Medicinrådet

Bilag til Medicinrådets anbefaling vedrørende alpelisib i kombination med fulvestrant til behandling af lokalt fremskreden eller metastatisk ER+/HER2- brystkræft med PIK3CA-mutation

Vers. 1.0

Bilagsoversigt

1. Medicinrådets sundhedsøkonomiske afrapportering vedr. alpelisib, version 1.0
2. Forhandlingsnotat fra Amgros vedr. alpelisib i kombination med fulvestrant
3. Høringssvar fra ansøger
4. Medicinrådets vurdering vedr. alpelisib i kombination med fulvestrant til behandling af ER+/HER2- metastatisk brystkræft, version 1.0
5. Ansøgers endelige ansøgning
6. Ansøgers tekniske dokument til den sundhedsøkonomiske ansøgning
7. Medicinrådets protokol for vurdering vedr. alpelisib til behandling af ER+/HER2- lokalt fremskreden eller metastatisk brystkræft med PIK3CA-mutation, version 1.0

Medicinrådet

Medicinrådets sundheds-økonomiske afrapportering

Alpelisib

ER+/HER2- lokalt fremskreden eller metastatisk brystkræft med PIK3CA-mutation

Version 1.0

Om Medicinrådet

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

Dokumentets formål

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

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

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Indholdsfortegnelse

1. Begreber og forkortelser ... 3

2. Konklusion ... 4

3. Introduktion ... 5
3.1 Patientpopulation ... 5
3.1.1 Komparator ... 5

4. Vurdering af den sundhedsøkonomiske analyse ... 6
4.1 Antagelser og forudsætninger for modellen ... 6
4.1.1 Modelbeskrivelse ... 6
4.1.2 Modelantagelser vedr. behandlingslængder ... 7
4.1.3 Analyseperspektiv ... 9
4.2 Omkostninger ... 9
4.2.1 Lægemiddelomkostninger ... 9
4.2.2 Hospitalsomkostninger ... 10
4.2.3 Testomkostninger ... 12
4.2.4 Patientomkostninger ... 13
4.3 Følsomhedsanalyser ... 14
4.4 Opsummering af basisantagelser ... 15

5. Resultater ... 15
5.1 Resultatet af Medicinrådets hovedanalyse ... 15
5.1.1 Resultatet af Medicinrådets følsomhedsanalyser ... 16

6. Budgetkonsekvenser ... 17
6.1 Estimat af patientantal og markedsandel ... 17
6.2 Medicinrådets budgetkonsekvensanalyse ... 19
6.2.1 Resultat af følsomhedsanalyser for budgetkonsekvensanalysen ... 20

7. Diskussion ... 21

8. Referencer ... 22

9. Versionslog ... 23

10. Bilag ... 24
10.1 Resultatet af ansøgers hovedanalyse ... 24
10.2 Resultatet af ansøgers budgetkonsekvensanalyse ... 24

1. Begreber og forkortelser

AI	Aromatasehæmmer *(aromatase inhibitor)*
AIP	Apotekernes indkøbspris
DBCG	Dansk Brystkræft Cancer Gruppe
DKK	Danske kroner
DRG	Diagnose Relaterede Grupper
ER+	Østrogen receptorpositiv
EPAR	*European public assessment report*
HER2-	Human epidermal vækstfaktorreceptor 2-negativ
Q-PCR	*Quantitative* (Q)-PCR
PCR	*Polymerase chain reaction*
PIK3CA	*Phosphatidylinositol-4,5-Bisphosphate 3-Kinase Catalytic Subunit Alpha*
SAIP	Sygehusapotekernes indkøbspris

2. Konklusion

Inkrementelle omkostninger og budgetkonsekvenser
I sammenligningen mellem alpelisib og abemaciclib (begge i kombination med fulvestrant) er de inkrementelle omkostninger ca. [redacted] DKK pr. patient. De inkrementelle omkostninger er primært drevet af lægemiddelomkostningerne for alpelisib. Når analysen er udført med apotekernes indkøbspris (AIP), er de inkrementelle omkostninger til sammenligning ca. 15.000 DKK pr. patient.

I sammenligningen mellem alpelisib i kombination med fulvestrant og fulvestrant monoterapi, er de inkrementelle omkostninger ca. [redacted] DKK pr. patient. Når analysen er udført med apotekernes indkøbspris (AIP), er de inkrementelle omkostninger til sammenligning ca. 159.000 DKK pr. patient.

Omkostningsanalyserne er relativt robuste for ændringer i centrale parameterinputs. Medicinrådet vurderer dog, at der er store metodiske usikkerheder forbundet med analyserne, idet den kliniske effektforskel er vurderet på baggrund af hhv. en indirekte sammenligning og sparsomt datagrundlag.

I sammenligningen med abemaciclib i kombination med fulvestrant vurderer Medicinrådet, at budgetkonsekvenserne for regionerne ved anbefaling af alpelisib i kombination med fulvestrant som mulig standardbehandling vil være ca. [redacted] DKK i det femte år efter en anbefaling. Når analysen er udført med AIP, er budgetkonsekvenserne ca. 800.000 DKK i det femte år.

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

3. Introduktion

Formålet med analysen er at estimere de gennemsnitlige inkrementelle omkostninger pr. patient og de samlede budgetkonsekvenser for regionerne ved anbefaling af alpelisib i kombination med fulvestrant som mulig standardbehandling på danske hospitaler. Alpelisib i kombination med fulvestrant er indiceret til behandling af patienter med østrogen receptorpositiv (ER+) og human epidermal vækstfaktorreceptor 2-negativ (HER2-), lokalt fremskreden eller metastatisk brystkræft med mutation i PIK3CA (Phosphatidylinositol-4,5-Bisphosphate 3-Kinase Catalytic Subunit Alpha)-genet.

Analysen er udarbejdet, fordi Medicinrådet har modtaget en endelig ansøgning fra Novartis. Medicinrådet modtog ansøgningen den 9. februar 2022.

3.1 Patientpopulation

Brystkræft er den hyppigste kræftform hos kvinder i Danmark og forekommer oftest hos kvinder over 50 år. Sygdommen kan opdeles i fire undertyper, afhængigt af om kræftcellerne er hormonfølsomme, dvs. om de udtrykker østrogenreceptor (ER) og/eller human epidermal vækstfaktorreceptor 2 (HER2) eller ej. I Danmark bliver omkring 3.200 patienter årligt diagnosticeret med ER+/HER2- brystkræft, dvs. at kræftcellerne udtrykker østrogenreceptorer, men ikke vækstfaktorreceptorer. Internationale studier har vist, at 30-40 % af patienter med lokalt fremskreden eller metastatisk ER+/HER2- brystkræft har mutation i PIK3CA-genet.

Yderligere information om sygdomsområdet kan findes i Medicinrådets vurderingsrapport.

3.1.1 Komparator

Medicinrådet har vurderet den kliniske værdi af alpelisib i kombination med fulvestrant på baggrund af følgende kliniske spørgsmål:

Klinisk spørgsmål 1:

Hvilken værdi har alpelisib i kombination med fulvestrant sammenlignet med CDK4/6-hæmmere i kombination med fulvestrant for patienter med lokalt fremskreden eller metastatisk ER+/HER2- brystkræft og mutation i PIK3CA-genet?

