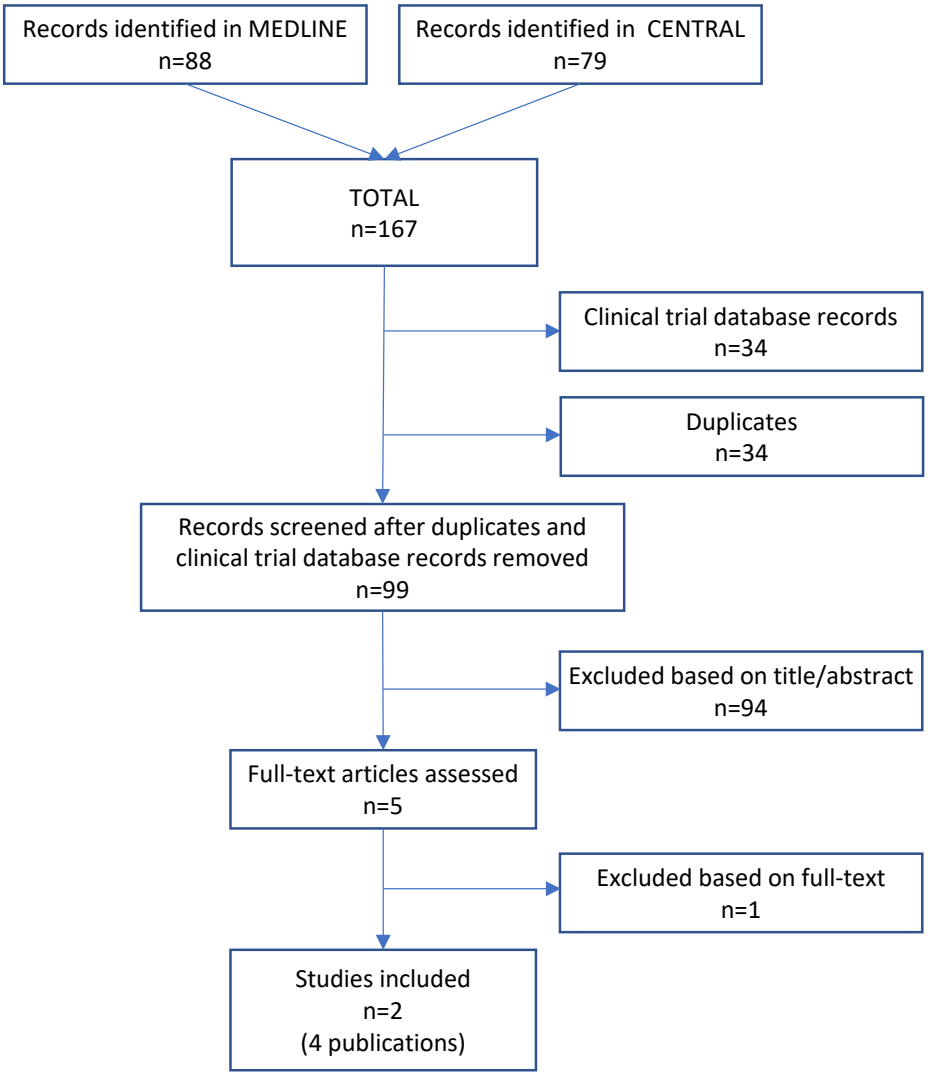
Systematic literature searches were performed in MEDLINE via PubMed and in CENTRAL via Cochrane Library on 22-May-2019 according to the search strategies provided in the protocol for assessment of dacomitinib [1]. No language or date limits were applied. The complete search strategies are summarised in Appendix 6.1, Table 7 and Table 8, respectively. A total of 88 records were identified in MEDLINE and 79 in CENTRAL. After removal of duplicates and clinical trial database records, 99 records were left for screening. The records were screened and assessed by two researchers independently based on the PICOs (patients, intervention, comparator, outcomes) and inclusion and exclusion criteria as described in the assessment protocol for dacomitinib.[1] The inclusion and exclusion criteria are summarised in Appendix 6.1, Table 9.

Based on screening at the title and abstract level, 94 references were excluded. Full-text screening was performed on 5 publications, and 1 publication was excluded based on full-text read. A PRISMA flow diagram of the selection process is provided in Figure 1. No disagreements were noted between researchers during the selection process.

In total, 3 publications related to the relevant studies were excluded at the title/abstract level or after full-text read. These are included in the list of excluded references in Appendix 6.1, Table 10.

After selection of relevant articles, data were extracted into a project-specific Microsoft Excel table by one researcher and a second researcher independently checked the data extraction for accuracy and completeness. No disagreements were noted.

FIGURE 1 PRISMA FLOW DIAGRAM



4.2 Relevant studies

The search retrieved two relevant clinical studies and two relevant publications for each study. Relevant studies and publications are summarised in Table 3.

TABLE 3 RELEVANT STUDIES INCLUDED IN THE ASSESSMENT

Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and cut-off dates for analyses)
Dacomitinib study (ARCHER 1050)			
Dacomitinib versus gefitinib as first-line treatment for patients with EGFR-mutation-positive non-small-cell lung cancer (ARCHER 1050): A randomised, open-label, phase 3 trial. Wu et al. Lancet Oncol. 2017;18(11):1454-1466 [2]	ARCHER 1050: A randomized, open-label phase 3 efficacy and safety study of dacomitinib (pf-	NCT01774721	May 2013 to July 2016

Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and cut-off dates for analyses)
Improvement in overall survival in a randomized study that compared dacomitinib with gefitinib in patients with advanced non-small-cell lung cancer and EGFR-activating mutations. Mok et al. J Clin Oncol. 2018;36(22):2244-2250 [3]	00299804) vs. gefitinib for the first-line treatment of locally advanced or metastatic NSCLC in subjects with EGFR-activating mutations		May 2013 to February 2017
Osimertinib study (FLAURA)			
Osimertinib in untreated EGFR-mutated advanced non–small-cell lung cancer Soria et a. NEJM. 2018;378(2):113-125 [4]	A phase III, double-blind, randomised study to assess the safety and efficacy of AZD9291 versus a standard of care epidermal growth factor receptor tyrosine kinase inhibitor as first line treatment in patients with epidermal growth factor receptor mutation positive, locally advanced or metastatic non-small-cell lung cancer	NCT02296125	December 2014 to June 2017
CNS response to osimertinib versus standard epidermal growth factor receptor tyrosine kinase inhibitors in patients with untreated EGFR-mutated advanced non–small-cell lung cancer Reungwetwattana et al. JCO. 2018;36(33):3290-3297 [5]			December 2014 to June 2017 (subset of patients who had CNS metastases documented on baseline brain scans)

4.3 Main characteristics of included studies

ARCHER 1050 was a randomised, controlled, open-label phase 3 study comparing the efficacy and safety of dacomitinib with gefitinib in patients with locally advanced or metastatic NSCLC with EGFR-activating mutations. Eligible patients were centrally randomised 1:1 to dacomitinib or gefitinib. Tumour assessment was performed by blinded independent reviewers.

FLAURA was a randomised, controlled, double-blind phase 3 study comparing the efficacy and safety of osimertinib with standard oral EGFR-TKI (gefitinib or erlotinib) in patients with locally advanced or metastatic NSCLC who had not previously received treatment for advanced disease, and were eligible to receive first line treatment with gefitinib or erlotinib.

The main characteristics for the ARCHER 1050 and FLAURA studies are summarised in appendix 6.2, Table 11 and Table 12, respectively.

5 Clinical questions

5.1 What is the added clinical value of dacomitinib compared to osimertinib in patients with NSCLC stage IIIB-IV and activating EGFR-mutation?

Population

Adult patients with locally advanced or metastatic NSCLC (stage IIIB/IV) and activating EGFR mutation, who has not previously received systemic treatment for their advanced disease (1st line treatment).

Intervention

Dacomitinib tablet, 45 mg once daily.

Comparator

Osimertinib tablet, 80 mg once daily.

5.1.1 Presentation of relevant studies

The ARCHER 1050 and FLAURA studies are used in the assessment of clinical question 5.1. Main characteristics of the studies are provided in appendix 6.2, Table 11 and Table 12.

The study populations of ARCHER 1050 and FLAURA differ in terms of CNS metastases. Whereas patients who had CNS metastases at study entry were ineligible for the ARCHER 1050 study, patients with CNS metastases whose condition was neurologically stable were eligible for participation in the FLAURA study. [2,4]

5.1.2 Results per study

ARCHER 1050 (Dacomitinib)

The ARCHER 1050 study was presented in two publications. Overall survival (OS) data was presented in Mok et al, 2018 [3], whereas data for adverse events, progression-free survival (PFS), Quality of life (QoL), and objective response rate (ORR) was presented in Wu et al, 2017 [2]. An overview of the results for ARCHER 1050 is provided in appendix 6.4, Table 13. For information on the statistical methods applied, please see appendix 6.3. Specific information, selected results and comments for the individual outcomes are provided below.

Overall survival

OS was defined as the time from randomisation to the date of death for any cause. No data was reported for OS at 12 months. During a median follow-up time of 31.1 months, 103 (45.4%) and 117 (52.0%) patients died in the dacomitinib and gefitinib arms of the ARCHER 1050 study, respectively. The estimated HR for overall survival was 0.760 [95% CI, 0.582; 0.993], p=0.044 (see figure 1 in Mok et al, 2018 [3]). Median OS was 34.1 months with dacomitinib versus 26.8 months with gefitinib. [3] OS data are provided in appendix 6.4, Table 13.

CNS progression

Patients who had CNS metastases were ineligible for the ARCHER 1050 study, and CNS progression was not included as a study endpoint. [2] Consequently, data on time to CNS progression is not available for dacomitinib. However, data on the number of patients with new CNS metastases registered during the study is available [3] and is further discussed in section 5.2.1.

Adverse events

Adverse events were assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.0. [2] Data for discontinuations due to treatment-related adverse events were presented. Data was not reported for treatment-related adverse events of grade 3-4. Data for "all-cause" grade 3-4 adverse events were reported separately, but have been combined in this application, as requested by the Danish Medicines Council, without consideration for possible double counting.

Generally, it is notable that adverse events are reported somewhat differently in Wu et al, 2017 and Vizimpro SmPC. Discrepancies are due to different ways of reporting data (pooling versus not pooling preferred terms of adverse events) and different data sets (ARCHER 1050 study versus data pooled across studies). [2,6]

Discontinuations due to adverse events

In the ARCHER 1050 study, permanent discontinuations because of adverse events related to the drug occurred in 10% of patients in the dacomitinib group (22 of 227) and 7% (15 of 224) in the gefitinib group.

The most frequent adverse events leading to discontinuations are listed in Table 4. The listed events account for 14 of 22 discontinuations. No data are available on the specific adverse events leading to discontinuations for the remaining 8 patients. [2]

TABLE 4 ADVERSE EVENTS LEADING TO DISCONTINUATIONS FOR ARCHER 1050 (DACOMITINIB)

Adverse events leading to discontinuations	DACOMITINIB (n=227)
Skin and subcutaneous tissue disorders	7 (3%)
Gastrointestinal disorders	4 (2%)
Interstitial lung disease or pneumonitis	3 (1%)
Unknown adverse events	8 (4%)
In total	**22 (10%)**

Data are extracted from Wu et al, 2017 [2]

Adverse events grade 3-4

Grade 3-4 events occurred in 53.3% (121 of 227) of patients in the dacomitinib group and 32.1% (72 of 224) of patients in the gefitinib group.

Grade 3-4 events reported in the dacomitinib group included diarrhea, paronychia, stomatitis, hypokalaemia and various forms of skin and subcutaneous disorders (dermatitis acneiform, rash, maculopapular rash and pustular rash). [2]

Qualitative description of dacomitinib's safety profile

The most common adverse events from ARCHER 1050 are listed in Table 5. Of the five most common adverse events for dacomitinib, all (except for one case of diarrhea) were grade 1-3. [2]

Diarrhea was the most common adverse event observed for dacomitinib. In the vast majority of cases, the diarrhea was grade 1-2, but in a few cases, it was more serious (diarrhea was the second most common grade 3-4 event) and in a single case, it was lethal. [2] Diarrhea is a common and in most cases manageable adverse event of many cancer treatments. According to the Vizimpro SmPC proactive management of diarrhea should start at the first signs, including adequate hydration combined with anti-diarrheal medicinal products. Anti-diarrheal medicinal products should be used and, if necessary, escalated to the highest recommended approved dose. Patients should maintain adequate oral hydration and patients who become dehydrated may require administration of intravenous fluids and electrolytes. [6]

Patients may benefit from dosing interruption and/or dose reduction of therapy with dacomitinib: In the pooled safety analysis by Zhou et al, fewer Grade 2 or 3 events of diarrhea were reported in the time intervals following both the first and second dacomitinib dose reductions compared with the number reported in the intervals before the dose reductions (among all patients who underwent dose reductions due to adverse drug reactions) [11].

TABLE 5 KEY ADVERSE EVENTS FOR ARCHER 1050 (DACOMITINIB)

Adverse events (all-cause)	**DACOMITINIB (n=227)**		
	Grades 1-2	Grade 3	Grade 4
Any adverse event	83 (37%)	116 (51%)	5 (2%)
The 5 most common in the dacomitinib group			
Diarrhea	178 (78%)	19 (8%)	0
Paronychia	123 (54%)	17 (7%)	0
Dermatitis acneiform	80 (35%)	31 (14%)	0
Stomatitis	91 (40%)	8 (4%)	0
Decreased appetite	63 (28%)	7 (3%)	0
Others			
Interstitial lung disease / pneumonitis (any grade)*	2.7%*		

Data are extracted from Wu et al, 2017, Table 3 [2]. **Data for interstitial lung disease / pneumonitis is extracted from Vizimpro SmPC, and is based on pooled data for 255 patients treated with 45 mg dacomitinib once daily as starting dose for first-line treatment of NSCLC with EGFR-activating mutations across clinical studies* [6].

Dermatitis acneiform is the third most prevalent adverse event for dacomitinib and the most frequent grade 3 event. Though severe cases of the condition can affect quality of life, it is a reversible and not potentially life-threatening adverse event. Treatment of acneiform rash may include outpatient care and medical treatment with topical steroids, topical antibiotics and oral antibiotics. [2,6]

Interstitial lung disease is a rare adverse event of dacomitinib. The frequency of ILD is not available for ARCHER 1050, however, the Vizimpro SmPC reports a frequency of 2.7% (7 of 255) of ILD or pneumonitis across clinical trials. One case was lethal. [6] The condition may cause irreversible lung fibrosis. [7] According to the Vizimpro SmPC, careful assessment of all patients with an acute onset or unexplained worsening of pulmonary symptoms (e.g., dyspnoea, cough, fever) should be performed to exclude ILD/pneumonitis, and treatment with dacomitinib should be withheld pending investigation of these symptoms. If ILD/pneumonitis is confirmed, dacomitinib should be permanently discontinued and appropriate treatment instituted as necessary. [6]

The conclusion in the Zhou et al paper analyzing the management of adverse events was that dacomitinib was generally tolerable. Most reported adverse drug reactions were known to be associated with EGFR tyrosine kinase inhibitors and were managed with standard medical management and dose modifications. Dose interruptions and dose reductions were reported in 47 and 52% of patients, respectively. Fewer Grade 3 key AEs were observed following dose reductions. Effective management of dacomitinib therapy can help to improve tolerability and patient experience of treatment-related symptoms, allowing patients to continue treatment. [11]

Progression-free survival

PFS was defined as the time from randomisation to the date of disease progression according to RECIST version 1.1 by masked Independent Review Committee (IRC) review or death due to any cause, whichever occurred first. Data was not presented for PFS at 12 months, but the median IRC PFS was 14.7 months [95% CI 11.1-16.6] in the dacomitinib group and 9.2 months [95% CI 9.1-11.0] in the gefitinib group (see figure 2 in Wu et al, 2017 [2]). Data for median PFS (as assessed by masked IRC and by investigators) are provided in appendix 6.4, Table 13. PFS based on investigator assessment was consistent with IRC PFS at 16.6 months for dacomitinib and 11.0 months for gefitinib.