Klinisk spørgsmål 2:

Hvilken værdi har alpelisib i kombination med fulvestrant sammenlignet med fulvestrant alene for patienter med lokalt fremskreden eller metastatisk ER+/HER2- brystkræft og mutation i PIK3CA-genet?

4. Vurdering af den sundhedsøkonomiske analyse

Ansøger har indsendt en sundhedsøkonomisk analyse, der består af en omkostningsanalyse og en budgetkonsekvensanalyse. I omkostningsanalysen estimeres de inkrementelle omkostninger pr. patient for alpelisib i kombination med fulvestrant sammenlignet med hhv. CDK4/6-hæmmere i kombination med fulvestrant og fulvestrant monoterapi. Medicinrådet vurderer nedenfor den sundhedsøkonomiske analyse, som ansøger har indsendt.

4.1 Antagelser og forudsætninger for modellen

4.1.1 Modelbeskrivelse

Ansøger har indsendt en simpel omkostningsanalyse til at estimere omkostningerne forbundet med behandling med alpelisib i kombination med fulvestrant sammenlignet med hhv. CDK4/6-hæmmere i kombination med fulvestrant og fulvestrant monoterapi.

Klinisk spørgsmål 1
I sammenligningen mellem alpelisib og CDK4/6-hæmmere (begge i kombination med fulvestrant) argumenterer ansøger for valget af en simpel omkostningsanalyse med, at der jf. ansøgers indirekte sammenligning ses en sammenlignelig effekt mellem behandlingerne. Den indirekte sammenligning, som er udarbejdet vha. Buchers metode, er baseret på data fra studierne SOLAR-1, PALOMA-3, MONALEESA-3 og MONARCH-2 [1–4]. Yderligere information om studierne og den indirekte sammenligning kan findes i Medicinrådets vurderingsrapport vedr. alpelisib i kombination med fulvestrant.

I ansøgers økonomiske analyse anvendes abemaciclib som CDK4/6-hæmmer-komparator, idet abemaciclib er det nuværende førstevalg i Medicinrådets lægemiddelrekommandation for CDK4/6-hæmmere til behandling af ER+/HER2-brystkræft.

Klinisk spørgsmål 2
Ansøger har – grundet sparsomt datagrundlag for patienter, der er progredieret på behandling med CDK4/6-hæmmer – ikke udarbejdet en formel klinisk sammenligning mellem alpelisib i kombination med fulvestrant og fulvestrant monoterapi. Ansøger estimerer omkostningerne forbundet med alpelisib i kombination med fulvestrant og fulvestrant monoterapi til denne patientpopulation ved anvendelse af en simpel omkostningsanalyse.

Ansøger antager, at 10 % af patienterne vil modtage kemoterapi fremfor fulvestrant monoterapi. På baggrund af dette har ansøger lavet en vægtet analyse for sammenligningen mellem alpelisib i kombination med fulvestrant og hhv. fulvestrant monoterapi og kemoterapi som komparatorer.

Medicinrådets vurdering af ansøgers model
Medicinrådet vurderer, at det er rimeligt at anvende en simpel omkostningsanalyse til at estimere omkostningerne forbundet med hhv. alpelisib, abemaciclib og fulvestrant. Det understreges dog, at ansøgers simple indirekte sammenligning mellem alpelisib og CDK4/6-hæmmere (begge i kombination med fulvestrant) er forbundet med stærke antagelser om stor sammenlignelighed mellem studierne, og at datagrundlaget for sammenligningen mellem alpelisib i kombination med fulvestrant og fulvestrant monoterapi er sparsomt. Yderligere information om Medicinrådets vurdering af ansøgers indirekte sammenligning kan findes i Medicinrådets vurderingsrapport vedr. alpelisib i kombination med fulvestrant.

Vedr. klinisk spørgsmål 2 vurderer fagudvalget, at en mindre gruppe af patienter, der progredierer på behandling med CDK4/6-hæmmer og aromatasehæmmer (AI), vil modtage kemoterapi fremfor fulvestrant monoterapi. Denne gruppe patienter er dog for heterogene til, at det er meningsfuldt at foretage en formel sammenligning med alpelisib i kombination med fulvestrant. Medicinrådet udfører dog en følsomhedsanalyse, hvor det antages, at 10 % af patienterne behandles med kemoterapi, for at belyse omkostningerne.

Medicinrådet accepterer ansøgers tilgang vedr. den økonomiske model, men understreger, at der er store usikkerheder forbundet med modellen grundet den indirekte sammenligning, der ligger til grund for vurderingen af alpelisib og abemaciclib (begge i kombination med fulvestrant, klinisk spørgsmål 1) og sparsomt datagrundlag for klinisk spørgsmål 2.

4.1.2 Modelantagelser vedr. behandlingslængder

Klinisk spørgsmål 1
I sammenligningen mellem alpelisib og abemaciclib (begge i kombination med fulvestrant) antager ansøger, at behandlingslængden for alpelisib og abemaciclib er 5,5 måneder. Dette estimat er baseret på den mediane behandlingslængde med alpelisib, som blev observeret i SOLAR-1-studiet [1]. Det antages, at behandlingslængden med fulvestrant er 8,2 måneder, svarende til den mediane behandlingslængde med fulvestrant i alpelisib/fulvestrant-armen i SOLAR-1-studiet.

Klinisk spørgsmål 2
Ved sammenligningen mellem alpelisib i kombination med fulvestrant og fulvestrant monoterapi anvender ansøger data fra BYLieve-studiet [5], hvori den mediane behandlingslængde for kombinationsbehandlingen var 5,1 måneder og 6,5 måneder for hhv. alpelisib og fulvestrant. Ansøger antager, at behandlingslængden for fulvestrant monoterapi er svarende til behandlingslængden med alpelisib (5,1 måneder).

Medicinrådets vurdering af ansøgers antagelser vedr. behandlingslængder

Klinisk spørgsmål 1
Der er usikkerheder forbundet med at anvende mediane værdier for behandlingslængden til at estimere lægemiddelomkostningerne, idet der kan være risiko for, at behandlingslængden underestimeres. Virksomheden oplyser, at den

gennemsnitlige behandlingslængde for alpelisib var 8 måneder i SOLAR-1-studiet, mens den gennemsnitlige behandlingslængde med fulvestrant var 10 måneder i alpelisib/fulvestrant-armen. Fagudvalget har ikke mulighed for at validere disse estimater, idet der endnu ikke er erfaring med behandling med alpelisib i dansk klinisk praksis. Medicinrådet anvender de gennemsnitlige estimater for behandlingslængden fra SOLAR-1-studiet i egen hovedanalyse.

Vedr. behandlingslængden med abemaciclib vurderer fagudvalget, at patienterne i nuværende dansk praksis behandles mellem 9 og 12 måneder med CDK4/6-hæmmer i kombination med fulvestrant. Dette stemmer overens med behandlingslængden, der er defineret i Medicinrådets behandlingsvejledning vedrørende CDK4/6-hæmmere til ER+/HER2- lokalt fremskreden eller metastatisk brystkræft [6]. I Medicinrådets hovedanalyse antages det, at patienterne gennemsnitligt behandles med abemaciclib i kombination med fulvestrant i 10 måneder.

Medicinrådet udarbejder en følsomhedsanalyse, hvor behandlingslængden antages at være ens mellem alpelisib i kombination med fulvestrant og abemaciclib i kombination med fulvestrant.

Klinisk spørgsmål 2
Som ovenfor vurderer Medicinrådet, at de gennemsnitlige estimater for behandlingslængden med alpelisib i kombination med fulvestrant skal anvendes i hovedanalysen fremfor mediane estimater. I BYLieve-studiet var den gennemsnitlige behandlingslængde for alpelisib 5,8 måneder, mens den gennemsnitlige behandlingslængde med fulvestrant var 6,7 måneder. Fagudvalget har ikke mulighed for at validere, hvorvidt estimaterne for behandlingslængden med alpelisib i kombination med fulvestrant afspejler dansk klinisk praksis, idet der ikke er erfaring med behandling med alpelisib.

Vedr. behandlingslængden for fulvestrant monoterapi vurderer fagudvalget, at patienterne i nuværende praksis behandles mellem 6 og 12 måneder, men det er usikkert at kvantificere eksakt. I Medicinrådets hovedanalyse antages det derfor, at behandlingen med fulvestrant monoterapi er svarende til den gennemsnitlige behandlingslængde med fulvestrant fra BYLieve-studiet (6,7 måneder).

Medicinrådet udarbejder en følsomhedsanalyse, hvor behandlingslængden antages at være ens mellem alpelisib i kombination med fulvestrant og fulvestrant monoterapi.

Estimaterne, som anvendes i Medicinrådets hovedanalyse, fremgår af Tabel 1.

Tabel 1. Medicinrådet gennemsnitlige estimater vedr. behandlingslængde for alpelisib, abemaciclib og fulvestrant

	Intervention	Komparator
Klinisk spørgsmål 1	Alpelisib: 8 mdr. Fulvestrant: 10 mdr.	Abemaciclib: 10 mdr. Fulvestrant: 10 mdr.

	Intervention	Komparator
Klinisk spørgsmål 2	Alpelisib: 5,8 mdr. Fulvestrant: 6,7 mdr.	Fulvestrant: 6,7 mdr.

Medicinrådet ændrer estimaterne vedr. behandlingslængde for alpelisib, abemaciclib og fulvestrant.

4.1.3 Analyseperspektiv

I overensstemmelse med Medicinrådets metoder har ansøger valgt et begrænset samfundsperspektiv til sin analyse. Analysen har en tidshorisont, der er ækvivalent med behandlingslængden, se afsnit 4.1.2.

Medicinrådets vurdering af ansøgers analyseperspektiv
Medicinrådet accepterer ansøgers valgte tidshorisont.

Medicinrådet accepterer ansøgers valg vedr. analyseperspektiv.

4.2 Omkostninger

I det følgende præsenteres ansøgers antagelser for omkostningerne i den sundhedsøkonomiske analyse af alpelisib i kombination med fulvestrant sammenlignet med hhv. abemaciclib og fulvestrant. Ansøger har inkluderet lægemiddelomkostninger og hospitalsomkostninger.

Ansøger har ikke inkluderet patientomkostninger, omkostninger forbundet med efterfølgende behandling og kommunale omkostninger.

4.2.1 Lægemiddelomkostninger

Ansøger har, jf. *Metodevejledning for omkostningsanalyser af nye lægemidler og indikationer i hospitalssektoren,* estimeret lægemiddelomkostninger på baggrund af apotekernes indkøbspris (AIP). Doser anvendt i ansøgers analyse er hentet fra de respektive lægemidlers *European public assessment report* (EPAR) og fremgår nedenfor:

- Alpelisib gives som tablet, 300 mg doseret én gang om dagen.
- Abemaciclib gives som tablet, 150 mg to gange dagligt.
- Fulvestrant mono-/kombinationsterapi gives som 500 mg intramuskulær injektion med én måneds interval. Der gives en *loading* dosis på 500 mg efter initialdosis.

Ansøger pointerer, at en standardtilgang til at inkludere den relative dosisintensitet (RDI) til beregning af lægemiddelomkostningerne ikke er relevant. Det skyldes, at der anvendes en flad pris på lægemiddelpakningerne for alpelisib og abemaciclib, hvilket

betyder, at en eventuel dosisreduktion ikke medfører, at lægemiddelomkostningerne reduceres. Ansøger antager dog, at en andel af patienterne midlertidigt ophører i behandling med alpelisib og abemaciclib i behandlingsforløbet.

I ansøgers analyse antages en behandlingscyklus at være på 28 dage, svarende til hvad én pakning af lægemidlerne dækker.

Medicinrådets vurdering af ansøgers antagelser vedr. lægemiddelomkostninger
Fagudvalget vurderer, at det er rimeligt at antage, at nogle patienter midlertidigt vil pausere behandling med abemaciclib og alpelisib. Et midlertidigt behandlingsstop kan bl.a. været forårsaget af bivirkninger, mindre kirurgiske procedurer eller af personlige årsager. Fagudvalget vurderer, at det er rimeligt at antage, at patienternes behandling med fulvestrant ikke pauseres i denne periode.

Medicinrådet har udskiftet AIP med sygehusapotekernes indkøbspris (SAIP), se Tabel 2.

Tabel 2. Anvendte lægemiddelpriser, SAIP (marts 2022)

Lægemiddel	Styrke	Mg/dosis	Pakningsstørrelse	Pris [DKK]	Kilde
Alpelisib	150 mg	300 mg	56 stk.	[redacted] *	Amgros
Abemaciclib	150 mg	300 mg	56 stk.	[redacted]	Amgros
Fulvestrant	250 mg	500 mg	2 stk.	[redacted]	Amgros

*Prisen er betinget af at Medicinrådet anbefaler alpelisib i kombination med fulvestrant til patientpopulationen i [redacted]. Prisen anvendes i Medicinrådets hovedanalyse.

Medicinrådet accepterer ansøgers valg vedr. lægemiddelomkostninger.

4.2.2 Hospitalsomkostninger

Initieringsomkostninger

Ansøger har inkluderet omkostninger forbundet med opstart af behandling, svarende til to ambulante besøg, som ansøger værdisætter med en DRG-takst svarende til 1.735 DKK.

Medicinrådets vurdering af ansøgers antagelser vedr. initieringsomkostninger
Fagudvalget vurderer, at ansøgers antagelser vedr. ressourceforbruget er rimelige.

Medicinrådet accepterer ansøgers tilgang vedr. initieringsomkostninger.

Monitoreringsomkostninger

Ansøger antager, at patienterne er til et ambulant follow-up-besøg hver måned, uanset om de er i behandling med abemaciclib, alpelisib eller fulvestrant, og værdisætter ressourceforbruget med en DRG-takst svarende til 1.735 DKK.

Ansøger har inkluderet omkostninger forbundet med håndtering af blodsukker for patienter, der behandles med alpelisib. Det antages, at patienterne selv monitorerer deres blodsukker.