Quality of life

Global QoL was maintained in patients treated with dacomitinib and there was a non-clinically meaningful improvement in global QoL for gefitinib. The difference between dacomitinib and gefitinib was small (numerical improvement from baseline: 0.20 for dacomitinib versus 4.94 for gefitinib; p=0.0002). The improvement from baseline in global QoL for patients treated with dacomitinib was not statistically significant. [2]

Objective response rate

ORR was defined as the proportion of patients who achieved an objective response (defined as a best overall response of either complete response or partial response, where best overall response is the best response recorded from the start of treatment until disease progression). ORR was 75% (170 of 227) in the dacomitinib group and 72% (161 of 225) in the gefitinib group. [2]

FLAURA (osimertinib)

The FLAURA study was presented in two publications. Data for CNS progression was presented in Soria et al, 2018 and further analysed in Reungwetwattana et al, 2018 [4,5], whereas data for AEs, PFS and ORR was presented in Soria et al, 2018. [4] Mature data on overall survival and data on QoL are not available for osimertinib. An overview of the results for FLAURA is provided in appendix 6.4, Table 14. For information on the statistical methods used, please see appendix 6.3. Specific information, selected results and comments for the individual outcomes are provided below.

Overall survival

OS was calculated from the date of randomisation to the date of death due to any cause. Due to immature data, median overall survival could not be calculated. The estimated hazard ratio was 0.63 [95% CI, 0.45; 0.88], p=0.007 (for statistical significance a P value of less than 0.0015 was required for this interim analysis). [4] At 12 months, 89% of patients in the osimertinib group and 82% of patients in the standard EGFR-TKI group remained alive. Available OS data are provided in appendix 6.4, Table 14.

CNS progression

Patients with CNS metastases whose condition was neurologically stable were eligible for participation in the FLAURA study. Baseline brain imaging was mandated only in patients with known or suspected CNS metastases. Time to CNS progression was evaluated in the subgroup of patients with measurable and/or non-measurable CNS lesions on baseline brain scan by blinded independent central neuroradiologic review. In this subgroup of 128 patients, 61 patients had osimertinib and 67 had standard EGFR-TKI. Median CNS progression-free survival was not reached with osimertinib [95% CI 16.5 months to not calculable] and 13.9 months [95% CI 8.3 months to not calculable] with standard EGFR-TKIs. Data on time to CNS progression was not available for those, who did not have a CNS lesion at study entry. [5]

Number of CNS progression events in patients with and without CNS metastases at study entry are available and is further discussed in section 5.2.1.

Adverse events

Adverse events were graded with the use of the NCI CTCAE version 4.0. [4] Data for discontinuations due to treatment-related adverse events were presented. Data for treatment-related adverse events of grade 3-4 was incompletely reported. In addition, "all-cause" grade 3-4 adverse events were not reported collectively. Data for "all-cause" grade 3-4 adverse events were reported separately, but have been combined in this application, as requested by the Danish Medicines Council, without consideration for possible double counting.

Discontinuations due to adverse events

In the FLAURA study, permanent discontinuations because of treatment related adverse events occurred in 10% of patients in the osimertinib group (27 of 279) and 14% (38 of 277) in the standard EGFR-TKI group. A summary of the reasons for discontinuation was not provided but the text describes prolonged QT interval as the reason for discontinuation in 4 patients (1%) from the osimertinib arm. [4]

Adverse events grade 3-4

Grade 3-4 events occurred in 31.9% (89 of 279) of patients in the osimertinib group and 41.2% (114 of 277) of patients in the standard EGFR-TKI group. Grade 3-4 events reported in the osimertinib group included decreased appetite, diarrhea, prolonged QT interval, pneumonia, anaemia and rash or acne. [4]

Qualitative description of osimertinib's safety profile

The most common adverse events from FLAURA are listed in Table 6. Of the five most common adverse events of osimertinib, all were grade 1-3, except for one case of stomatitis (grade 4).

TABLE 6 KEY ADVERSE EVENTS FOR FLAURA (OSIMERTINIB)

Adverse events (all-cause)	OSIMERTINIB (n=279)			
	Grade 1	Grade 2	Grade 3	Grade 4
Any adverse event	34 (12%)	144 (52%)	83 (30%)	6 (2%)
The 5 most common in the osimertinib group				
Rash or acne	134 (48%)	24 (9%)	3 (1%)	0
Diarrhea	120 (43%)	35 (13%)	6 (2%)	0
Dry skin	87 (31%)	12 (4%)	1 (<1%)	0
Paronychia	52 (19%)	44 (16%)	1 (<1%)	0
Stomatitis	65 (23%)	13 (5%)	1 (<1%)	1 (<1%)
Others				

Prolonged QT interval on ECG	11 (4%)	11 (4%)	5 (2%)	1 (<1%)
Pneumonia		1 (<1%)	6 (2%)	
Interstitial lung disease (any grade)	11 (4%)			

Data are extracted from Soria et al, 2018, Table 3 and text [4]

Diarrhea was, together with rashes and acnes, the most common adverse event observed for osimertinib. The vast majority of cases was grade 1-2, but in a few cases, it was more serious (diarrhea was, together with pneumonia, QT prolongation and decreased appetite the most common grade 3 events). [4] Diarrhea is a common adverse event of many cancer treatments.

QT prolongation was among the most common grade 3-4 adverse events. Electrocardiogram (ECG) QT prolongation made up most of the adverse events in the cardiac effects (QT) category, with 28 patients (10%) in the osimertinib group. Dose interruptions and reductions due to QT prolongation were reported in 8 (3%) and 5 patients (2%), respectively. Four patients (1%) in the osimertinib group discontinued treatment due to adverse events of ECG QT prolongation. The maximum change from baseline QTcF was reported to occur at week 12, after which QTcF values remained generally stable. [4] Clinical manifestations of prolonged QT interval include syncope and sudden cardiac death from fatal cardiac arrhythmia (torsades de pointes), and as such, QT prolongation is a potentially life-threatening adverse event. The management of effects on cardiac repolarization necessitates collaboration between oncologists and cardiologists and calls for careful ECG monitoring. [8]

Changes in cardiac contractility have also been observed in patients treated with osimertinib. According to the Tagrisso SmPC, left ventricular ejection fraction (LVEF) has decreased greater than or equal to 10% and a drop to less than 50% occurred in 3.9% (35 of 908) patients treated with osimertinib across clinical trials [9]. In the FLAURA study, a drop in LVEF to less than 50% occurred in 8 of 257 patients (3%) in the osimertinib group. Cardiac effects (cardiac failure) were reported in 12 patients (4%) in the osimertinib group. Most adverse events in this category were ejection fraction decrease (10 of 12 patients in the osimertinib group), which led to dose interruption in 1 patient (<1%). [4]

Pneumonia was observed in 7 patients (3%) of which 6 (2%) were grade 3 or more [4]

Interstitial lung disease was observed in 11 patients (4%) in the osimertinib group. [4] The condition may cause lung fibrosis and is potentially lethal. [7] No fatal events of ILD were reported in the FLAURA study. According to the Tagrisso SmPC, ILD or ILD-like adverse reactions (e.g. pneumonitis) were reported in 3.9% and were fatal in 0.4% of 1142 patients receiving osimertinib across studies. Careful assessment of all patients with acute onset and/or unexplained worsening of pulmonary symptoms (dyspnoea, cough, fever) should be performed to exclude ILD. Treatment with osimertinib should be interrupted pending investigation of these symptoms. If ILD is diagnosed, osimertinib should be permanently discontinued and appropriate treatment initiated as necessary. Most cases of ILD identified in clinical studies have improved or resolved with interruption of treatment. [9]

In general, adverse events are reported somewhat differently in Soria et al, 2018 and Tagrisso SmPC. Discrepancies are due to different ways of reporting data (pooling versus not pooling preferred terms of adverse events) and different data sets (FLAURA study versus data pooled across studies). [4,9] Data pooled across studies presented in the Tagrisso SmPC are data from FLAURA (first-line treatment) pooled with data from the AURA studies (second-line treatment or higher). [9]

Progression-free survival

PFS was defined as the time from randomisation to objective disease progression or death from any cause in the absence of progression. PFS was determined by investigator assessment according to RECIST version 1.1. and median PFS was 18.9 for osimertinib and 10.2 for Standard EGFR-TKI (see figure 1A in Soria et al, 2018 [4]). A sensitivity analysis of PFS was performed based on data from blinded independent central review (IRC) of RECIST assessment for all the patients. The median PFS (IRC) was 17.7 months [95% CI 15.1-21.4] in the osimertinib group and 9.7 months [95% CI 8.5-11.0] in the standard EGFR-TKI group. [4] Data for median PFS as assessed by masked IRC and by investigators and data for PFS at 12 months are provided in appendix 6.4, Table 14.

Quality of life

No QoL data are available for osimertinib.

Overall response rate

ORR was defined as the proportion of randomized patients with an evaluation of complete response or partial response at one or more visits. ORR was 80% in the osimertinib group and 76% in the standard EGFR-TKI group. [4]

5.1.3 Comparative analyses

The results of the indirect comparisons conducted are summarised in appendix 6.5, Table 15. Specific comments for the individual endpoints are provided below.

Overall survival

A comparative analysis of median overall survival was not conducted due to unavailable data for osimertinib.

The difference in overall survival at 12 months between dacomitinib and osimertinib did not reach statistical significance (HR: 1.20 [95% CI 0.79; 1.85], p=0.3911). The relative difference (RD) for overall survival at 12 months was estimated to be -0.021 [95% CI -0.084; 0.023] (appendix 6.5, Table 15).

CNS progression

Time to CNS progression was not an endpoint for the ARCHER 1050 study and only reported for the subgroup of patients with CNS metastases at study entry as documented by brain imaging for the FLAURA study. [2,4] Hence, no indirect comparison was made for this outcome.

Still, both studies contain data on the proportion of patients without brain metastases at study entry, who experienced CNS progression during the study. [2,4] Therefore, an indirect comparison analysis was conducted for this endpoint. The results are presented in section 5.2.1 together with some considerations on the comparability of the data.

Adverse events

Due to the limitations of the published data, indirect comparisons of adverse events following dacomitinib and osimertinib treatment were made for the following categories:

- Discontinuations due to treatment related adverse events.
- "all cause" grade 3-4 adverse events

Discontinuations due to adverse events
The indirect comparison for discontinuations due to adverse events was not statistically significant (relative risk (RR) 2.05 [95% CI 0.94; 4.49], p=0.0719). By looking at the individual study results it is seen that the proportion of patients with discontinuations due to adverse events is the same for osimertinib and dacomitinib (9.7%). The result of the indirect comparison reflects the fact that proportions of patients discontinuing treatment due to adverse events in the comparator groups are higher in the FLAURA study than in the ARCHER 1050 study.

The calculated RD for dacomitinib was: 0.10 [95% CI --0.006; 0.34].

Adverse events grade 3-4
An indirect comparison analysis was conducted for adverse events grade 3-4. The risk of grade 3-4 adverse events was statistically significantly higher for dacomitinib as compared to osimertinib (RR was 2.14 [95% CI 1.56; 2.94], p<0.0001).

The calculated RD for dacomitinib was: 0.36 [95% CI 0.18; 0.62].

Qualitative comparison of safety profiles for dacomitinib and osimertinib
The most common adverse events are quite similar for dacomitinib and osimertinib, in that both compounds have diarrhea, paronychia and stomatitis in addition to adverse events associated with the skin/subcutaneous tissue (dermatitis acneiform for dacomitinib and rash and acne for osimertinib) on their top 5 of most common adverse events of any grade. [2,4]

Clear safety profile discrepancies between dacomitinib and osimertinib include the risk of cardiac events (such as QT prolongation and effects on cardiac contractility) in patients treated with osimertinib and the absence of such potentially life-threatening events in patients treated with dacomitinib. [2,4] Regarding QT prolongation, treatment with osimertinib involves a risk of QT interval prolongation, which may lead to increased risk for ventricular tachyarrhythmias (e.g. torsade de pointes) or sudden death. As to changes in cardiac contractility, treatment with osimertinib decreases LVEF greater than or equal to 10% and a drop to less than 50% has occurred in 3.9% across clinical trials. The risk for cardiac events implies that patients with cardiac risk factors need close cardiac monitoring while on treatment with osimertinib, and some patient subgroups should avoid treatment with osimertinib. [9]

In addition to cardiac effects, interstitial lung disease is an adverse event of special concern, as it may lead to irreversible lung damage and is potentially lethal. [7] The frequency of interstitial lung disease was higher for osimertinib as compared to dacomitinib. [2,4] As regards the management of ILD/pneumonitis, it is recommended for both dacomitinib and osimertinib to interrupt treatment in patients with symptoms of ILD/pneumonitis, and to discontinue treatment with dacomitinib/osimertinib permanently and initiate appropriate treatment, if ILD/pneumonitis is confirmed. [6,9]

Treatment with dacomitinib involves a risk of developing dermatitis acneiform. Although this is a condition which affects general well-being and quality of life, it is manageable and by no means life-threatening. Prophylactic treatment and dose reduction preventive steps can reduce the risk of developing skin-related adverse reactions. Should such adverse events occur, treatment with topical antibiotics, topical steroids or oral antibiotics can reduce the severity of the reactions. [6, 11]

Progression-free survival

An indirect comparison analysis could not be performed for median PFS but indirect comparison analyses were conducted for the proportion of patients with PFS at 12 months as assessed by independent review as well as by investigators (appendix 6.5, Table 15). The difference was not statistical significant. The analysis showed that there was a numerically higher risk of progression at 12 months for dacomitinib compared to osimertinib by independent review (HR: 1.31 [95% CI 0.95; 1.81], p=0.1026) and the difference was similar, still not significant, as measured by investigators (HR: 1.35 [95% CI 0.99; 1.84], p=0.0592).

It was not possible to calculate an RD by independent review because no 12-month PFS data by independent review was available for osimertinib. The RD by investigator assessment was -0.085 [95% CI -0.187; 0.003] (appendix 6.5, Table 15).

Quality of life

No comparison was possible, as no QoL data was available for osimertinib.

5.2 Other considerations

5.2.1 Patients with CNS metastases

CNS metastasis was an exclusion criterion for the ARCHER 1050 study. The reason for excluding this group of patients was that the capacity of dacomitinib in brain penetration was not known when the study was designed and there is a lack of adequate CNS penetration with gefitinib. [2]

Still, the ARCHER 1050 study presents data for the number of patients who experienced disease progression in CNS. Whereas the brain was the primary site for disease progression in 11 patients in the gefitinib group, this was only the case for one patient in the dacomitinib group. [3]

A subgroup analysis of the participants of the FLAURA study with no known/treated CNS metastases at trial entry showed, that the number of patients with CNS progression was 7 of 226 (3%) in the osimertinib group and 15 of 214 (7%) in the standard EGFR-TKI group. [4]

An indirect comparison analysis was conducted for the proportion of patients without CNS metastases at baseline, who had experienced CNS progression during the study (see also appendix 6.5, Table 15). RR was 0.20 [95% CI 0.02; 1.88], p=0.1754. Thus, the risk of CNS progression was numerically lower for dacomitinib as compared to osimertinib. The difference was not statistically significant.

Regarding the assessment criteria for excluding the presence of CNS metastases at study entry, the studies were comparable. According to the ARCHER 1050 study 'Patients were ineligible if they had any history of brain or leptomeningeal metastases.' The FLAURA study (where patients with CNS metastases were not excluded) reported that 'Baseline brain imaging was mandated only in patients with known or suspected CNS metastases.' It can therefore be assumed that the FLAURA data on 'Patients with no known/treated CNS metastases at trial entry' is comparable to the data on the patient group included in the ARCHER 1050 study. [2,4]

Regarding the assessment criteria for confirming CNS progression during the study, ARCHER 1050 reported that 'CNS imaging will be done only as applicable, i.e. if there is neurologic examination to suggest CNS involvement.' [2] No details are available for the symptoms leading to CNS imaging in the subgroup of patients with no CNS metastases at study entry in the FLAURA study.