Medicinrådets vurdering af ansøgers antagelser vedr. monitoreringsomkostninger
Fagudvalget vurderer, at patienterne i opstarten af behandling (op til 6 måneder) vil monitoreres én gang månedligt, hvorefter patienterne monitoreres hver tredje måned. Fagudvalget påpeger dog, at der vil være regionale forskelle i frekvensen af monitoreringsbesøg.

Vedr. monitorering af blodsukker vurderer fagudvalget, at der vil være en mindre del af patienterne, der ikke vil kunne monitorere deres blodsukker selv, og at disse har behov for hjælp til dette.

Medicinrådet accepterer ansøgers tilgang vedr. monitoreringsomkostninger.

Bivirkningsomkostninger

Ansøger har inkluderet omkostninger forbundet med håndtering af bivirkninger. Ressourceforbruget værdisættes med DRG-takster, hvoraf de fleste bivirkninger antages at kunne håndteres ambulant.

Medicinrådets vurdering af ansøgers antagelser vedr. bivirkningsomkostninger
Fagudvalget pointerer, at ressourceforbruget forbundet med håndtering af bivirkninger vil afhænge af, om bivirkningen er af mild eller svær karakter. Det er dog af mindre betydning for analysens resultater at regulere enhedsomkostningerne for ressourceforbruget, hvorfor ansøgers estimater anvendes i Medicinrådets hovedanalyse.

Bivirkningsfrekvenser og anvendte takster kan ses i Tabel 3.

Tabel 3. Rapporterede bivirkningsfrekvenser ved behandling med alpelisib i kombination med fulvestrant, abemaciclib i kombination med fulvestrant og fulvestrant monoterapi samt enhedsomkostninger for bivirkningerne

	Alpelisib i kombination med fulvestrant [%]	Abemaciclib i kombination med fulvestrant [%]	Fulvestrant monoterapi [%]	DRG-kode	Takst
Mavesmerter	0,0	2,5	0,0	09MA98	1.735
Anæmi	4,9	7,2	1,7	16PR02	4.732
Fald i leukocyttælling	0,0	8,8	0,3	09MA98	1.735
Diarré	7,0	11,7	0,5	09MA98	1.735
Dyspnø	0,0	2,7	0,0	09MA98	1.735
Fatigue	5,6	2,3	0,0	09MA98	1.735
Hyperglykæmi	36,6	0,0	0,6	09MA98	1.735
Hypertension	4,6	0,0	0,0	09MA98	1.735

	Alpelisib i kombination med fulvestrant [%]	Abemaciclib i kombination med fulvestrant [%]	Fulvestrant monoterapi [%]	DRG-kode	Takst
Hypokaliæmi	6,3	0,0	0,0	23MA05	31.983
Hypocalcæmi	2,1	0,0	0,0	23MA05	31.983
Stigning i ALT*	4,2	5,1	1,8	07MA14	1.735
Stigning i AST**	0,0	2,9	0,0	07MA14	1.735
Infektion	0,0	6,2	0,0	04MA05	52.345
Leukopeni	0,0	8,8	0,0	-	0
Lymfopeni	0,0	3,1	0,0	-	0
Kvalme	2,8	2,1	0,0	06MA11	5.297
Neutropeni, asymptomatisk	0,0	25,4	0,0	09MA98	1.735
Udslæt	19,4	0,0	0,0	09MA98	1.735
Stomatitis	2,5	0,5	0,0	04MA05	52.345
Trombocytopeni	0,0	3,2	0,0	-	0
Venøs tromboemboli	0,0	2,0	0,0	09MA98	1.735

*Alanintransaminase. **Aspartattransaminase.

Medicinrådet accepterer ansøgers tilgang vedr. bivirkningsomkostninger.

4.2.3 Testomkostninger

Ansøger har inkluderet omkostninger forbundet med diagnostisk test af PIK3CA-mutation. Ansøger antager, at testen, der vil blive anvendt til identifikation af mutationen, vil være af typen *polymerase chain reaction* (PCR).

Testomkostningerne er estimeret ved anvendelse af en DRG-takst (31PR03 "Genetisk risikovurdering og rådgivning") og med en antagelse om, at andelen af patienter, der testes positiv for PIK3CA-mutation, er 36,43 % [7]. Dette medfører en gennemsnitlig testomkostning på 9.461,45 DKK pr. patient, som bliver testet positiv for PIK3CA-mutation. Estimaterne, som ansøger anvender til at udregne den gennemsnitlige testomkostning, fremgår af Tabel 4.

Tabel 4. Estimater vedr. diagnostisk test af PIK3CA-mutation i ansøgers analyse

	Estimat	Reference
Incidens PIK3CA-mutation	36,43 %	Andersson et al. [7]
Enhedsomkostning	3.444 DKK	DRG 2021 [8]

Medicinrådets vurdering af ansøgers antagelser vedr. testomkostninger
Fagudvalget er enig med ansøger i, at patienterne vil skulle testes for PIK3CA-mutation, hvis alpelisib i kombination med fulvestrant anbefales af Medicinrådet. I denne sammenhæng gør fagudvalget opmærksom på, at det optimale tidspunkt for testning er ved progression, og at patienterne vil blive testet i henhold til lokale aftaler mellem onkologisk og patologisk afdeling.

Det anslås, at ca. 330 patienter i alt skal testes for PIK3CA-mutation pr. år for at finde de patienter, som kandiderer til behandling med alpelisib i kombination med fulvestrant. Fordelingen af patientantallet mellem populationerne, der er relevante for klinisk spørgsmål 1 og 2, er hhv. 160 og 170 patienter.

Fagudvalget påpeger, at teststrategien på de enkelte afdelinger kan være forskellig på tværs afhængigt af anvendelsen af testtypen *Next Generation Sequencing* (NGS) og/eller *Quantitative Polymerase Chain Reaction* (Q-PCR). I Medicinrådets hovedanalyse antages det, at alle patienter testes med en NGS-test. Medicinrådet udarbejder en følsomhedsanalyse, hvor det antages, at patienterne også modtager en Q-PCR-test.

Til at værdisætte PCR- og NGS-testen anvendes en enhedsomkostning på hhv. 2.000 DKK og 5.000 DKK. Det øvrige ressourceforbrug – foruden den diagnostiske test – der er forbundet med detektion af PIK3CA-mutation, er ikke inkluderet i den sundhedsøkonomiske analyse.

For populationen beskrevet i klinisk spørgsmål 1 bliver de samlede årlige testomkostninger 800.000 DKK (160 patienter x 5.000 DKK), mens de samlede årlige testomkostninger for populationen beskrevet i klinisk spørgsmål 2 bliver 850.000 DKK (170 patienter x 5.000 DKK). I Medicinrådets hovedanalyse antages det, at 35 % af patienterne har PIK3CA-mutation, hvilket svarer til en gennemsnitlig testomkostning pr. patient, som er kandidat til behandling med alpelisib i kombination med fulvestrant, på ca. 14.300 DKK.

Medicinrådet antager, at ca. 330 patienter i alt skal testes årligt for at finde patienterne med PIK3CA-mutation, og at enhedsomkostningen for en PCR- og NGS-test er hhv. 2.000 DKK og 5.000 DKK.

4.2.4 Patientomkostninger

Ansøger har ikke inkluderet omkostninger forbundet med den effektive tid, som patienterne bruger på behandling med alpelisib, abemaciclib og fulvestrant samt transport til og fra hospitalet. Ansøger begrunder dette med, at tidsforbruget for patienterne er ens, uanset hvilken behandling patienterne modtager.

Medicinrådets vurdering af ansøgers antagelser vedr. patientomkostninger
Fagudvalget vurderer, at ansøgers antagelse vedr. patientomkostninger er rimelig for sammenligningen mellem alpelisib og abemaciclib (begge i kombination med fulvestrant), men at der sandsynligvis vil være forskel i patientomkostninger i sammenligningen mellem alpelisib i kombination med fulvestrant og fulvestrant monoterapi. Det skyldes, at bivirkningsprofilen er tungere ved behandling med alpelisib,

og at der er behov for regelmæssige blodprøver og blodsukkermålinger. Idet fagudvalget endnu ikke har klinisk erfaring med behandling med alpelisib, kan det eksakte ressourceforbrug ikke kvantificeres til brug i analysen.

Medicinrådet accepterer ansøgers tilgang vedr. patientomkostninger, men påpeger, at de inkrementelle omkostninger for sammenligningen mellem alpelisib i kombination med fulvestrant og fulvestrant monoterapi sandsynligvis er underestimeret.

4.3 Følsomhedsanalyser

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

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

Tabel 5. Ansøgers følsomhedsanalyser og beskrivelse

Følsomhedsanalyse	Beskrivelse
Følsomhedsanalyse 1 – inkludering af lægemiddelspild	Der antages et lægemiddelspild svarende til en halv pakning pr. lægemiddel (hhv. alpelisib og abemaciclib).
Følsomhedsanalyse 2 – ekskludering af testomkostninger	Det antages, at diagnostisk test af PIK3CA-mutation vil blive udarbejdet, uanset om alpelisib i kombination med fulvestrant anbefales eller ikke.
Følsomhedsanalyse 3 – anvendelse af gennemsnitlige behandlingslængder	De gennemsnitlige behandlingslængder fra hhv. SOLAR-1- og BYLieve-studiet anvendes fremfor mediane estimater.

Medicinrådets vurdering af ansøgers valg af følsomhedsanalyser
Medicinrådet præsenterer følsomhedsanalysen, der fremgår af Tabel 5, vedr. inkludering af lægemiddelspild. Medicinrådet udarbejder desuden en følsomhedsanalyse, hvori det antages, at patienterne ikke pauserer behandling løbende, og hvor behandlingslængderne med lægemidlerne antages at være ens. Endvidere præsenteres en følsomhedsanalyse, hvor enhedsomkostningen for diagnostisk test for PIK3CA-mutation både inkluderer PCR og NGS, og en følsomhedsanalyse for klinisk spørgsmål 2, hvor det antages, at 10 % af patienterne modtager kemoterapi fremfor fulvestrant monoterapi.

Medicinrådet vælger at præsentere udvalgte af ansøgers følsomhedsanalyser og udarbejder yderligere følsomhedsanalyser vedr. pausering af behandling, inkludering af omkostninger forbundet med kemoterapi og behandlingslængde for lægemidlerne.

4.4 Opsummering af basisantagelser

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

Tabel 6. Basisantagelser for ansøgers og Medicinrådets hovedanalyse

Basisantagelser	Ansøger	Medicinrådet
Sammenligning		
Intervention	Alpelisib i kombination med fulvestrant	Alpelisib i kombination med fulvestrant
Komparator	Abemaciclib i kombination med fulvestrant og fulvestrant monoterapi	Abemaciclib i kombination med fulvestrant og fulvestrant monoterapi
Inkluderede omkostninger	Lægemiddelomkostninger	Lægemiddelomkostninger
	Hospitalsomkostninger	Hospitalsomkostninger
Behandlingslængde, klinisk spørgsmål 1		
Intervention	Alpelisib: 5,5 mdr.	Alpelisib: 8 mdr.
	Fulvestrant: 8,2 mdr.	Fulvestrant: 10 mdr.
Komparator	Abemaciclib: 5,5 mdr.	Abemaciclib: 10 mdr.
	Fulvestrant: 8,2 mdr.	Fulvestrant: 10 mdr.
Behandlingslængde, klinisk spørgsmål 2		
Intervention	Alpelisib: 5,1 mdr.	Alpelisib: 5,8 mdr.
	Fulvestrant: 6,5 mdr.	Fulvestrant: 6,7 mdr.
Komparator	Fulvestrant monoterapi: 5,1 mdr.	Fulvestrant monoterapi: 6,7 mdr.
Inkludering af kemoterapi som komparator (klinisk spørgsmål 2)	Ja	Nej

5. Resultater

5.1 Resultatet af Medicinrådets hovedanalyse

Medicinrådets hovedanalyse bygger på samme antagelser som ansøgers hovedanalyse med undtagelse af de væsentligste ændringer, der fremgår af Tabel 8.

For sammenligningen mellem alpelisib og abemaciclib (begge i kombination med fulvestrant) bliver de gennemsnitlige inkrementelle omkostninger ca. [redacted] DKK pr.

patient i Medicinrådets hovedanalyse. Er analysen udført med AIP, bliver den inkrementelle omkostning pr. patient ca. 15.000 DKK.

Resultaterne fra Medicinrådets hovedanalyse er præsenteret i Tabel 7.

Tabel 7. Resultatet af Medicinrådets hovedanalyse vedr. klinisk spørgsmål 1, DKK

	Alpelisib i kombination med fulvestrant	Abemaciclib i kombination med fulvestrant	Inkrementelle omkostninger
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Hospitalsomkostninger	40.887	25.532	15.354
Totale omkostninger	[redacted]	[redacted]	[redacted]

De gennemsnitlige inkrementelle omkostninger bliver ca. [redacted] DKK pr. patient i Medicinrådets hovedanalyse for sammenligningen mellem alpelisib i kombination med fulvestrant og fulvestrant monoterapi. Er analysen udført med AIP, bliver den inkrementelle omkostning pr. patient ca. 159.000 DKK.

Resultaterne fra Medicinrådets hovedanalyse er præsenteret i Tabel 8.

Tabel 8. Resultatet af Medicinrådets hovedanalyse vedr. klinisk spørgsmål 2, DKK

	Alpelisib i kombination med fulvestrant	Fulvestrant monoterapi	Inkrementelle omkostninger
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Hospitalsomkostninger	34.659	14.424	20.235
Totale omkostninger	[redacted]	[redacted]	[redacted]

5.1.1 Resultatet af Medicinrådets følsomhedsanalyser

Ved samme antagelser som i Medicinrådets hovedanalyse for meromkostninger har Medicinrådet udført en følsomhedsanalyse på parametrene listet i Tabel 9.