As to the question about whether CNS metastases should be a contraindication for treatment with dacomitinib, data are not available to support nor reject this. However, the indication for dacomitinib as provided by EMA does not mention CNS metastases and thus does not have CNS metastases as a contraindication. [6]

5.2.2 Sequencing of treatment

The ARCHER 1050 study has provided some relevant information on the impact of subsequent therapy. After discontinuation of study treatment, a total of 253 patients (113 in the dacomitinib group and 140 in the gefitinib group) received a subsequent systemic therapy. Of these, the 22 patients (9.7%) in the dacomitinib arm whose subsequent therapy was a third generation EGFR-TKI (such as osimertinib) had a median OS of 36.7 months [95% CI 30.1 months to *not reached*]. In comparison, the 63 (27.8%) in the dacomitinib arm whose subsequent therapy was chemotherapy had a median OS of 29.5 months [95% CI 25.1 to 37.7]. Although numbers are small, this could suggest that giving dacomitinib as first line therapy and osimertinib as subsequent treatment may further increase overall survival. [3]

6 Appendices

6.1 Literature search

TABLE 7 PUBMED SEARCH

Search	Add to builder	Query	Items found
#19	Add	Search **(#17 and #18)**	88
#18	Add	Search **(randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR randomised[tiab] OR placebo[tiab] OR "clinical trials as topic"[mh:noexp] OR randomly[tiab] OR trial [ti])**	1259585
#17	Add	Search **(#15 not #16)**	670
#16	Add	Search **(animals[mh] not humans[mh])**	4582685
#15	Add	Search **(#9 and #14)**	672
#14	Add	Search **(#10 or #11 or #12 or #13)**	857
#13	Add	Search **(osimertinib[tiab] or Tagrisso*[tiab] or AZD-9291[tiab] or AZD9291[tiab])**	679
#12	Add	Search **osimertinib[nm]**	191
#11	Add	Search **(dacomitinib[tiab] or vizimpro*[tiab] or PF00299804[tiab] or PF-00299804[tiab])**	176
#10	Add	Search **PF 00299804[nm]**	93
#9	Add	Search **(#1 or #2 or #6 or #7 or #8)**	99771
#8	Add	Search **((adenocarcinoma[tiab]) and (lung*[tiab]))**	28785
#7	Add	Search **adenocarcinoma of lung[mh]**	7156
#6	Add	Search **(#3 and #4 and #5)**	70027
#5	Add	Search **(neoplasm* or cancer[tiab] or cancers[tiab] or carcinoma*[tiab] or adenocarcinoma*[tiab])**	3217560
#4	Add	Search **lung*[tiab]**	632844
#3	Add	Search **(nonsmall cell[tiab] or non-small cell[tiab] or squamous cell[tiab] or large cell[tiab])**	164786
#2	Add	Search **nsclc[tiab]**	37711
#1	Add	Search **carcinoma, non-small-cell lung[mh]**	47974

TABLE 8 CENTRAL SEARCH

#1	[mh "carcinoma, non-small-cell lung"]	Limits	3702
#2	("non small cell lung cancer" or "large cell lung carcinoma" or "adenocarcinoma of lung" or "lung adenocarcinoma" or "squamous cell lung carcinoma"):kw	Limits	4244
#3	nsclc:ti,ab	Limits	8002
#4	(("non small cell" or "nonsmall cell" or "squamous cell" or "large cell") near/4 lung near/4 (cancer* or carcinoma* or neoplasm* or adenocarcinoma*)):ti,ab	Limits	10326
#5	#1 or #2 or #3 or #4	Limits	12484
#6	(PF00299804 or "PF 00299804" or dacomitinib or vizimpro*):ti,ab,kw	Limits	71
#7	(osimertinib or AZD-9291 or AZD9291 or Tagrisso*):ti,ab,kw	Limits	155
#8	#6 or #7	Limits	217
#9	#5 and #8	Limits	184
#10	("conference abstract" or review):pt	Limits	171315
#11	NCT*:au	Limits	136411
#12	clinicaltrials gov:so	Limits	139308
#13	#10 OR #11 OR #12	Limits	310683
#14	#9 NOT #13	Limits	79

TABLE 9 INCLUSION AND EXCLUSION CRITERIA

Inclusion criteria	**Population:** Adult patients with locally advanced or metastatic NSCLC (stage IIIB/IV) and activating EGFR mutation, who has not previously received systemic treatment for their advanced disease **Intervention(s):** Dacomitinib tablet, 45 mg once daily **Comparator(s):** Osimertinib tablet, 80 mg once daily **Outcomes:** OS, CNS-progression, adverse reactions, PFS, quality of life (EORTC-QLQ-C30) **Study design:** Randomised controlled trials **Language restrictions:** None **Other search limits or restrictions applied:** None
Exclusion criteria	Non-randomised, uncontrolled studies Phase 1 and 2a studies Studies including patients who had any previous systemic treatment (including chemotherapy) for their advanced disease

TABLE 10 LIST OF STUDIES EXCLUDED BASED ON TITLE/ABSTRACT OR FULL-TEXT READ

Reference	Reason for exclusion
Excluded on title/abstract level	
Osimertinib versus standard of care EGFR TKI as first-line treatment in patients with EGFRm advanced NSCLC: FLAURA Asian subset. Cho et al. J Thorac Oncol. 2019;14(1):99-106.	Asian subset. Data also included in the publication of the complete dataset (Soria et al, 2018)

Reference	Reason for exclusion
Osimertinib versus standard-of-care EGFR-TKI as first-line treatment for EGFRm advanced NSCLC: FLAURA Japanese subset. Ohe et al. Jpn J Clin Oncol. 2019;49(1):29-36.	Japanese subset. Data also included in the publication of the complete dataset (Soria et al, 2018)
Excluded after full text screening	
Postprogression outcomes for osimertinib versus standard-of-care EGFR-TKI in patients with previously untreated EGFR-mutated advanced non-small cell lung cancer. Planchard et al. Clin Cancer Res. 2019;25(7):2058-2063.	No relevant outcomes included. Includes intermediate clinical outcomes between PFS and OS that further define efficacy and used to support immature OS data

6.2 Main characteristics of included studies

6.2.1 ARCHER 1050 study

TABLE 11 MAIN STUDY CHARACTERISTICS - ARCHER 1050 (DACOMITINIB)

Trial name (official title from clinicaltrials.gov)	ARCHER 1050: A randomized, open-label phase 3 efficacy and safety study of dacomitinib (PF-00299804) vs. gefitinib for the first-line treatment of locally advanced or metastatic NSCLC in subjects with EGFR-activating mutations
NCT number	NCT01774721
Objective	The overall objective of the study was to evaluate the efficacy and safety of dacomitinib versus gefitinib as first-line therapy in patients with advanced EGFR-mutation-positive NSCLC
Publications – title, author, journal, year	Dacomitinib versus gefitinib as first-line treatment for patients with EGFR-mutation-positive non-small-cell lung cancer (ARCHER 1050): A randomised, open-label, phase 3 trial. Wu et al. Lancet Oncol. 2017;18(11):1454-1466 [2] Improvement in overall survival in a randomized study that compared dacomitinib with gefitinib in patients with advanced non-small-cell lung cancer and EGFR-activating mutations. Mok et al. J Clin Oncol. 2018;36(22):2244-2250 [3]
Study type and design	The ARCHER 1050 study was a multinational, multicentre, randomised, open-label, phase 3 study comparing the efficacy and safety of dacomitinib (PF-00299804) with gefitinib in patients with locally advanced or metastatic NSCLC with epidermal growth factor receptor EGFR-activating mutations. Eligible patients were randomly assigned 1:1 to receive dacomitinib or gefitinib. Randomisation was stratified by race (self-reported; Japanese vs Chinese vs other east Asian vs non-Asian) and EGFR mutation type (exon 19 deletion vs Leu858Arg mutation). Randomisation was performed centrally, with allocation generated by interactive web response system (IWRS), stratified by race and EGFR mutation type. Patients and investigators were not masked to the study treatments. Tumour assessment by independent review was masked. Central imaging was masked to the reviewers. Sites were unmasked to study drug, but the vendors and sponsor remained masked. Study sponsor personnel were unmasked at database lock for the primary analysis of PFS. In both study groups, treatment was discontinued after progression of disease, initiation of new anticancer therapy, unacceptable toxicities, non-compliance, withdrawal of consent, or death. Treatment beyond radiological progression was permitted as long as there was evidence of clinical benefit as determined by the investigator in consultation with the sponsor. Tumour imaging assessments (CT or MRI) were done at screening, at the end of cycles 1 and 2, and then at every other cycle until the end-of-treatment visit. Objective tumour responses were measured using RECIST version 1.1 and assessed by a masked independent radiological central (IRC) review and by the investigator. Patients who discontinued treatment in the absence of progression were expected to be followed up every 8 weeks until disease progression. Safety parameters were assessed on day 1 of each 28-day cycle. AEs were assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.0. Patient-reported outcomes (PROs) were assessed at days 1 (baseline), 8, and 15 of cycle one, on day 1 of subsequent cycles, at the end-of-treatment visit, and at the post-treatment follow-up visit, using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 items (EORTC QLQ-C30) the corresponding lung cancer module (QLQ-LC13),21 and the EuroQoL Group 5-Dimension Self-Report Questionnaire (EQ-5D).

Follow-up time	Median duration of follow-up for PFS in the ITT treat population, at the first data cut-off (July 2016) was 22.1 months (95% CI 20.3–23.9); 22.1 months (20.2–23.9) in the dacomitinib group and 23·0 months (20.3–25.8) in the gefitinib group. At the second data cut-off (February 2017), the median follow-up times for the final OS analysis were 31.1 months with dacomitinib and 31.4 months with gefitinib.
Population (inclusion and exclusion criteria) (from clincialtrials.gov)	<u>Inclusion criteria</u> • Evidence of histo- or cytopathology confirmed, advanced NSCLC (with known histology) with the presence of EGFR-activating mutation (exon 19 deletion or the L858R mutation in exon 21) • It was acceptable for subjects with the presence of the exon 20 T790M mutation together with either EGFR-activating mutation (exon 19 deletion or the L858R mutation in exon 21) to be included in this study • Minimum of 12 months disease-free interval between completion of systemic therapy and recurrence of NSCLC • Adequate tissue sample had to be available for central analyses • Adequate renal, hematologic, liver function • ECOG performance status of 0-1 • Radiologically measurable disease <u>Exclusion criteria</u> • Any evidence of mixed histology that included elements of small cell or carcinoid lung cancer • Any other mutation other than exon 19 deletion or L858R in exon 21, with or without the presence of the exon 20 T790M mutation • Any history of brain metastases or leptomeningeal metastases • Any previous anti-cancer systemic treatment of early, locally advanced, or metastatic NSCLC • Uncontrolled medical disorders
Intervention	Dacomitinib 45 mg tablets once daily (n=227) or gefitinib 250 mg tablets once daily (n=225) in 28-day cycles. Dacomitinib dose reductions for a maximum of 2 dose levels (30 mg/day and 15 mg/day) were permitted for treatment-related toxicity in the case of grade 3 or worse toxicity or prolonged grade 2 AEs lasting more than one cycle. After dose reduction, based upon investigator assessment, treatment was resumed at the dose level per protocol. Dose interruptions (<2 weeks or longer in consultation with the sponsor) were permitted per protocol. Gefitinib was only available as a 250 mg dose. If treatment was interrupted for grade 3, grade 4, or intolerable grade 2 toxicity, gefitinib was resumed at a daily or every-other-day dosing at the investigator's discretion. Median duration of treatment at the first data cut-off (July 2016) was 15.3 months (IQR 6.9–20.9) in the dacomitinib group and 12.0 months (7.3–18.4) in the gefitinib group. At this timepoint, 66 (29%) patients in the dacomitinib group and 38 (17%) in the gefitinib group were still receiving study treatment. At the second data cut-off (February 2017,) for the final analysis of OS, there were 49 patients (21.6%) in the dacomitinib arm and 18 patients (8.0%) in the gefitinib arm who were still receiving study treatment.

Baseline characteristics

Characteristic	Dacomitinib N= 227 n (%)	Gefitinib N= 225 n (%)
Age, years		
Median (inter-quartile range)	62 (53-68)	61 (54-68)
<65	133 (59%)	140 (62%)
≥65	94 (41%)	85 (38%)
Gender		
Male	81 (36%)	100 (44%)
Female	146 (64%)	125 (56%)
Race (self-identified)		
White	56 (25%)	49 (22%)
Black	1 (<1%)	0
Asian	170 (75%)	176 (78%)
Japanese	40 (18%)	41 (18%)
Chinese	114 (50%)	117 (52%)
Other east Asian	16 (7%)	18 (8%)
ECOG performance status		
0	75 (33%)	62 (28%)
1	152 (67%)	163 (72%)
Disease stage at screening		
Stage IIIB	18 (8%)	16 (7%)
Stage IV	184 (81%)	183 (81%)
Unknown[1]	25 (11%)	26 (12%)
Smoking status		
Never	147 (65%)	144 (64%)
Former	65 (29%)	62 (28%)
Current	15 (7%)	19 (8%)
Type of EGFR mutation[2]		
Exon 19 deletion[3]	134 (59%)	133 (59%)
Leu858Arg[4]	93 (41%)	92 (41%)

ECOG=Eastern Cooperative Oncology Group
[1]Newly diagnosed with stage IV at time of study entry
[2]EGFR mutations (at randomisation) were identified from tumour specimens
[3]At randomisation, 2 patients in the gefitinib group (and none in the dacomitinib group) had the Thr79Met mutation
[4]At randomisation, 2 patients in the dacomitinib group (and none in the gefitinib group) had the Thr790Met mutation

Primary and secondary endpoints

<u>Primary endpoint</u>

- Progression-free survival (PFS) as determined by masked Independent Radiologic Central (IRC) review

<u>Secondary endpoints included</u>

- PFS based on investigator assessment
- The proportion of patients who achieved an objective response (both masked IRC review and investigator assessment)
- Duration of response (both masked IRC review and investigator assessment)
- Overall survival (defined as the time from randomisation to the date of death for any cause)

	• Overall survival at 30 months (probability of a patient being alive at 30 months from date of randomisation) • Safety • Patient-reported outcome endpoints included overall change from baseline and time to deterioration in pain, dyspnoea, fatigue, or cough on the EORTC QLQ-C30 and EORTC QLQ-LC13 scales
Method of analysis	All randomised patients (the ITT population) were included in the efficacy analysis. A log-rank test, stratified by EGFR mutation status at randomisation and race, was used to assess PFS, time to treatment failure, and duration of response. A Cox proportional hazards model, stratified by EGFR mutation status and race as used in the log-rank test, was used to calculate HRs and 95% CIs for PFS and time to treatment failure in the ITT population and duration of response among the objective responders in the ITT population. P-values were determined by the log-rank test with adjustment for the same stratification factors. All reported p-values were two-sided. The Schoenfeld residuals test was used to test the proportional hazards assumption. Patients in the ITT population who received at least one dose of study drug were included in the safety analysis.
Subgroup analyses	Not applicable for this application

6.2.2 FLAURA study

TABLE 12 MAIN STUDY CHARACTERISTICS – FLAURA (OSIMERTINIB)