Tabel 9. Resultatet af Medicinrådets følsomhedsanalyse sammenlignet med hovedanalysen, DKK

	Inkrementelle omkostninger	
Scenarie	**Klinisk spørgsmål 1**	**Klinisk spørgsmål 2**
Resultatet af hovedanalysen	[redacted]	[redacted]

	Inkrementelle omkostninger	
Scenarie	**Klinisk spørgsmål 1**	**Klinisk spørgsmål 2**
Lægemiddelspild inkluderes	[redacted]	[redacted]
PCR-test inkluderes	[redacted]	[redacted]
Kemoterapi inkluderes som komparator (10 %)	-	[redacted]
Ingen pausering af behandling	[redacted]	[redacted]
Ens behandlingslængde mellem alpelisib i kombination med fulvestrant og komparatorer	[redacted]	[redacted]
Ikke betinget lægemiddelpris for alpelisib	[redacted]	[redacted]

6. Budgetkonsekvenser

Budgetkonsekvenserne pr. år er baseret på antagelsen om, at alpelisib i kombination med fulvestrant vil blive anbefalet som mulig standardbehandling. Man ser derfor på to scenarier for hvert af de to respektive kliniske spørgsmål:

- Alpelisib i kombination med fulvestrant bliver anbefalet som mulig standardbehandling af Medicinrådet til indikationen, som denne analyse omhandler.
- Alpelisib i kombination med fulvestrant bliver ikke anbefalet som mulig standardbehandling.

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

6.1 Estimat af patientantal og markedsandel

Ansøger har baseret sin budgetkonsekvensanalyse på de patientantal, som er præsenteret i Medicinrådets protokol vedr. alpelisib i kombination med fulvestrant [9], dog med en nedjustering af patientantallene. For populationerne i klinisk spørgsmål 1 og 2 antager ansøger, at antallet af patienter, der kandiderer til behandling med alpelisib i kombination med fulvestrant, er hhv. 30 og 100 patienter. Markedsoptaget antages at være 20 % i år 1 efterfulgt af en årlig stigning på 10 %.

Medicinrådets vurdering af ansøgers budgetkonsekvensanalyse
I alt forventes ca. 115 patienter pr. år at være kandidater til behandling med alpelisib i kombination med fulvestrant. Som udgangspunkt vil fagudvalget følge Medicinrådets

anbefaling om ibrugtagning af alpelisib i kombination med fulvestrant, hvis kombinationsbehandlingen bliver anbefalet. Fagudvalget påpeger dog, at klinikerne vil være forsigtige med at igangsætte behandling med alpelisib i kombination med fulvestrant hos ældre og skrøbelige patienter, indtil der foreligger erfaring med håndtering af bivirkningsprofilen. Af den grund anvendes der i Medicinrådets hovedanalyse et markedsoptag på 70 % i år 1 efterfulgt af en stigning på 10 % pr. år. Fordelingen af de ca. 115 patienter mellem de to kliniske spørgsmål fremgår af Tabel 10 og Tabel 11.

Tabel 10. Medicinrådets estimat af antal nye patienter pr. år, klinisk spørgsmål 1

	År 1	År 2	År 3	År 4	År 5
			Anbefales		
Alpelisib i kombination med fulvestrant	39	44	50	55	55
Abemaciclib i kombination med fulvestrant	17	11	6	0	0
			Anbefales ikke		
Alpelisib i kombination med fulvestrant	0	0	0	0	0
Abemaciclib i kombination med fulvestrant	55	55	55	55	55

Tabel 11. Medicinrådets estimat af antal nye patienter pr. år, klinisk spørgsmål 2

	År 1	År 2	År 3	År 4	År 5
			Anbefales		
Alpelisib i kombination med fulvestrant	42	48	54	60	60
Fulvestrant monoterapi	18	12	6	0	0
			Anbefales ikke		
Alpelisib i kombination med fulvestrant	0	0	0	0	0

	År 1	År 2	År 3	År 4	År 5
Fulvestrant monoterapi	60	60	60	60	60

Ansøger har udarbejdet følsomhedsanalyser, hvor patientantallet og markedsoptaget varieres med 25 %. Medicinrådet præsenterer disse følsomhedsanalyser.

Medicinrådet har udført sin egen budgetkonsekvensanalyse, hvor det årlige samlede patientantal antages at være 115 patienter. Endvidere anvendes et markedsoptag på 70 % i år 1 efterfulgt af en stigning på 10 % pr. år.

6.2 Medicinrådets budgetkonsekvensanalyse

Medicinrådet estimerer, at anvendelse af alpelisib i kombination med fulvestrant (i sammenligning med abemaciclib i kombination med fulvestrant) vil resultere i budgetkonsekvenser på ca. [redacted] DKK i det femte år efter en anbefaling. Resultatet er præsenteret i Tabel 12.

Er analysen udført med AIP, bliver budgetkonsekvenserne ca. 800.000 DKK i år 5.

Tabel 12. Medicinrådets analyse af totale budgetkonsekvenser vedr. klinisk spørgsmål 1, [redacted] DKK, ikke-diskonterede tal

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

Medicinrådet estimerer, at anvendelse af alpelisib i kombination med fulvestrant (i sammenligning med fulvestrant monoterapi) vil resultere i budgetkonsekvenser på ca. [redacted] DKK i det femte år efter en anbefaling. Resultatet er præsenteret i Tabel 13.

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

Tabel 13. Medicinrådets analyse af totale budgetkonsekvenser vedr. klinisk spørgsmål 2, [redacted] DKK, ikke-diskonterede tal

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

6.2.1 Resultat af følsomhedsanalyser for budgetkonsekvensanalysen

Ved samme antagelser som i Medicinrådets hovedanalyse af budgetkonsekvenserne mellem alpelisib og abemaciclib (begge i kombination med fulvestrant), men med en justering af patientantallet og markedsoptag, vil omkostningerne i år 5 befinde sig imellem ca. [redacted] og ca. [redacted] DKK, se Tabel 14.

Tabel 14. Medicinrådets følsomhedsanalyse af totale budgetkonsekvenser med justeret markedsoptag og patientantal (-/+25 %), [redacted] DKK, ikke-diskonterede tal, klinisk spørgsmål 1

Scenarie: -25 %	År 1	År 2	År 3	År 4	År 5
Anbefales	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anbefales ikke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Totale budgetkonsekvenser	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenarie: +25 %	**År 1**	**År 2**	**År 3**	**År 4**	**År 5**
Anbefales	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anbefales ikke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Totale budgetkonsekvenser	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Ved samme antagelser som i Medicinrådets hovedanalyse af budgetkonsekvenserne mellem alpelisib i kombination med fulvestrant og fulvestrant monoterapi, men med en justering af patientantallet og markedsoptag, vil omkostningerne i år 5 befinde sig imellem ca. [redacted] og ca. [redacted] DKK, se Tabel 15.

Tabel 15. Medicinrådets følsomhedsanalyse af totale budgetkonsekvenser med justeret markedsoptag og patientantal (-/+25 %), [redacted] DKK, ikke-diskonterede tal, klinisk spørgsmål 2

Scenarie: -25 %	År 1	År 2	År 3	År 4	År 5
Anbefales	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anbefales ikke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Totale budgetkonsekvenser	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenarie: +25 %	**År 1**	**År 2**	**År 3**	**År 4**	**År 5**
Anbefales	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anbefales ikke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Totale budgetkonsekvenser	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

7. Diskussion

Behandling med alpelisib i kombination med fulvestrant er forbundet med inkrementelle omkostninger på ca. [redacted] DKK pr. patient sammenlignet med behandling med abemaciclib i kombination med fulvestrant (klinisk spørgsmål 1). For patienter, der er progredieret på behandling med CDK4/6-hæmmer i kombination med AI (klinisk spørgsmål 2), er behandling med alpelisib i kombination med fulvestrant er forbundet med inkrementelle omkostninger på ca. [redacted] DKK pr. patient sammenlignet med behandling med fulvestrant monoterapi. De inkrementelle omkostninger er primært drevet af lægemiddelomkostningerne for alpelisib for begge analyser. Medicinrådet vurderer, at der er store metodiske usikkerheder forbundet med analyserne, idet den kliniske effektforskel er vurderet på baggrund af hhv. en indirekte sammenligning og sparsomt datagrundlag.

Omkostningsanalyserne er relativt robuste for ændringer i centrale parameterinputs. Resultaterne af følsomhedsanalyserne befinder sig alle over hovedanalysens resultater, hvorfor hovedanalysen kan betragtes som et konservativt estimat. Den ændring af parameter, der har størst betydning for analysens resultater, er ved antagelse om ækvivalent behandlingslængde mellem alpelisib i kombination med fulvestrant og de respektive komparatorer. I denne følsomhedsanalyse øges de inkrementelle omkostninger pr. patient med ca. [redacted] DKK (klinisk spørgsmål 1) og ca. [redacted] DKK (klinisk spørgsmål 2). Differencen i resultaterne af de øvrige følsomhedsanalyser sammenlignet med hovedanalysen befinder sig i spændet mellem ca. [redacted] DKK.

Budgetkonsekvensanalyserne er forbundet med en række usikkerheder, herunder antagelse om patientantal og markedsoptag samt hvilken standardbehandling der anvendes i dansk klinisk praksis. Når markedsoptaget ned- og opjusteres med 25 %, vil budgetkonsekvenserne hhv. reduceres og øges med ca. [redacted] DKK (klinisk spørgsmål 1) og ca. [redacted] DKK (klinisk spørgsmål 2).

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9. Versionslog

Versionslog		
Version	**Dato**	**Ændring**
1.0	18. maj 2022	Godkendt af Medicinrådet.

10. Bilag

10.1 Resultatet af ansøgers hovedanalyse

I ansøgers hovedanalyse for sammenligningen mellem alpelisib og abemaciclib (begge i kombination med fulvestrant) bliver den inkrementelle omkostning pr. patient ca. [redacted] DKK. Resultaterne fra ansøgers hovedanalyse er præsenteret i Tabel 16.

Tabel 16. Resultatet af ansøgers hovedanalyse vedr. klinisk spørgsmål 1, DKK

	Alpelisib i kombination med fulvestrant	Abemaciclib i kombination med fulvestrant	Inkrementelle omkostninger
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Hospitalsomkostninger	32.640	22.159	10.481
Totale omkostninger	[redacted]	[redacted]	[redacted]

I ansøgers hovedanalyse for sammenligningen mellem alpelisib i kombination med fulvestrant og fulvestrant monoterapi, hvor ansøger samtidig antager, at 10 % af patienterne behandles med kemoterapi, bliver den inkrementelle omkostning pr. patient ca. [redacted] DKK. Resultaterne fra ansøgers hovedanalyse er præsenteret i Tabel 17.

Tabel 17. Resultatet af ansøgers hovedanalyse vedr. klinisk spørgsmål 2, DKK

	Alpelisib i kombination med fulvestrant	Fulvestrant monoterapi	Kemoterapi	Vægtede inkrementelle omkostninger
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]	[redacted]
Hospitalsomkostninger	29.446	11.426	12.877	17.875
Totale omkostninger	[redacted]	[redacted]	[redacted]	[redacted]

10.2 Resultatet af ansøgers budgetkonsekvensanalyse

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

Med ovenstående antagelser om patientantal og markedsandel estimerer ansøger, at anvendelse af alpelisib i kombination med fulvestrant – i sammenligningen med abemaciclib i kombination med fulvestrant – vil resultere i budgetkonsekvenser på ca. [redacted] DKK i år 5. Ansøgers estimat af budgetkonsekvenserne fremgår af Tabel 18.

Tabel 18. Ansøgers hovedanalyse for totale budgetkonsekvenser, [redacted] DKK, ikke-diskonterede tal, klinisk spørgsmål 1

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

I sammenligningen med fulvestrant monoterapi estimerer ansøger, at anvendelse af alpelisib i kombination med fulvestrant vil resultere i budgetkonsekvenser på ca. [redacted] DKK i år 5. Ansøgers estimat af budgetkonsekvenserne fremgår af Tabel 19.

Tabel 19. Ansøgers hovedanalyse for totale budgetkonsekvenser, mio. DKK, ikke-diskonterede tal, klinisk spørgsmål 2

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

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26.04.2022

MGK/ECH

Forhandlingsnotat

Dato for behandling i Medicinrådet	18.05.2022
Leverandør	Novartis
Lægemiddel	Piqray (alpelisib)
Ansøgt indikation	Piqray er indiceret i kombination med fulvestrant til behandling af postmenopausale kvinder, og mænd, med hormonreceptor (HR)-positiv, human epidermal vækstfaktorreceptor 2 (HER2)-negativ, lokalt fremskreden eller metastatisk brystkræft med en PIK3CA-mutation efter sygdomsprogression efter tidligere endokrin behandling som monoterapi.

Forhandlingsresultat

Amgros har opnået følgende priser på Piqray (alpelisib):

Tabel 1: Forhandlingsresultat – betinget af anbefaling

Lægemiddel	Styrke/dosis/form	Pakningsstørrelse	AIP (DKK)	Forhandlet SAIP (DKK)	Rabatprocent ift. AIP
Piqray (alpelisib)	150 mg/ 300 mg/ tablet	56 stk.	24.730,17	[redacted]	[redacted]

Prisen er **betinget** af Medicinrådets anbefaling [redacted]

Tabel 2: Forhandlingsresultat – hvis Medicinrådet ikke anbefaler

Lægemiddel	Styrke/dosis/form	Pakningsstørrelse	AIP (DKK)	Forhandlet SAIP (DKK)	Rabatprocent ift. AIP
Piqray (alpelisib)	150 mg/ 300 mg/ tablet	56 stk.	24.730,17	[redacted]	[redacted]

[redacted]

[redacted] Leverandøren har mulighed for at sætte prisen yderligere ned i hele aftaleperioden. [redacted]

Informationer fra forhandlingen

[redacted]

Konkurrencesituationen

[redacted].

Tabel 3 nedenfor viser de årlige lægemiddel priser for lægemidler inkluderet i klinisk spørgsmål 1 og 2 i Medicinrådets vurderingsrapport.