Trial name (official title from clinicaltrials.gov)	A Phase III, double-blind, randomised study to assess the safety and efficacy of AZD9291 versus a standard of care epidermal growth factor receptor tyrosine kinase inhibitor as first line treatment in patients with epidermal growth factor receptor mutation positive, locally advanced or metastatic non-small cell lung cancer
NCT number	NCT02296125
Objective	The main objective was to assess the efficacy and safety of osimertinib versus a standard of care EGFR-TKI in patients with locally advanced or metastatic NSCLC
Publications – title, author, journal, year	Osimertinib in untreated EGFR-mutated advanced non-small-cell lung cancer. Soria et al. N Engl J Med. 2018;378(2):113-125 [4] CNS response to osimertinib versus standard epidermal growth factor receptor tyrosine kinase inhibitors in patients with untreated EGFR-mutated advanced non–small-cell lung cancer Reungwetwattana et al. JCO. 2018;36(33):3290-3297 [5]
Study type and design	The FLAURA study was a randomised, controlled double-blind, phase 3 trial in patients with locally advanced or metastatic NSCLC who had not previously received treatment for advanced disease, and were eligible to receive first line treatment with gefitinib or erlotinib. Patients were stratified according to tumour EGFR mutation status (Ex19del or L858R) and race (Asian or non-Asian) and were randomly assigned in a 1:1 ratio to receive either oral osimertinib or a standard oral EGFR-TKI (gefitinib or erlotinib). Treatment continued until disease progression, the development of unacceptable side effects, or withdrawal of consent. Treatment beyond the point of disease progression (as assessed by the investigator according to RECIST version 1.1) was allowed as long as there was continued clinical benefit, as judged by the investigator. A protocol amendment on April 13, 2015, allowed patients who had been assigned to a standard EGFR-TKI to cross over to open-label osimertinib after confirmation of objective disease progression by blinded independent central review and post-

	progression documentation of T790M-positive mutation status by means of plasma or tissue testing (local or central). Intervening anticancer therapy was not allowed before crossover to open-label osimertinib. All patients underwent tumour imaging (CT or MRI) at baseline within 4 weeks before randomization. Subsequent assessments were every 6 weeks for the first 18 months then every 12 weeks until disease progression. Patients with known or suspected central nervous system (CNS) metastases at trial entry were mandated to have baseline brain scans and patients with confirmed CNS metastases received follow-up brain scans. Any new lesions found in the CNS during the trial were identified as new lesions. PFS was defined as the time from randomisation to objective disease progression or death from any cause in the absence of progression, irrespective of withdrawal from the trial or treatment with another anticancer therapy before progression. Adverse events were graded using CTCAE, version 4.0.
Follow-up time	The median duration of follow up for PFS was 15.0 months (range 0 to 25.1) in the osimertinib group and 9.7 months (range, 0 to 26.1) in the standard EGRF-TKI group

Population (inclusion and exclusion criteria)
(from clinicaltrials.gov)
	<u>Inclusion criteria</u>
	• Male or female, aged at least 18 years
	• Pathologically confirmed adenocarcinoma of the lung
	• Locally advanced or metastatic NSCLC, not amenable to curative surgery or radiotherapy
	• The tumour harbours one of the 2 common EGFR mutations known to be associated with EGFR-TKI sensitivity (Ex19del, L858R)
	• Mandatory provision of an unstained, archived tumour tissue sample in a quantity sufficient to allow for central analysis of EGFR mutation status
	• Patients had to be treatment-naïve for locally advanced or metastatic NSCLC and eligible to receive first-line treatment with gefitinib or erlotinib as selected by the participating centre. Prior adjuvant and neo-adjuvant therapy was permitted (chemotherapy, radiotherapy, investigational agents)
	• Provision of informed consent prior to any study specific procedures, sampling, and analysis
	• World Health Organization Performance Status of 0 to 1 with no clinically significant deterioration over the previous 2 weeks and a minimum life expectancy of 12 weeks
	
	<u>Exclusion criteria</u>
	• Treatment with any of the following:
	  • Prior treatment with any systemic anti-cancer therapy for locally advanced/metastatic NSCLC
	  • Prior treatment with an EGFR-TKI
	  • Major surgery within 4 weeks of the first dose of study drug
	  • Radiotherapy treatment to more than 30% of the bone marrow or with a wide field of radiation within 4 weeks of the first dose of study drug
	  • Patients currently receiving medications or herbal supplements known to be potent inducers of cytochrome P450 (CYP) 3A4
	  • Alternative anti-cancer treatment
	  • Treatment with an investigational drug within five half-lives of the compound or any of its related material
	• Any concurrent and/or other active malignancy that has required treatment within 2 years of first dose of study drug
	• Spinal cord compression, symptomatic and unstable brain metastases, except for those patients who had completed definitive therapy, were not on steroids, had a stable neurologic status for at least 2 weeks after completion of the definitive therapy and steroids

<table>
<tr><td></td><td>

Any evidence of severe or uncontrolled systemic diseases, including uncontrolled hypertension and active bleeding diatheses; or active infection including hepatitis B, hepatitis C and human immunodeficiency virus (HIV)
Refractory nausea and vomiting, chronic gastrointestinal diseases, inability to swallow the formulated product, or previous significant bowel resection that would preclude adequate absorption of AZD9291
Any of the following cardiac criteria:

Mean resting corrected QT interval (QTc) >470 msec, obtained from 3 ECGs, using the screening clinic ECG machine derived QTcF value
Any clinically important abnormalities in rhythm, conduction, or morphology of resting ECG
Any patient with any factors that increase the risk of QTc prolongation or risk of arrhythmic events or unexplained sudden death under 40 years of age in first-degree relatives or any concomitant medication known to prolong the QT interval

Past medical history of interstitial lung disease (ILD), drug induced ILD, radiation pneumonitis which required steroid treatment, or any evidence of clinically active ILD
Involvement in the planning and/or conduct of the study

</td></tr>
<tr><td>Intervention</td><td>
Oral osimertinib, 80 mg once daily or a standard EGFR-TKI: gefitinib at a dose of 250 mg once daily or erlotinib at a dose of 150 mg once daily.

The dosing was interrupted in patients experiencing an AE of CTCAE grade 3 or worse and/or unacceptable toxicity (any grade). If the toxicity resolved or reverted to CTCAE grade ≤1 within 2 weeks of onset, the trial drug was restarted at the same dose, or a reduced dose (40 mg osimertinib, 100 mg erlotinib, no dose reduction for gefitinib as only available as a 250 mg dose).

At the time of data cut-off, the median duration of total treatment exposure was 16.2 months (range 0.1 to 27.4) for patients receiving osimertinib and 11.5 months (range, 0 to 26.2) for those receiving a standard EGFR-TKI. At the time of data cut-off, 141 patients (51%) in the osimertinib group and 64 (23%) in the standard EGFR-TKI group continued to receive trial treatment.
</td></tr>
<tr><td>Baseline characteristics</td><td>
<table>
<tr><th>Characteristic</th><th>Osimertinib (N= 279) n (%)</th><th>Standard EGFR-TKI (N= 277) n (%)</th></tr>
<tr><td>Age– years</td><td></td><td></td></tr>
<tr><td>Median (inter-quartile range)</td><td>64 (26-85)</td><td>64 (35-93)</td></tr>
<tr><td colspan="3">Gender</td></tr>
<tr><td>Male</td><td>101 (36%)</td><td>105 (38%)</td></tr>
<tr><td>Race (reported by the patient)</td><td></td><td></td></tr>
<tr><td>White</td><td>101 (36%)</td><td>100 (36%)</td></tr>
<tr><td>Asian</td><td>174 (62%)</td><td>173 (62%)</td></tr>
<tr><td>Other (includes black, American Indian, Alaska Native)</td><td>4 (1%)</td><td>4 (1%)</td></tr>
<tr><td>Smoking status</td><td></td><td></td></tr>
<tr><td>Never</td><td>182 (65%)</td><td>175 (63%)</td></tr>
<tr><td>Current</td><td>8 (3%)</td><td>9 (3%)</td></tr>
<tr><td>Former</td><td>89 (32%)</td><td>93 (34%)</td></tr>
<tr><td>WHO performance status</td><td></td><td></td></tr>
<tr><td>0</td><td>112 (40%)</td><td>116 (42%)</td></tr>
<tr><td>1</td><td>167 (60%)</td><td>160 (58%)</td></tr>
</table>
</td></tr>
</table>

	Missing data	0	1 (<1)
	Histologic type		
	Adenocarcinoma	275 (99)	272 (98)
	Other[1]	4 (1)	5 (2)
	Overall disease classification		
	Metastatic[2]	264 (95)	262 (95)
	Locally advanced[3]	14 (5)	15 (5)
	Missing data	1 (<1)	0
	Metastases		
	Visceral metastases[4]	94 (34)	103 (37)
	CNS metastases[5]	53 (19)	63 (23)
	EGFR mutation type at randomisation		
	Exon 19 deletion	175 (63)	174 (63%)
	L858R	104 (37)	103 (37%)
	EGFR mutation type by central test[6]		
	Exon 19 deletion	158 (57)	155 (56)
	L858	97 (35)	90 (32)
	No mutation detected, invalid test or inadequate sample	24 (9)	32 (12)
	EGFR-TKI comparator		
	Gefitinib	Not applicable	183 (66)
	Erlotinib	Not applicable	94 (34)

[1]Five patients (two in the osimertinib group and three in the standard EGFR-TKI group) had large-cell carcinoma; 3 patients (1 in the osimertinib group and 2 in the standard EGFR-TKI group) had adenosquamous carcinoma; and 1 patient (in the osimertinib group) had a carcinoid tumour

[2]The patient had any metastatic site of disease

[3]The patient had only locally advanced sites of disease

[4]Visceral metastases were determined programmatically from baseline data for which the disease site was described as adrenal, ascites, brain or CNS, gastrointestinal, genitourinary, hepatic (including gallbladder), liver, other CNS, pancreas, peritoneum, or spleen. Also included were other metastatic sites, such as those occurring in the eye and thyroid, as identified as extrathoracic visceral sites by AstraZeneca physicians

[5]CNS metastases were determined programmatically from baseline data for the CNS lesion site, medical history, surgery, or radiotherapy

[6]A patient could have more than one type of mutation

Primary and secondary endpoints	<u>Primary endpoint</u> • Duration of PFS as determined by investigator assessments, according to RECIST, version 1.1. A sensitivity analysis of PFS was performed based on data from blinded independent central review of RECIST assessments for all the patients <u>Secondary endpoints included</u> • Overall survival • Objective response rate (ORR) • The duration of response • The disease control rate (rate of complete response, partial response, or stable disease lasting ≥6 weeks before any disease-progression event) • The depth of response (change in target-lesion size from baseline) • Safety • Participants reported outcome by Cancer Therapy Satisfaction Questionnaire 16 Items (CTSQ-16 Questionnaire), EORTC QLQ-LC13 and EORTC QLQ-C30

Method of analysis	The full analysis set included all randomly assigned patients, including patients who were randomised but did not subsequently receive treatment, and was used for all efficacy assessments. Adverse events were assessed in the safety analysis set, consisting of all the patients who received at least one dose of study treatment. A log-rank test, stratified according to race (Asian vs. non-Asian) and mutation type (Exon 19 deletion vs L858R), was used to compare PFS between treatment groups, with application of the Breslow approach to handle tied events. Furthermore, the hazard ratio and corresponding 95% confidence interval was estimated. Data for patients who had not had a progression event or had not died at the time of the analysis were censored at the time of the last RECIST assessment that could be evaluated.
Subgroup analyses	Not applicable for this application

6.3 Statistical considerations

For all binary endpoints the 95% confidence interval for the proportion was calculated by treatment group and study using a normal approximation without continuity correction. Furthermore, the risk difference and relative risk were calculated using a normal approximation without continuity correction.

For the following endpoints:

Overall survival
Any adverse event Grade 3-4
CNS progression (proportion)
Discontinuation of treatment due to adverse reactions (proportion of patients)
PFS (independent), proportion of patients
PFS (investigator), proportion of patients

indirect comparisons between dacomitinib and osimertinib were performed. OS and PFS were analysed as time to event endpoints yielding an indirect HR with 95% CI. An absolute risk difference was calculated when ACR could be found for the comparator (ACR percentage given in Table 15). For the binary endpoints an indirect RR with 95% confidence interval was calculated with ACR from the comparator. Indirect comparisons were not computed for endpoints reported as median (see page 16 in the guidance from the Medicines Council).

All other results presented in this application were taken directly from the published material.

6.4 Results per study

6.4.1 Results of the ARCHER 1050 study

TABLE 13 BY-STUDY RESULTS FOR ARCHER 1050 (DACOMITINIB)

Trial name:	ARCHER 1050: a randomized, open-label phase 3 efficacy and safety study of dacomitinib (PF-00299804) vs. gefitinib for the first-line treatment of locally advanced or metastatic NSCLC in subjects with EGFR-activating mutations										
NCT number:	NCT01774721										
				Estimated absolute difference in effect			**Estimated relative difference in effect**			**Description of methods used for estimation**	**References**
Outcome	**Study arm**	**N**	**Result (95% CI)**	**Difference**	**95% CI**	**P value**	**Ratio**	**95% CI**	**P value**		
Overall survival (adjusted) (proportion alive at 12 months)	Dacomitinib	227	Not reported								
	Gefitinib	225	Not reported								
Median overall survival (months)	Dacomitinib	227	34.1 (29.5-37.7)				HR: 0.76	0.582–0.993	0.0438	Cox proportional hazard models (adjusted for stratification factors) were used to estimate the HR and associated 95% CI. ITT analysis set. See appendix 6.3 for statistical methods	Mok 2018; figure 2
	Gefitinib	225	26.8 (23.7–32.1)								
CNS progression (proportion of patients)	Dacomitinib	227	0.4% (0.1; 2.5)	RD: -0.044	-0.074; -0.015	0.0031	RR: 0.09	0.01-0.69	0.0207	ITT analysis set. See appendix 6.3 for statistical methods	Mok 2018; p2247
	Gefitinib	225	4.9% (2.8; 8.5)								
Discontinuation of treatment due to adverse events (proportion of patients)	Dacomitinib	227	9.7% (6.5; 14.2)	RD: 0.030	-0.021; 0.080	0.2453	RR: 1.45	0.77; 2.72	0.2499	Safety analysis set. See appendix 6.3 for statistical methods	Wu 2017; p1461
	Gefitinib	224	6.7% (4.1; 10.8)								

Trial name:	ARCHER 1050: a randomized, open-label phase 3 efficacy and safety study of dacomitinib (PF-00299804) vs. gefitinib for the first-line treatment of locally advanced or metastatic NSCLC in subjects with EGFR-activating mutations										
NCT number:	NCT01774721										
				Estimated absolute difference in effect			**Estimated relative difference in effect**			**Description of methods used for estimation**	**References**
Outcome	**Study arm**	**N**	**Result (95% CI)**	**Difference**	**95% CI**	**P value**	**Ratio**	**95% CI**	**P value**		
Serious adverse reactions (related) (proportion of patients)	Dacomitinib	227	9.3% (6.1; 13.7)	RD: 0.048	0.001; 0.094	0.0431	RR: 2.07	1.00; 4.30	0.0505	Safety analysis set. See appendix 6.3 for statistical methods	Wu 2017; p1460
	Gefitinib	224	4.5% (2.4; 8.0)								
Serious adverse events of any cause (proportion of patients)	Dacomitinib	227	27.3% (21.9; 33.5)	RD: 0.05	-0.030; 0.129	0.2190	RR: 1.22	0.89; 1.69	0.2216	Safety analysis set. See appendix 6.3 for statistical methods	Wu 2017; p1460
	Gefitinib	224	22.3% (17.4; 28.2)								
Any adverse event grade 3-4 (proportion of patients)	Dacomitinib	227	53.3% (46.6, 59.9)	RD: 0.21	0.10; 0.35	<0.0001	RR: 1.66	1.32; 2.08	<0.0001	Safety analysis set. Data pooled without consideration for double counting. See appendix 6.3 for statistical methods	Wu 2017; table 3
	Gefitinib	224	32.1% (26.1, 38.7)								
PFS, investigator (proportion of patients not progressed at 12 months)	Dacomitinib	227	Not reported								
	Gefitinib	225	Not reported								
Median PFS, independent (months)	Dacomitinib	227	14.7 (11.1; 16.6)				HR:0.59	0.47; 0.74		ITT analysis set. See appendix 6.3 for statistical methods	Wu 2017; figure 2A
	Gefitinib	225	9.2 (9.1; 11.0)								

Trial name:	ARCHER 1050: a randomized, open-label phase 3 efficacy and safety study of dacomitinib (PF-00299804) vs. gefitinib for the first-line treatment of locally advanced or metastatic NSCLC in subjects with EGFR-activating mutations										
NCT number:	NCT01774721										
				Estimated absolute difference in effect			**Estimated relative difference in effect**			**Description of methods used for estimation**	**References**
Outcome	**Study arm**	**N**	**Result (95% CI)**	**Difference**	**95% CI**	**P value**	**Ratio**	**95% CI**	**P value**		
Median PFS, Investigator (months)	Dacomitinib	227	16.6 (12.9; 18.4)				HR:0.62	0.50; 0.78		ITT analysis set. See appendix 6.3 for statistical methods	Wu 2017; figure 2B
	Gefitinib	225	11.0 (9.4; 12.1)								
Global quality of life EORTC QLQ-C30	Dacomitinib	227	0.20			0.0002				Data as published. ITT analysis set	Wu 2017; figure 5 and p1463
	Gefitinib	225	4.94								

6.4.2 Results of the FLAURA study

TABLE 14 BY-STUDY RESULTS FOR FLAURA (OSIMERTINIB)

Trial name:	FLAURA: A phase III, double-blind, randomised study to assess the safety and efficacy of AZD9291 versus a standard of care epidermal growth factor receptor tyrosine kinase inhibitor as first line treatment in patients with epidermal growth factor receptor mutation positive, locally advanced or metastatic non small cell lung cancer										
NCT number:	NCT02296125										
				Estimated absolute difference in effect			**Estimated relative difference in effect**			**Description of methods used for estimation**	**References**
Outcome	**Study arm**	**N**	**Result (95% CI)**	**Difference**	**95% CI**	**P value**	**Ratio**	**95% CI**	**P value**		
Overall survival (adjusted) (proportion alive at 12 months)	Osimertinib	279	89% (85; 92)				HR: 0.63	0.45; 0.88	0.007	Data as published. See appendix 6.3 for statistical methods	Soria 2018, table 2 and p121
	Gefitinib/ erlotinib	277	82% (77; 86)								
	Osimertinib	279	Data not mature				HR: 0.63	0.45; 0.88	0.007	-	

Trial name:	FLAURA: A phase III, double-blind, randomised study to assess the safety and efficacy of AZD9291 versus a standard of care epidermal growth factor receptor tyrosine kinase inhibitor as first line treatment in patients with epidermal growth factor receptor mutation positive, locally advanced or metastatic non small cell lung cancer									
NCT number:	NCT02296125									
				Estimated absolute difference in effect			**Estimated relative difference in effect**			**Description of methods used for estimation**	**References**
Outcome	**Study arm**	**N**	**Result (95% CI)**	**Difference**	**95% CI**	**P value**	**Ratio**	**95% CI**	**P value**		
Median overall survival (months)	Gefitinib/ erlotinib	277	Data not mature								Soria 2018, p120
CNS progression (proportion of patients)	Osimertinib	226	3.1% (1.5; 6.3)	RD: -0.039	-0.080; 0.002	0.0614	RR: 0.44	0.18; 1.06	0.0681	Patients with no known/treated CNS metastases at baseline. See appendix 6.3 for statistical methods	Soria 2018, table S4
	Gefitinib/ erlotinib	214	7.0% (4.3; 11.2)								
Median CNS progression-free survival (months)	Osimertinib	61	NC (16.5; NC)				HR: 0.48	0.26; 0.86	0.014	Only patients with measurable / non-measurable CNS lesions at study entry. NC: not calculable. Data as published	Reungwet-wattana 2018, table 2, p3293
	Gefitinib/ erlotinib	67	13.9 (8.3; NC)								
Discontinuation of treatment due to adverse events (proportion of patients)	Osimertinib	279	9.7% (6.5; 13.8)	RD: -0.041	-0.076; 0.017		RR: 0.71	0.44; 1.12	0.1409	ITT analysis set. See appendix 6.3 for statistical methods	Soria 2018, p121
	Gefitinib/ erlotinib	277	13.7% (9.9; 18.3)								
Any adverse event grade 3-4 (proportion of patients)	Osimertinib	279	31.9% (26.5; 37.7)	RD: -0.093	-0.156; -0.0132		RR: 0.78	0.62; 0.97	0.0244	Safety analysis set. Data pooled without consideration for double counting. See appendix 6.3 for statistical methods	Soria 2018, table 3
	Gefitinib/ erlotinib	277	41.2% (35.3; 47.2)								

Trial name:	FLAURA: A phase III, double-blind, randomised study to assess the safety and efficacy of AZD9291 versus a standard of care epidermal growth factor receptor tyrosine kinase inhibitor as first line treatment in patients with epidermal growth factor receptor mutation positive, locally advanced or metastatic non small cell lung cancer										
NCT number:	NCT02296125										
				Estimated absolute difference in effect			**Estimated relative difference in effect**			**Description of methods used for estimation**	**References**
Outcome	**Study arm**	**N**	**Result (95% CI)**	**Difference**	**95% CI**	**P value**	**Ratio**	**95% CI**	**P value**		
PFS, investigator (proportion of patients not progressed at 12 months)	Osimertinib	279	68.2% (62.3; 73.5)				HR: 0.46	0.37; 0.57		ITT analysis set. PFS at 12 months. See appendix 6.3 for statistical methods	Tagrisso EPAR, p50
	Gefitinib/ erlotinib	277	42.3% (36.3; 48.2)								
Median PFS, independent (months)	Osimertinib	279	17.7 (15.1; 21.4)				HR: 0.45	0.36; 0.57		ITT analysis set. See appendix 6.3 for statistical methods	Soria et al. 2018 supplement p13
	Gefitinib/ erlotinib	277	9.7 (8.5; 11.0)								
Median PFS, investigator (months)	Osimertinib	279	18.9 (15.2; 21.4)				HR: 0.46	0.37; 0.57		ITT analysis set. See appendix 6.3 for statistical methods	Soria et al. 2018, figure 1, p117
	Gefitinib/ erlotinib	277	10.2 (9.6; 11.1)								
Global quality of life EORTC QLQ-C30	Osimertinib	279	Not reported								
	Gefitinib/ erlotinib	277	Not reported								

6.5 Results per PICO (clinical question)

TABLE 15 COMPARATIVE ANALYSES FOR CLINICAL QUESTION 1

Results per outcome	Studies included in the analysis	Absolute difference in effect			Relative difference in effect			Methods used for quantitative synthesis
		Difference	CI	P value	HR/OR/RR	CI	P value	
Overall survival at 12 months	-	-0.021	-0.084 – 0.023	-	HR: 1.20-	0.79; 1.85-	0.3911	ACR is 89% at 12M; Soria et al 2018, table 2
Median overall survival	-	-	-	-	-	-	-	Not possible; median OS data for osimertinib not available
CNS progression (proportion of patients)	Mok 2018 Soria 2018	-0.025	-0.030; 0.028		RR: 0.20	0.02; 1.88	0.1603	See appendix 6.3 for statistical methods. For dacomitinib only the frequency available hence RR instead of HR
CNS progression (time to progression)	-	-	-	-	-	-	-	Not possible; data not available for dacomitinib
Discontinuation of treatment due to adverse reactions (proportion of patients)	Wu 2017 Soria 2018	RD: 0.10	-0.006-0.34		RR: 2.05	0.94; 4.49	0.0719	See appendix 6.3 for statistical methods
Any adverse event grade 3-4 (proportion of patients)	Wu 2017 Soria 2018	RD: 0.36	0.18; 0.62		RR: 2.14	1.56; 2.94	<0.0001	See appendix 6.3 for statistical methods
PFS at 12 months, independent (proportion of patients)	Wu 2017 Soria 2018				HR: 1.31	0.95; 1.81	0.1026	No ACR available to calculate RD. See appendix 6.3 for statistical methods
PFS at 12 months, investigator (proportion of patients)	Wu 2017 Soria 2018	RD: -0.085	-0.187; 0.003		HR: 1.35	0.99; 1.84	0.0592	ACR is 68.2%; Tagrisso EPAR, p50. See appendix 6.3 for statistical methods
Median PFS, independent (months)	Wu 2017 Soria 2018							Indirect comparisons were not computed for endpoints reported as median, according to guidelines from the Medicines Council
Global quality of life EORTC QLQ-C30	-	-	-	-	-	-	-	Not possible; QoL data not available for osimertinib

7 References

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Medicinrådet

Medicinrådets vurdering af dacomitinib til behandling af uhelbredelig ikke-småcellet lungekræft med aktiverende EGFR-mutation

Versionsnr.: 1.0

Medicinrådet

Om Medicinrådet

Medicinrådet er et uafhængigt råd, som udarbejder anbefalinger og vejledninger om lægemidler til de fem regioner.

Medicinrådet vurderer, om nye lægemidler og indikationsudvidelser kan anbefales som mulig standardbehandling og udarbejder fælles regionale behandlingsvejledninger.

Nye lægemidler og indikationsudvidelser vurderes i forhold til effekt, eksisterende behandling og pris. Det skal give lavere priser og lægemidler, der er til størst mulig gavn for patienterne.

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

Om vurderingen

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

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

Lægemidlet vurderes efter Håndbog for Medicinrådets proces og metode vedr. nye lægemidler og indikationsudvidelser – version 2. Se Medicinrådets metodehåndbog for yderligere information.

Dokumentoplysninger	
Godkendelsesdato	25. september 2019
Ikrafttrædelsesdato	25. september 2019
Dokumentnummer	57114
Versionsnummer	1.0

Medicinrådet, Dampfærgevej 27-29, 3. th., 2100 København Ø
www.medicinraadet.dk
Sprog: dansk
Format: pdf
Udgivet af Medicinrådet, 25. september 2019

Indhold

1 Lægemiddelinformationer

Lægemidlets oplysninger	
Handelsnavn	Vizimpro
Generisk navn	Dacomitinib
Firma	Pfizer
ATC-kode	L01XE47
Virkningsmekanisme	2.-generations epidermal vækstfaktorreceptor (EGFR) tyrosinkinasehæmmer (TKI)
Administration/dosis	Tablet 45 mg én gang dagligt indtil progression eller intolerable bivirkninger. Tabletter fås som 45, 30 og 15 mg.
EMA-indikation	Førstelinjebehandling af voksne patienter med lokalt fremskreden eller metastatisk ikke-småcellet lungecancer (NSCLC) med aktiverende epidermal vækstfaktorreceptor (EGFR)-mutationer.

2 Medicinrådets konklusion

Medicinrådet vurderer, at dacomitinib til patienter med uhelbredelig ikke-småcellet lungekræft med aktiverende EGFR-mutation giver en **negativ værdi** sammenlignet med osimertinib. Evidensens kvalitet vurderes at være 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.

• **Samlet værdi kan ikke kategoriseres:** På grund af usikkerheder omkring effektforhold, er det ikke muligt at kategorisere lægemidlets samlede værdi.

3 Forkortelser

ARR:	Absolut risikoreduktion
CI:	Konfidensinterval (*Confidence Interval*)
CHMP:	*Committee for Medicinal Products for Human Use*
CNS:	Centralnervesystemet
DOR:	Responsvarighed (*Duration Of Response*)
EGFR:	Epidermal vækstfaktorreceptor (*Epidermal Growth Factor Receptor*)
EMA:	Det Europæiske Lægemiddelagentur (*European Medicines Agency)*
EORTC-CTAE:	*European Organisation for Research and Treatment of Cancer – Common Terminology Criteria for Adverse Events*
EORTC QLQ-C30:	*European Organisation for Research and Treatment of Cancer Quality-of-life Questionnaire-Core 30*
EPAR:	*European public assessment report*
GRADE:	System til vurdering af evidens (*Grading of Recommendations Assessment, Development and Evaluation*)
HR:	*Hazard ratio*
IASLC:	*International Association for the Study of Lung Cancer*
ITT:	*Intention to treat*
NSCLC:	Ikke små-cellet lungekræft (*Non-small-cell lung cancer*)
OR:	*Odds ratio*
ORR:	Objektiv responsrate (*overall response rate*)
OS:	Overlevelse (*Overall survival*)
PFS:	Progressionsfri overlevelse (*Progression-free survival*)
PICO:	*Population, Intervention, Comparator, Outcome*
RECIST:	*Response Evaluation Criteria in Solid Tumors*
RR:	Relativ risiko
SAE:	Alvorlig uønsket hændelse (*Serious Adverse Event*)
TKI:	Tyrosinkinasehæmmer (*Tyrosine kinase inhibitor*)

TNM:	*Tumor, Node, Metastasis* klassifikation for lungekræft

4 Formål

Formålet med Medicinrådets vurdering af dacomitinib til behandling af uhelbredelig ikke-småcellet lungekræft (NSCLC) med aktiverende epidermal vækstfaktorreceptor (EGFR)-mutationer, er at vurdere den værdi, lægemidlet har i forhold til et eller flere lægemidler til samme patientgruppe.

Med udgangspunkt i vurderingen og en omkostningsanalyse udarbejdet af Amgros beslutter Medicinrådet, om dacomitinib kan anbefales som mulig standardbehandling.

5 Baggrund

NSCLC med aktiverende EGFR-mutationer

I 2017 blev 4.856 danskere diagnosticeret med lungekræft [1], og dermed er lungekræft en af de hyppigst forekommende kræftsygdomme i Danmark [2]. Lungekræft inddeles i fire stadier (I-IV) afhængigt af udbredelsesgrad [3]. Stadieinddelingen foretages jævnfør *Tumor, Node, Metastasis* (TNM)-klassifikation for lungekræft. De epidemiologiske data i dette afsnit stammer fra TNM version 7-klassifikationen. TNM 8 er efterfølgende indført i Danmark [3]. Stadie III betyder, at tumor enten har en vis størrelse, indvækst i nærliggende struktur eller spredning til regionale lymfeknuder. Metastatisk lungekræft betegnes som stadie IV og er uhelbredelig. Nogle patienter med lungekræft i stadie III betragtes også som havende uhelbredelig lungekræft og behandles som patienter i stadie IV.

Der findes to overordnede typer lungekræft: småcellet lungekræft og ikke-småcellet lungekræft (NSCLC). Ca. 85 % af de patienter, som blev diagnosticerede med lungekræft i Danmark i 2017, havde NSCLC. Ca. 25 % af patienterne med uhelbredelig NSCLC har planocellulær tumor og ca. 75 % af ikke-planocellulær tumor. Langt de fleste ikke-planocellulære tumorer er adenokarcinomer [1].

Der kendes flere biomarkører for NSCLC, hvoraf enkelte har betydning for behandlingen og prognosen. En undergruppe af disse er aktiverende EGFR-mutationer, der findes hos ca. 8 % af de testede patienter med adenokarcinomer, hvor mutationsraten er højest [1,4–6]. Ifølge Dansk Lunge Cancer Gruppes årsrapport var der registreret 161 patienter i Danmark i 2017, som havde en aktiverende EGFR-mutation. Det reelle antal af lungekræftpatienter med en aktiverende EGFR-mutation er formodentlig omkring 200, da EGFR-status ikke var registreret for 18,7 % af patienter med adenokarcinom [1].

Ca. 1/3 af patienter med NSCLC og en aktiverende EGFR-mutation vil i deres sygdomsforløb progrediere med metastaser til centralnervesystemet (CNS) [7,8]. Patienter med CNS-metastaser oplever betydelig morbiditet og reduceret livskvalitet, ofte med neurologiske symptomer og kognitiv påvirkning.

Nuværende behandling

For uhelbredelig NSCLC er behandlingsmålet symptomlindring og levetidsforlængelse. Behandlingen er systemisk i form af kemoterapi, immunterapi eller targeteret behandling [1,6,9]. Patienter med en aktiverende EGFR-mutation får targeteret behandling i form af en EGFR-tyrosinkinasehæmmer (EGFR-TKI) som førstelinjebehandling. Patienter med aktiverende EGFR-mutation har en længere forventet overlevelse end patienter med NSCLC uden aktiverende EGFR-mutation, hvis de får targeteret behandling.

Gefitinib, afatinib og erlotinib blev tidligere ligestillet til førstelinjebehandling af Rådet for Dyr Sygehusmedicin (RADS). Osimertinib blev d. 10. april 2019 anbefalet af Medicinrådet som mulig standardbehandling i første linje til patienter med uhelbredelig NSCLC og aktiverende EGFR-mutation. I dansk klinisk praksis anvendes osimertinib efter anbefalingen som førstevalg.

Fagudvalget vurderer, at omkring 140 patienter (ud af estimatet på ca. 200 patienter som har en EGFR-aktiverende mutation) årligt er kandidater til førstelinjebehandling med EGFR-TKI [1]. Targeteret behandling benyttes kun til patienter med uhelbredelig sygdom. Nogle patienter med EGFR-aktiverende mutation vil få kurativt intenderet behandling for lungekræft i et tidligere stadie. Behandlingen med EGFR-TKI gives indtil sygdomsprogression eller intolerable bivirkninger. Patienter, der progredierer under førstelinjebehandling med osimertinib, bliver derefter typisk behandlet jævnfør retningslinjerne for ikke-planocellulær NSCLC [9].

Anvendelse af det nye lægemiddel

Dacomitinib er en andengenerations EGFR-TKI, der virker gennem hæmning af EGFR-signalering. Ved at blokere EGFR mindsker dacomitinib tumors vækst samt spredning.

Dacomitinib opnåede markedsføringstilladelse fra det Europæiske Lægemiddelagenturs (EMA) den 2. april 2019 for indikationen: førstelinjebehandling af voksne patienter med lokalt fremskreden eller metastatisk NSCLC med aktiverende epidermal vækstfaktorreceptor (EGFR)-mutationer.

Dacomitinib administreres peroralt. Standarddosis er 45 mg én gang dagligt. Behandling med dacomitinib fortsætter indtil progression eller intolerable bivirkninger.

6 Metode

De præspecificerede metoder i protokollen er udarbejdet af Medicinrådet.

Ansøger har anvendt og fulgt den præspecificerede metode, jf. protokol som blev godkendt i Medicinrådet den 15. maj 2019. Ansøgers endelige ansøgning blev modtaget den 12. juni 2019. Vurderingen af dacomitinib til NSCLC med aktiverende EGFR-mutationer er behandlet i Medicinrådets 12-ugersproces. Ansøgningen er valideret af Medicinrådet.

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

Både den relative og absolutte effekt indgår i kategoriseringen af et lægemiddel. Dette foregår i en trinvis proces. Fagudvalget kategoriserer først den relative foreløbige kategori på baggrund af væsentlighedskriterierne og den absolutte foreløbige kategori på baggrund af de præspecificerede mindste klinisk relevante forskelle. Her er der tale om en ren kvantitativ proces. Herefter fastlægger fagudvalget den aggregerede kategori for hvert effektmål ved at sammenholde de foreløbige kategorier. Her kan fagudvalget inddrage deres kliniske indsigt. Når den samlede kategori for lægemidlets værdi skal fastlægges, sammenvejer fagudvalget alle effektmål. Effektmålenes kategorier kombineres med effektmålenes vægt, og eventuelle kliniske overvejelser inddrages. Den samlede kategorisering af lægemidlets værdi er således delvis en kvantitativ og delvis en kvalitativ proces, hvor der foretages en klinisk vurdering af det foreliggende datagrundlag. Vurdering af evidensens kvalitet foretages med udgangspunkt i GRADE og udtrykker tiltroen til evidensgrundlaget for de enkelte effektstørrelser og den endelige kategori for klinisk værdi. Evidensens kvalitet inddeles i fire niveauer: høj, moderat, lav og meget lav. GRADE-metoden er et internationalt anerkendt redskab til systematisk vurdering af evidens og udarbejdelse af anbefalinger. I denne vurdering er metoden anvendt til at vurdere evidensens kvalitet.

7 Litteratursøgning

Ansøger har foretaget en systematisk søgning efter kliniske studier, der undersøgte dacomitinibs effekt og studier, der undersøgte osimertinibs effekt, jf. søgestrengen i protokollen. Ansøgers PRISMA-diagram og litteraturgennemgang fremgår af ansøgningen.

Søgningen resulterede i identifikationen af fire publikationer fra to kliniske studier (ARCHER 1050 og FLAURA), som begge er randomiserede, fase III-studier, og som opfylder Medicinrådets præspecificerede kriterier. Studierne kan således bidrage til besvarelsen af det kliniske spørgsmål i protokollen.

Ingen af studierne sammenligner dacomitinib og osimertinib direkte, og der er derfor lavet indirekte analyser. Datagrundlaget for analyserne er baseret på de kliniske studier for de to lægemidler samt EPAR.

Tabel 1: Oversigt over publikationer anvendt i vurderingen af dacomitinib.

Reference	Studie-ID	NCT nummer	Lægemiddel
Dacomitinib versus gefitinib as first-line treatment for patients with EGFR-mutation-positive non-small cell lung cancer (ARCHER 1050): A randomised, open-label, phase 3 trial. Wu *et al.*, Lancet oncology, 2017, 18, [10]	ARCHER 1050	NCT01774721	Dacomitinib
Improvement in overall survival in a randomized study that compared dacomitinib with gefitinib in patients with advanced non-small-cell lung cancer and EGFR-activating mutations. Mok *et al.*, JCO, 2018, 36 [11]			
Osimertinib in untreated EGFR-mutated advanced non–small-cell lung cancer Soria *et al.*, NEJM, 2018, 378 [12]	FLAURA	NCT02296125	Osimertinib
CNS response to osimertinib versus standard epidermal growth factor receptor tyrosine kinase inhibitors in patients with untreated EGFR-mutated advanced non–small-cell lung cancer Reungwetwattana *et al.*, JCO, 2018, 36 [13]			

8 Databehandling

Indirekte sammenligning

Ansøger har foretaget en indirekte sammenligning af dacomitinib og osimertinib for at besvare det kliniske spørgsmål.

I ARCHER 1050 er dacomitinib sammenlignet med gefitinib, mens osimertinib i FLAURA er sammenlignet med en blandet komparator-arm bestående af erlotinib og gefitinib. Fagudvalget har i "Baggrund for behandlingsvejledning for uhelbredelig ikke-småcellet lungekræft" taget stilling til, at erlotinib og gefitinib kan ligestilles. Her blev der benyttet data fra CTONG0901-studiet [14], der viser, at der ikke er klinisk

betydende forskelle ved førstelinjebehandling imellem gefitinib og erlotinib for effektmålet *OS*, *behandlingsophør grundet uønskede hændelser* og frekvensen af *uønskede hændelser grad 3-4*. Udover den direkte sammenligning fra CTONG0901 er der identificeret flere publicerede metaanalyser, som understøtter ligestillingen [15,16].

I fraværet af en direkte sammenligning mellem dacomitinib og osimertinib accepterer fagudvalget at benytte en kvantitativ indirekte sammenligning.

Opfølgningstid

Der er forskellig opfølgningstid i de kliniske studier af dacomitinib og osimertinib. Fagudvalget tager dette i betragtning for de effektmål, hvor det kan have betydning for vurderingen.

Vurdering af datagrundlag

Fagudvalget vurderer, at datagrundlaget for *overall survival* (OS) er så usikkert at det ikke er meningsfyldt at vurdere effektforskellen imellem osimertinib og dacomitinib. Dette uddybes i beskrivelsen af effektmålet.

Der er ikke indleveret data på *CNS-progression* som *time-to-event* effektmål for dacomitinib. Da der ikke indgik patienter med CNS-metastaser i ARCHER 1050 studiet vurderer fagudvalget at denne population kan have en bedre prognose end populationen i FLAURA, hvor 21 % havde hjernemetastaser. Dermed er der, for dette effektmål, for stor forskel på populationerne til at dacomitinib kan sammenlignes med osimertinib.

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

9 Lægemidlets værdi

9.1 Konklusion klinisk spørgsmål 1

Hvilken klinisk merværdi har dacomitinib til patienter med NSCLC-stadie IIIB-IV med aktiverende EGFR-mutation sammenlignet med osimertinib?

I tabellen herunder fremgår den samlede kategori for lægemidlet og kvaliteten af den samlede evidens. Tabellen viser også absolutte og relative effektforskelle samt foreløbige og aggregerede værdier.

Tabel 2: Kategorier og resultater

Effektmål	Måleenhed MKRF, defineret i protokol	Vigtighed	Forskel i absolutte tal		Forskel i relative tal		Aggregeret værdi pr. effektmål
			Forskel (95% CI)	Foreløbig værdi	Forskel (95% CI)	Foreløbig værdi	
Overlevelse	Median forskel 3 mdr.	Kritisk	ARCHER 1050 Dacomitinib: 34,1 mdr. [29,5; 37,7] Gefitinib: 26,8 mdr. [23,7;32,1] FLAURA NR	Kan ikke kategoriseres		Kan ikke kategoriseres	Kan ikke kategoriseres
	Andel patienter 5 %-point forskel efter 12 måneder			Kan ikke kategoriseres			
CNS-progression	Median forskel 3 mdr. eller 5 %-point forskel efter 12 måneder	Kritisk	ARCHER 1050 NR FLAURA[1] Osimertinib: NR [16,5; NR] Gefitinib/Erlotinib: 13,9 [8,5; NR]	Kan ikke kategoriseres		Kan ikke kategoriseres	Kan ikke kategoriseres
Bivirkninger	Andel patienter der ophører behandlingen pga. bivirkninger. 5 %-point forskel	Kritisk	10 %-point [-0,6; 34]	Kan ikke kategoriseres	RR 2,05 [0,94; 4,49]	Kan ikke kategoriseres	Negativ værdi
	Andel patienter, der oplever en eller flere grad 3-4 bivirkninger. 5 %-point forskel		36 %-point [18; 62]	Negativ værdi	RR 2,14 [1,56; 2,94]	Negativ værdi	
	Gennemgang af bivirkningsprofil.		Negativ værdi				
PFS	Median forskel[2] 3 mdr. eller 5 %-point forskel efter 12 måneder	Vigtig	ARCHER 1050 Dacomitinib: 14,7 mdr. [11,1; 16,6] Gefitinib: 9,2 mdr. [9,1-11,0] FLAURA Osimertinib: 17,7 mdr. [15,1; 21,4] Gefitinib/Erlotinib: 9,7 mdr. [8,5; 11,0] Forskel: -2,5 mdr.	Kan ikke kategoriseres	HR 1,31 [0,95; 1,81]	Kan ikke kategoriseres	Kan ikke kategoriseres
Livskvalitet	Forskel i gennemsnitlig ændring i EORTCQLQ-C30 10 point	Vigtig	-	-	-	-	Kan ikke kategoriseres
Samlet kategori for lægemidlets værdi		Negativ					
Kvalitet af den samlede evidens		Meget lav					

[1]Undersøgt for subpopulation af patienter med CNS-metastaser ved studiestart. NR: Median ikke nået (”Not reached”)

9.1.1 Gennemgang af studier

Karakteristika

ARCHER 1050: Er et randomiseret, ublindet (open-label) fase III studie der undersøgte effekt og sikkerhed af dacomitinib sammenlignet med gefitinib, som førstelinjebehandling til patienter med uhelbredelig NSCLC og aktiverende EGFR-mutation. Patienterne var randomiseret 1:1 til dacomitinib (n =227) eller gefitinib (n = 225). Randomiseringen var stratificeret efter type af EGFR mutation, samt selv-rapporteret etnicitet. Effektanalyser er baseret på alle randomiserede patienter (n = 452), og sikkerhedsanalyser er baseret på alle randomiserede patienter, der modtog mindst én studiedosis (n = 451). Studiets primære effektmål var *PFS*, sekundære effektmål inkluderede *OS, behandlingsophør grundet uønskede hændelser* og *alvorlige uønskede hændelser grad 3-4*. Overkrydsning fra gefitinib til dacomitinib behandling var ikke tilladt.

FLAURA: Er et randomiseret, dobbelt-blindet fase III studie der undersøgte effekt og sikkerhed af osimertinib sammenlignet med gefitinb/erlotinib, som førstelinjebehandling til patienter med uhelbredelig NSCLC og aktiverende EGFR-mutation. Patienterne var randomiseret 1:1 til osimertinib (n =279) eller gefitinib (n = 277). Randomiseringen var stratificeret efter type af EGFR mutation, samt etnicitet. Effektanalyser er baseret på alle randomiserede patienter (n = 556), og sikkerhedsanalyser er baseret på alle randomiserede patienter, der modtog mindst én studiedosis (n = 556). Studiets primære effektmål var *PFS*, sekundære effektmål inkluderede *OS, behandlingsophør grundet uønskede hændelser* og *alvorlige uønskede hændelser grad 3-4*. Overkrydsning fra gefitinib/erlotinib til osimertinib behandling var tilladt efter progression (bedømt af en uafhængig komité) og ved identificering af T790M mutation.

Detaljerede inklusions- og eksklusions kriterier for begge studier er vist i Tabel 8, Bilag 2.

Tabel 3: Studiekarakteristika

Studie ID	Intervention, n patienter	Komparator, n patienter	Opfølgning (median mdr.)*	Afrapporterede effektmål	Kilder
ARCHER 1050	Dacomitinib, n = 227	Gefitinib, n = 225	31,1 / 31,4	*OS, behandlingsophør grundet AE's, PFS, AE's grad 3-4* og *livskvalitet*	[10,11]
FLAURA	Osimertinib, n = 279	Gefitinib/erlotinib, n = 277	15 / 9,7	*OS, behandlingsophør grundet AE's, PFS, AE's grad 3-4* og *CNS PFS*	[12,13]

*Median opfølgning ved seneste anvendte afrapportering.

Population

I Tabel 4 fremgår baselinekarakteristika for patientpopulationer i de inkluderede studier:

Tabel 4: Baselinekarakteristika for populationer i de inkluderede studier

	ARCHER 1050	FLAURA
Alder, median	61	64
Kvinder, %	60,0	63
> 65 år, %	39,5	46,4
PS 0-1, %	100	> 99
CNS-metastaser, %	0	21
Rygning	35,6	36
Stadie IV, %	91,5	95
Adenokarcinom, %	100	98,5
Etnicitet: Kaukasisk, % Asiatisk, % Andet, %	 25 75 < 1	 36 62 1
EGFR-mutation Exon 19 deletion, % L858R, %	 59 41	 63 37

Fagudvalget vurderer, at de to studier er sammenlignelige og at der er en acceptabel overensstemmelse imellem studiepopulationerne og den danske patientpopulation. Fagudvalget bemærker dog, at patienter med CNS-metastaser er ekskluderet fra ARCHER 1050-studiet, hvorimod 21 % af patienterne i FLAURA studiet havde CNS-metastaser. Fagudvalget vurderer dermed, at populationen i ARCHER 1050 kan have bedre prognose end populationen i FLAURA, hvilket også kan medføre forskelle på effektmålene *OS*, *PFS*, *CNS-progression*, og *livskvalitet*.

9.1.2 Resultater og vurdering

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

OS (kritisk)

Da lokal fremskredent og metastatisk NSCLC er uhelbredelig, vurderes forbedret *OS* med mindst mulig toksicitet som afgørende. Derfor vurderer fagudvalget, at *OS* er et kritisk effektmål.

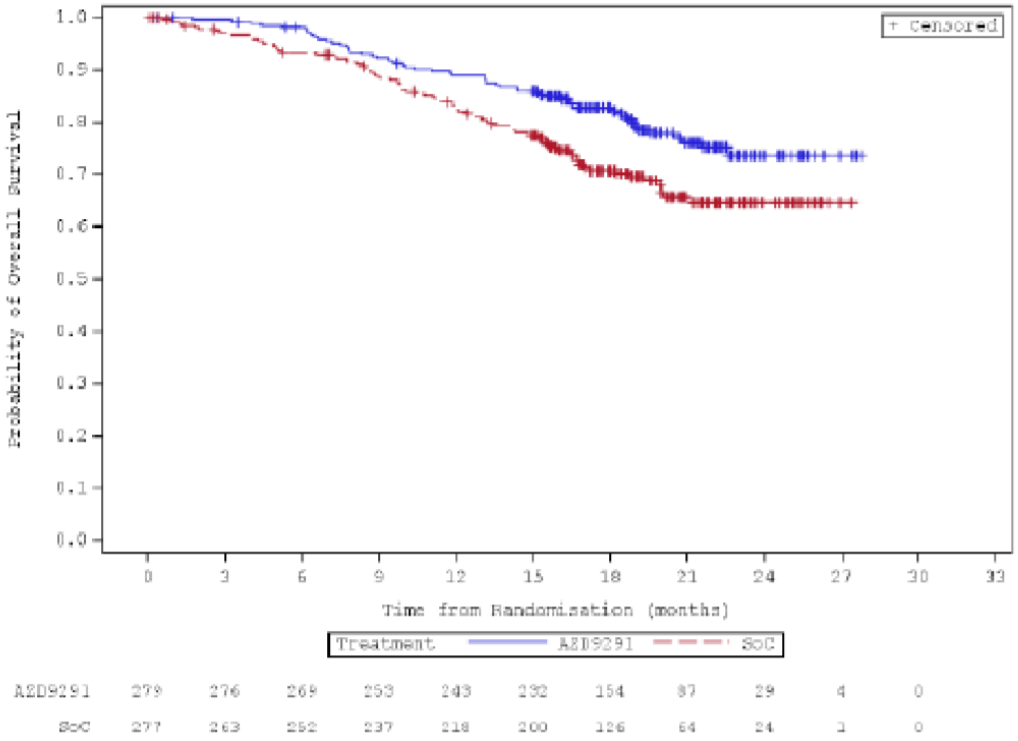
Der er en markant forskel i opfølgningstid i de to studier, ~31 måneder for dacomitinib i ARCHER 1050 og ~15 måneder for osimertinib i FLAURA-studiet.

OS-data fra FLAURA-studiet, med den længst mulige opfølgningstid, er en interim-analyse inkluderet i EPAR, se Figur 1, hvor hændelsesraten er hhv. 20,8 % og 30,0 % i osimertinib-armen og gefitinib/erlotinib-armen. En median forskel kan derfor ikke beregnes.

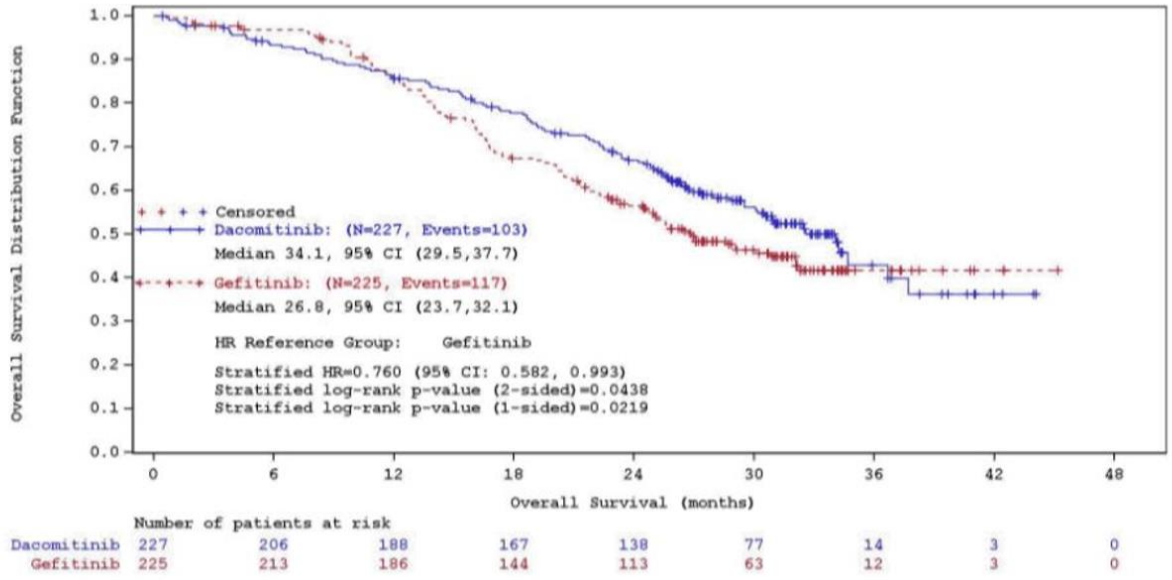
I ARCHER 1050-studiet er median *OS* 34,1 måned for dacomitinib-armen og 26,8 måned for gefitinib-armen. Der er mange censureringer, før medianen nås, særligt i dacomitinib-armen. Derudover krydser overlevelseskurven for dacomitinib og gefitinib hinanden to gange, hvorfor antagelsen om *proportional hazards* er tvivlsom, se Figur 2.

Den relative effektforskel mellem osimertinib og dacomitinib er opgjort som en HR på 1,20 [0,79; 1,85], hvilket ikke er statistisk signifikant. Da antagelsen om *proportional hazards* ikke er opfyldt for ARCHER-studiet, og medianen ikke er nået i FLAURA-studiet, vurderer fagudvalget, at datagrundlaget er så usikkert, at det ikke er meningsfyldt at vurdere den relative effektforskel imellem osimertinib og dacomitinib. Dermed har dacomitinib en foreløbig **værdi, der ikke kan kategoriseres** vedr. effektmålet *OS*.

Figur 1: Overlevelseskurve, FLAURA studiet [17] **fra EPAR**



Figur 2: overlevelseskurve, ARCHER 1050 [18] **fra EPAR**



Fagudvalget konstaterer, at den store forskel i opfølgningstid og manglende *proportional hazards* for *OS* data i ARCHER 1050-studiet, medfører at vurderingen af effektmålet *OS* ikke kan foretages på det foreliggende datagrundlag. På aggregeret niveau vurderer fagudvalget, at dacomitinib har en **værdi, der ikke kan kategoriseres** vedr. effektmålet *OS*.

CNS-progression (kritisk)

NSCLC med aktiverende EGFR-mutation metastaserer til CNS hos ca. en tredjedel af patienterne, hvilket medfører betydelig morbiditet og reduceret livskvalitet. Derfor anser fagudvalget *CNS-progression* som et kritisk effektmål.

I ARCHER-1050 studiet er patienter med CNS-metastaser ekskluderet ved studiestart.
I FLAURA-studiet havde 21 % af de inkluderede patienter CNS-metastaser. Dermed er der, for dette effektmål, for stor forskel på populationerne til at dacomitinib kan sammenlignes med osimertinib, og dermed kan værdien af dacomitinib ikke vurderes for effektmålet *CNS-progression*.

Fagudvalget bemærker, at der for osimertinib er demonstreret en god effekt sammenlignet med førstegenerations EGFR-TKIer (erlotinib og gefitinib) på effektmålet *CNS-progression*. Median tid til *CNS-progression* var for osimertinib-armen ikke nået [16,5; NR], og var for gefitinib/erlotinib-armen 13,9 mdr [8,5, NR]. Den relative effektforskel er opgjort som HR på 0,48 [0,26; 0,86] ved mediane opfølgningstider på 7 mdr. for gefitinib/erlotinib og 12,4 mdr. for osimertinib.

Bivirkninger, (kritisk)

Forekomst af alvorlige bivirkninger grad 3-4 er et udtryk for alvorlig toksicitet af lægemidlet [19]. Fagudvalget finder, at ophør med en effektiv behandling grundet bivirkninger er kritisk for patienterne. På den baggrund vurderes det, at *bivirkninger* er et kritisk effektmål.

Behandlingsophør på grund af bivirkninger

Effektmålet var i protokollen for dacomitinib opgjort som andelen af patienter, der ophører behandlingen grundet *bivirkninger*. I FLAURA studiet er behandlingsophør grundet uønskede hændelser rapporteret. Fagudvalget vurderer, at disse data kan benyttes til at besvare det kliniske spørgsmål. Hermed er *behandlingsophør grundet uønskede hændelser* også benyttet for ARCHER 1050, selvom behandlingsophør grundet bivirkninger er opgjort for dette studie.

Dacomitinib medfører 5,6 %-point flere behandlingsophør end gefitinib, mens osimertinib medfører 4,4 %-point færre behandlingsophør end gefitinib/erlotinib, hvilket resulterer i en absolut effektforskel på 10 %-point til fordel for osimertinib. Baseret på den absolutte effektforskel har dacomitinib dermed foreløbigt en **værdi, der ikke kan kategoriseres** vedr. effektmålet *behandlingsophør grundet uønskede hændelser*.

Den relative effektforskel er opgjort som en RR på 2,05 [0,94; 4,49], hvilket ikke er statistisk signifikant. Derudover er konfidensintervallet bredt, hvilket betyder, at forskellen imellem lægemidlerne kunne være en lille merværdi, ingen merværdi eller en negativ værdi. Baseret på den relative effektforskel har dacomitinib dermed foreløbigt en **værdi, der ikke kan kategoriseres** vedr. effektmålet *behandlingsophør grundet uønskede hændelser*.

Bivirkninger grad 3-4

Den absolutte effektforskel for *uønskede hændelser grad 3-4* er på 36 %-point til fordel for osimertinib hvilket er større end MKRF. Baseret på den absolutte effektforskel har dacomitinib dermed foreløbigt en **negativ værdi,** vedr. effektmålet *uønskede hændelser grad 3-4.*

Den relative effektforskel er opgjort som en RR på 2,14 [1,56; 2,94], hvilket er til fordel for osimertinib. Baseret på den relative effektforskel har dacomitinib dermed foreløbigt en **negativ værdi** vedr. effektmålet *uønskede hændelser grad 3-4*.

Kvalitativ gennemgang af bivirkninger

Ud fra fagudvalgets praktiske erfaring med osimertinib i førstelinjebehandling vurderes det, at hvad angår både frekvens og reversibilitet af uønskede hændelser er osimertinib sammenlignelig med gefitinib/erlotinib. Dette er i overensstemmelses med EMAs EPAR for osimertinib [20], hvor det samlede sikkerhedsdata indikerer, at behandling med osimertinib er mindst lige så veltolereret som gefitinib/erlotinib. Fagudvalget vurderer, at kardielle bivirkninger og monitorering ikke er en betragtelig udfordring i dansk klinisk praksis ved behandling med osimertinib.

Fagudvalget har endnu ingen klinisk erfaring med anvendelse af dacomitinib. I EMAs EPAR for dacomitinib [18] vurderes det, at lægemidlets tåles dårligere af patienterne end gefitinib.

Ud fra det kliniske studie vurderer fagudvalget, at de hyppigste grad 3-4 bivirkninger ved dacomitinib (hudtoksicitet, diarré og mundbetændelse) vil være meget generende for patienterne og påvirke deres dagligdag mere end de hyppigste grad 3-4 bivirkninger ved gefitinib/erlotinib og osimertinib.

På aggregeret niveau vurderer fagudvalget, at dacomitinib har en **negativ værdi** vedr. effektmålet *bivirkninger.*

PFS (vigtig)

Fagudvalget vurderer, at det har stor betydning for patienterne at forblive i behandling med en EGFR-TKI længst muligt, pga. den favorable bivirkningsprofil sammenlignet med kemoterapi, der anvendes i efterfølgende behandlingslinjer. Derfor vurderer fagudvalget, at *PFS* er et vigtigt effektmål.

I ARCHER 1050-studiet er median PFS 14,7 måneder for dacomitinib-armen og 9,2 måneder for gefitinib-armen. I FLAURA-studiet er median *PFS* 17,7 måneder for osimertinib-armen og 9,7 måneder for gefitinib/erlotinib. I begge studier er *PFS* bedømt af en uafhængig komité. Fagudvalget bemærker, at der ikke er væsentlig forskel på *PFS* i komparatorgrupperne i de to studier.

Den absolutte effektforskel mellem dacomitinib og osimertinib er 2,5 måneder, hvilket er mindre end MKRF. Baseret på den absolutte effektforskel har dacomitinib dermed foreløbigt en **værdi, der ikke kan kategoriseres** vedr. effektmålet *PFS*.

Den relative effektforskel er opgjort som en HR på 1,31 [0,95; 1,81], hvilket ikke er statistisk signifikant. Derudover er konfidensintervallet bredt, hvilket betyder, at forskellen imellem lægemidlerne kunne være en lille merværdi, ingen merværdi eller en negativ værdi. Baseret på den relative effektforskel har dacomitinib dermed foreløbigt en **værdi, der ikke kan kategoriseres** vedr. effektmålet *PFS*.

Fagudvalget konstaterer at den korte opfølgningstid i FLAURA studiet medfører usikkerhed vedr. vurdering af *PFS* for osimertinib. Dette opvejes delvist af, at forskellen mellem osimertinib og gefitinib/erlotinib ses før flertallet af censureringerne. På aggregeret niveau vurderer fagudvalget, at dacomitinib har en **værdi, der ikke kan kategoriseres** vedr. effektmålet *PFS*.

Livskvalitet

I denne vurdering er livskvalitet baseret på følgende instrument: European Organisation for Research and Treatment of Cancer Quality-of-life Questionnaire-Core 30 (EORTC QLQ-C30) [21].

I ARCHER 1050 er der en global værdi på 0,2 for dacomitinib og på 4,94 for gefitinib. Forskellen er dermed mindre end de prædefinerede 10 point som ville svare til en 'lille ændring' for livskvalitet jf. protokollen.

Der er ikke publiceret livskvalitets data for FLAURA. I EPAR'en for osimertinib konkluderer EMA, at der efter 9 måneder ikke er en klinisk meningsfuld forskel på livskvalitet ved behandling med osimertinib sammenlignet med erlotinib/gefitinib.

Fagudvalget bemærker, at hverken dacomitinib eller osimertinib har dokumenteret en bedre effekt end førstegenerations EGFR-TKI'er på dette effektmål.

På aggregeret niveau vurderer fagudvalget at dacomitinib har en **værdi, der ikke kan kategoriseres** for effektmålet *livskvalitet.*

9.1.3 Evidensens kvalitet

Evidensens kvalitet for vurdering af dacomitinib til behandling af NSCLC med aktiverende EGFR-mutationer er samlet set vurderet som værende **meget lav**. Fagudvalget har foretaget en vurdering af evidensens kvalitet i overensstemmelse med GRADE-retningslinjer (Tabel 7, bilag 1). Den samlede evidenskvalitet er nedgraderet et niveau for inkonsistens ('inconsistency') for alle effektmålene, da vurderingen er baseret på ét studie. Den samlede evidenskvalitet er nedgraderet to niveauer for indirekthed ('indirectness') for alle effektmål, idet interventionerne for det kliniske spørgsmål er sammenlignet indirekte,

og der er forskel mellem studierne vedr. inklusion af patienter med hjernemetastase. Den samlede evidenskvalitet er nedgraderet et niveau for upræcist estimat (’imprecision’) for effektmålene *OS*, *ophør grundet bivirkninger* samt *PFS*. Evidensens kvalitet er således **meget lav** for alle effektmål anvendt ved det kliniske spørgsmål, undtagen effektmålene *OS, livskvalitet* og *CNS-progression*, hvor evidensen kvalitet ikke kan vurderes grundet manglende datagrundlag.

9.1.4 Konklusion for klinisk spørgsmål 1

Fagudvalget har vurderet dacomitinib sammenlignet med osimertinib på tre kritiske og to vigtige effektmål:

På det første kritiske effektmål, *OS*, kunne værdien af dacomitinib ikke kategoriseres. Der er endnu ikke median overlevelsesdata for osimertinib, og for dacomitinib var antagelsen om *proportional hazards* ikke opfyldt for overlevelseskurverne. Derfor kunne effektmålet ikke vurderes kvantitativt.

På det andet kritiske effektmål, *CNS-progression*, kunne værdien af dacomitinib heller ikke kategoriseres, da der ikke indgik patienter med CNS-metastaser i studiet af dacomitinib. Der er dokumenteret en god effekt af osimertinib på dette effektmål sammenlignet med erlotinib og gefitinib. Fagudvalget vurderer således, at osimertinib er det bedste lægemiddel på dette effektmål, indtil en effekt af dacomitinib er dokumenteret.

På det tredje kritiske effektmål, *bivirkninger*, kan dacomitinib kategoriseres med en negativ værdi.

På det første vigtige effektmål, *PFS*, havde dacomitinib en værdi, der ikke kan kategoriseres. Den absolutte forskel i medianer er mindre end MKRF og har intet konfidensinterval. Den relative forskel mellem lægemidlerne havde et bredt konfidensinterval, der både kunne rumme en negativ og positiv værdi af dacomitinib.

På det andet vigtige effektmål, *livskvalitet*, kunne værdien af dacomitinib ikke kategoriseres. Vurderingen på dette effektmål tæller hverken positivt eller negativt for dacomitinib, da hverken dacomitinib eller osimertinib har en dokumenteret bedre effekt end førstegenerations EGFR-TKIer på dette effektmål.

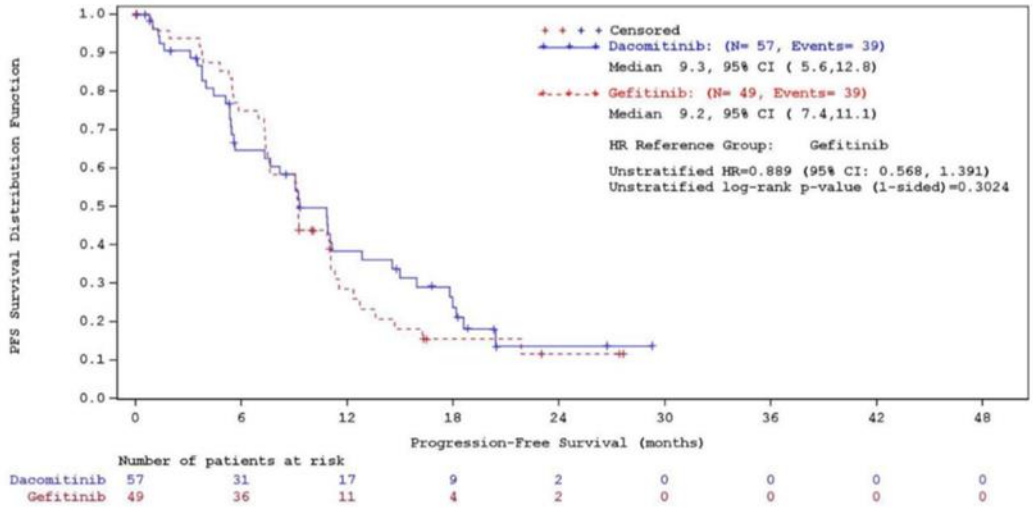
Samlet betyder dette, at der ikke på noget effektmål er dokumenteret en positiv værdi for dacomitinib sammenlignet med osimertinib. Til gengæld er der på et kritisk effektmål, *bivirkninger*, en negativ værdi af dacomitinib og på et andet kritisk effektmål (*CNS-progression*) ingen dokumentation for effekt af dacomitinib, men dokumentation for god effekt af osimertinib. Derfor bliver den samlede vurdering en negativ værdi.

Fagudvalget vurderer, at dacomitinib til patienter med uhelbredelig ikke-småcellet lungekræft med aktiverende EGFR-mutation giver en **negativ værdi** sammenlignet med osimertinib. Evidensens kvalitet vurderes at være meget lav.

10 Andre overvejelser

Fagudvalget gør opmærksom på, at der i det kliniske studie af dacomitinib ikke blev dokumenteret en gevinst på *PFS* i forhold til komparator for subgruppen af ikke-asiatiske patienter. Den relative effekt for *intention to treat* populationen var HR 0,59 [0,47; 0,74], mens den relative effekt for subgruppen af non-asiatiske patienter var HR 0,89 [0,57; 1,39]. Fagudvalget og EMAs EPAR har ikke nogen forklaring på dette forhold, der kan være et tilfældigt fund. Disse data indgik ikke i kategoriseringen af lægemidlet, men bestyrker vurderingen af en negativ værdi af dacomitinib i dansk klinisk praksis, hvor størstedelen af patienterne er ikke-asiater.

Figur 3: Progressionsfri overlevelse for subgruppe af ikke-asiatiske patienter fra EPAR



11 Fagudvalgets vurdering af samlet værdi og samlet evidensniveau

Fagudvalget vurderer, at dacomitinib til patienter med uhelbredelig ikke-småcellet lungekræft med aktiverende EGFR-mutation giver en **negativ værdi** sammenlignet med osimertinib. Evidensens kvalitet vurderes at være meget lav.

12 Rådets vurdering af samlet værdi og samlet evidensniveau

Medicinrådet vurderer, at dacomitinib til patienter med uhelbredelig ikke-småcellet lungekræft med aktiverende EGFR-mutation giver en **negativ værdi** sammenlignet med osimertinib. Evidensens kvalitet vurderes at være meget lav.

13 Relation til eksisterende behandlingsvejledning

I Medicinrådets behandlingsvejledning offentliggjort august 2019 blev dacomitinib vurderet til førstelinjebehandling af uhelbredelig ikke-småcellet lungekræft med aktiverende EGFR-mutation. Her blev

dacomitinib ligestillet med afatinib, erlotinib og gefitinib som andet valg efter osimertinib. Medicinrådet vurderede, der var klinisk betydende forskelle mellem lægemidlerne, hvor osimertinib var bedre end de øvrige lægemidler. Fagudvalgets vurdering af en negativ merværdi af dacomitinib sammenlignet med osimertinib er således konsistent med behandlingsvejledningen.

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15 Sammensætning af fagudvalg og kontaktinformation til Medicinrådet

Medicinrådets fagudvalg vedrørende lungekræft

Formand	**Indstillet af**
Christa Haugaard Nyhus Overlæge	Lægevidenskabelige Selskaber
Medlemmer	**Udpeget af**
Kan ikke udpege	Region Nordjylland
Halla Skuladottir Overlæge, dr.med.	Region Midtjylland
Stefan Starup Jeppesen Overlæge, ph.d	Region Syddanmark
Jeanette Haar Ehlers Overlæge	Region Sjælland
Lotte Engell-Nørregård Afdelingslæge, ph.d.	Region Hovedstaden
Henrik Hager Overlæge	Inviteret af formanden
Nille Behrendt Overlæge	Dansk Patologiselskab
Peder Fabricius Ledende overlæge	Dansk Selskab for Lungemedicin
Nina Hannover Bjarnason Overlæge, dr.med.	Dansk Selskab for Klinisk Farmakologi
Annie Lorenzen Klinisk farmaceut	Dansk Selskab for Sygehusapoteksledelse
Finn Klausen Patient/patientrepræsentant	Danske Patienter
Lisbeth Søbæk Hansen Patient/patientrepræsentant	Danske Patienter

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16 Versionslog

Version	Dato	Ændring
1.0	25. september 2019	Godkendt af Medicinrådet.

17 Bilag 1: GRADE-evidensprofiler

17.1 Cochrane Risk of Bias

Tabel 5: RoB FLAURA [12]

Bias	Vurdering	Begrundelse
Random sequence generation (Selection bias)	Lav risiko for bias	"Patients were stratified according to tumor EGFR mutation status (Ex19del or L858R) and race (Asian or non- Asian) and were randomly assigned in a 1:1 ratio to receive either oral osimertinib (at a dose of 80 mg once daily) or a standard oral EGFR-TKI (gefitinib at a dose of 250 mg once daily or erlotinib at a dose of 150 mg once daily)."
Allocation concealment (Selection bias)	Uklar risiko for bias	**Kommentar**: Det beskrives ikke, om tilordningssekvensen er åbent tilgængelig.
Blinding of participants and personnel (Performance bias)	Lav risiko for bias	"Double-blind (…) trial".
Blinding of outcome assessment (Detection bias)	Lav risiko for bias	"The primary end point was the duration of progression-free survival as determined by investigator assessments, according to RECIST, version 1.1. A sensitivity analysis of progression-free survival was performed on the basis of data from blinded independent central review of RECIST assessments for all the patients". **Kommentar**: analysen af det primære endepunkt var blindet.
Incomplete outcome data (Attrition bias)	Lav risiko for bias	"The full analysis set included all randomly assigned patients and was used for efficacy assessments. Adverse events were assessed in the safety analysis set, consisting of all the patients who received at least one dose of randomly assigned treatment". **Kommentar**: Der er ikke forskel på andelen af patienter i *full analysis set* og *safety analysis set*.
Selective reporting (Reporting bias)	Lav risiko for bias	Protokol er tilgængelig, og alle studiets præspecificerede effektmål af interesse er blevet rapporteret som beskrevet i protokollen.
Other bias	Lav risiko for bias	Der synes ikke at være årsager til anden bias for dette studie.

Tabel 6: ARCHER 1050 [10]

Bias	Vurdering	Begrundelse
Random sequence generation (Selection bias)	Lav risiko for bias	"Eligible patients were randomly assigned 1:1 to receive dacomitinib or gefitinib. Randomisation was stratified by race (self-reported; Japanese vs Chinese vs other east Asian vs non-Asian) and EGFR mutation type (exon 19 deletion vs Leu858Arg mutation). A randomisation list was generated using a computer-generated random code that was assigned by a central interactive web response system (IWRS)"
Allocation concealment (Selection bias)	Lav risiko for bias	"The IWRS was managed by a vendor (Cenduit Services; Bangalore, India) who had no clinical involvement with the trial. The allocation sequence, based on a randomisation requirement specification form (prepared by the IWRS vendor in accordance with the requirements of the study sponsor), was generated by the IWRS. The investigators at the clinical sites enrolled the patients by using the IWRS, entered each patient's race and EGFR mutation type (the stratification variables), and assigned each patient to a treatment group on the basis of the IWRS output. "
Blinding of participants and personnel (Performance bias)	Uklar risiko for bias	"In this open label study, investigators and patients were not masked to treatment assignment". **Kommentar**: studiet var ikke dobbeltblindet.
Blinding of outcome assessment (Detection bias)	Lav risiko for bias	"Tumour assessment by independent review was masked". **Kommentar**: analysen af det primære endepunkt blev foretaget både af investigators (ublindet) og af *en 'independent review committee´* blindet.
Incomplete outcome data (Attrition bias)	Lav risiko for bias	"All randomised patients (the intention-to-treat population) were included in the efficacy analysis" **Kommentar**: Effekt er undersøgt for hele ITT-populationen.
Selective reporting (Reporting bias)	Lav risiko for bias	**Kommentar**: Protokol er tilgængelig, og alle studiets præspecificerede effektmål (effekt og sikkerhedsmål) af interesse er blevet rapporteret som beskrevet i protokollen.
Other bias	Lav risiko for bias	Der synes ikke at være årsager til andre bias for dette studie.

17.2 GRADE-evaluering af evidenskvaliteten

Tabel 7: GRADE

For effektmålene *OS*, *CNS-progression* og *livskvalitet* kunne fagudvalget ikke foretage en kvantitativ sammenligning på baggrund af det indleverede datagrundlag.

Certainty assessment							Median / Rate		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Dacomitinib**	**Osimertinib**	**Relative (95% CI)**	**Absolute (95% CI)**		
Ophør grundet bivirkninger												
2	randomised trials	not serious	serious [a]	serious [b]	serious [c]	none	22/227 (9,7%)	27/279 (9,7 %)	**RR 2,05** (0,94 to 4,49)	10 %-point* (-0,6; 34)	⨁◯◯◯ VERY LOW	CRITICAL
Grad 3-4 bivirkninger												
2	randomised trials	serious [d]	serious [a]	serious [b]	not serious	none	121/227 (53,3 %)	89/279 (31,9 %)	**RR 2,14** (1,56 to 2,94)	36%-point* (18; 62)	⨁◯◯◯ VERY LOW	CRITICAL
PFS												
2	randomised trials	not serious	serious [a]	serious [b]	serious [c]	none	14,7 mdr.	17,7 mdr.	**HR 1,31** (0,95 to 1,81)	-2,5 mdr.*	⨁◯◯◯ VERY LOW	IMPORTANT

CI: Confidence interval; **HR:** Hazard Ratio; **RR:** Risk ratio
a. Der foreligger kun et studie for hver intervention for den pågældende sammenligning.
b. Indirekte sammenligning
c. Konfidensintervallet overlapper MKRF, og er bredt. Dermed kan data for effektmålet give anledning til forskellige kategorier
d. ARCHER 1050 er open-label
* Absolutte forskelle beregnet vha. relative forskelle og ACR jf. Medicinrådets Metodehåndbog

18 Bilag 2: Inklusions og eksklusionskriterier

Tabel 8: Inklusions- og eksklusionskriterier

Inklusionskriterier	
ARCHER 1050	FLAURA
- >18 år gammel (>20 år i Japan og Sydkorea) - Nydiagnosticeret, stadie IIIB/IV NSCLC eller recidiv (histologisk eller *cytopatologisk* bekræftet) - Min. 12 måneders sygdomsfri periode mellem (neo)adjuverende behandling og recidiv - Sygdom målbar ved RECIST kriterier - Min. 1 læsion der ikke havde modtaget stråleterapi - Dokumenteret EGFR mutation (Exon 19 deletion, Leu858Arg, med eller uden Thr790Met) - ECOG performance status 0-1 - *Velfungerende* nyre, lever og hæmatologisk funktion	- >18 år gammel - Patologisk bekræftet adenokarcinom - CNS-metastaser (neurologisk stabile) - Behandlings naiv for fremskreden eller metastatisk lungekræft - Dokumenteret EGFR mutation (Exon 19 deletion, Leu858Arg, med eller uden andre EGFR mutationer) - ECOG performance status 0-1
Eksklusionskriterier	
- Histologisk eller cytopatologisk tegn på småcellet eller neuroendokrine tumorer (eller øvrig blandet histologi) - Atypiske EGFR mutationer - CNS metastaser - Nuværende eller tidligere pneumoni eller interstitiel lungesygdom - Tidligere systemisk behandling for fremskreden eller metastatisk lungekræft - Tidligere behandling med EGFR-TKI (eller anden TKI) - Betydelig kardiovaskulær sygdom eller svær kontrollerbar kardiovaskulær sygdom	- Større kirurgisk indgreb (< 4 uger før første studiedosis) - Helkropsstråleterapi eller strålebehandling af >30% af rygmarven (< 4 uger før første studiedosis) - Nuværende eller tidligere pneumoni eller interstitiel lungesygdom - Behandling med lægemidler (inkl. urtemedicin) som er potente aktivatorer af cytochrome P450 - Behandling med alternativ eller eksperimentel kræftterapi - Tidligere systemisk behandling for fremskreden eller metastatisk lungekræft - Tidligere behandling med EGFR-TKI (eller anden TKI) - Betydelig kardiovaskulær sygdom eller svær kontrollerbar kardiovaskulær sygdom