Tabel 3: Sammenligning af lægemiddelpriser

Lægemiddel	Styrke/dosis/form	Pakningsstørrelse	Pakningspris SAIP (DKK)	Antal pakninger/år	Årlig lægemiddelpris SAIP pr. år (DKK)
Piqray (alpelisib)	150 mg/ 300 mg/ tablet	56 stk.	[redacted]	13	[redacted]
Verzenios (abemaciclib)	150 mg/ 300 mg/ tablet	56 stk.	[redacted]	13	[redacted]
Fulvestrant "Teva" (fulvestrant)	250 mg/ 500 mg/ i.m.	2 stk.	[redacted]	13	[redacted]

Tabel 4 viser de samlede lægemiddelpriser for lægemiddelkombinationerne inkluderet i klinisk spørgsmål 1 og 2 i Medicinrådets vurderingsrapport.

Tabel 4: Årlige lægemiddelpriser for kliniske spørgsmål 1 og 2

Klinisk spørgsmål	Lægemidler	Årlig lægemiddelpris SAIP pr. år (DKK)
Klinisk spørgsmål 1	Piqray (alpelisib) + Fulvestrant "Teva" (fulvestrant)	[redacted]
	Verzenios (abemaciclib) + Fulvestrant "Teva" (fulvestrant)	[redacted]
Klinisk spørgsmål 2	Piqray (alpelisib) + Fulvestrant "Teva" (fulvestrant)	[redacted]
	Fulvestrant "Teva" (fulvestrant)	[redacted]

Status fra andre lande

Norge: Under vurdering
Sverige: Anbefalet[1]
England: Under vurdering[2]

Konklusion

[redacted]

[1] https://www.tlv.se/download/18.129f584917976cd4f813d933/1621593555337/bes210520_piqray.pdf

[2] https://www.nice.org.uk/guidance/indevelopment/gid-ta10825

Fra:	Friis Thorsen, Stine
Til:	Andreas Willerslev-Olsen
Cc:	Nielsen, Marianne Holst; Jespersen, Anders; Moeller, Anders Holmen
Emne:	RE: alpelisib vurdering
Dato:	28. marts 2022 17:21:01
Vedhæftede filer:	image001.png Piqray-II-008-G-PO-EN-marked-Final.pdf

Kære Medicinråd, Kære Andreas,

I forbindelse med Fagudvalgets vurdering af alpelisib i kombination med fulvestrant til behandling af ER+/HER2- metastatisk brystkræft, har Novartis modtaget Medicinrådets vurdering. Efter en nøje gennemgang af rådets vurdering har Novartis en række kommentarer, der ender ud i en anmodning om, at Medicinrådet revurderer kategoriseringen af alpelisib. Alpelisib er den første PIK3CA hæmmer, som er godkendt af EMA og FDA, til behandling af ER+/HER2- PIK3CA muteret metastatisk brystkræft. Siden EMA-godkendelse, er alpelisib blevet godkendt af en lang række sundhedsmyndigheder i de europæiske lande og er således nu tilskudsberettiget i Østrig, Holland, Schweitz, Luxemburg, Sverige, Slovenien, Italien, Spanien, Finland og Kroatien.

Behov for målrettet behandling af PIK3CA muterede patienter

Som fagudvalget skriver, har patienter med PIK3CA-muteret ER+/HER2-negativ fremskreden brystkræft en dårligere prognose end patienter med wild type (WT) sygdom. Dette skyldes en forhøjet PI3K signalering, der kan bidrage til malign transformation, progression og endokrin resistens (Aleskandarany et al., 2010; Fu et al., 2014; Lai et al., 2008; Li et al., 2006; Mosele et al., 2020; Qin et al., 2018; Sobhani et al., 2018), hvilket understøttes af data fra de tre CDK4/6 studier, MONALEESA-3, PALOMA-3 og MONARCH-2, som anvendes i den indirekte sammenligning i ansøgningen. For alle tre studier gælder det, at mPFS for CDK4/6-hæmmer + fulvestrant er kortere for den PIK3CA muterede population vs. WT-populationen. Det samme er gældende for placebo-fulvestrant armene i disse studier, som viser markant kortere mPFS for den PIK3CA muterede population vs. WT. Eksempelvis er mPFS for den muterede populations på 5,7 mdr. vs. 12,7 mdr. for WT-populationen i placebo-armen i MONARCH-2.
Ligeledes viser data fra SAFIR02-studiet, at PIK3CA muterede brystkræftpatienter har en dårligere respons og overlevelse på kemoterapi sammenlignet med WT-patienter med ER+/HER2-negativ (Mosele et al., 2020).
Der er således behov for målrettet behandling, der adresserer konsekvenserne af PIK3CA-mutation og giver optimal behandling efter progression på endokrin behandling plus en CDK4/6-hæmmer. Som fagudvalget netop understreger, er standardbehandling i dag hhv. fulvestrant monoterapi eller kemoterapi til patienter, som progredierer hhv. sent eller tidligt på CDK4/6-hæmmer + aromatase hæmmer behandling - begge behandlinger, som har vist en ringere klinisk effekt i subgruppen af PIK3CA muterede patienter sammenlignet med WT-patienter (Hosford & Miller, 2014).

Alpelisib i 2. linje behandling

Med fokus på alpelisib som 2. linje behandling af ER+/HER2- PIK3CA muteret metastatisk brystkræft, ønsker Novartis at gøre opmærksom på, at EMAs produktresumé i øjeblikket opdateres med data bl.a. på overlevelse fra SOLAR-1 clinical study report hos patienter med tidligere CDK4/6-hæmmer-behandling (n=20). Median OS i alpelisib plus fulvestrant-armen var 29,8 måneder (95 % CI: 6,7; 38,2) sammenlignet med 12,9 måneder (95 % CI: 2,5; 34,6) i placebo plus fulvestrant-armen (HR=0,67; 95 % CI: 0,21; 2,18). Data som støtter op om brugen af alpelisib

i denne patientgruppe, og som kan lægges til datagrundlaget tilhørende klinisk spørgsmål 2. EMA Smpc opdateringen har modtaget positive opinion og den vil være tilgængelig på EMA's hjemmeside i løbet af 1-2 måneder. Vedhæftet er den endelige engelske version af Piqray SmPc, hvori ovenstående data er at finde på side 20 markeret med gult.
I evalueringsrapporten fremgår det, at der for alpelisib, er en negativ klinisk merværdi for sikkerhed grundet højere incidens af grad ¾ bivirkninger. Vi anerkender, at der er en numerisk forskel på andelen af bivirkninger mellem mono fulvestrant og alpelisib + fulvestrant behandling. Dette vil være forventeligt, når man tilføjer et medikament i et behandlingsregime (kombinationsbehandling). Imidlertid er størstedelen af de rapporterede grad 3/4 bivirkninger forbundet med behandling med alpelisib hyperglykæmi (36,6 %). Denne bivirkning er en "on target effect" og er defineret ved en tærskelværdi, som er reversibel og håndterbar. Hvis der ses bort fra denne 'on target effect' er bivirkningsprofilerne præparaterne imellem meget lig hinanden.

Omkostning ved detektion af PIK3CA mutation
Omkostningen ved testning for PIK3CA mutationen baseres i Medicinrådets evaluering af alpelisib, på omkostningen af en NGS-test. Novartis mener imidlertid ikke det er rimeligt at pålægge den fulde NGS- omkostning til omkostningsberegningen for behandling med alpelisib, idet NGS giver et langt bredere diagnostisk billede end hvad der er behov for ifm. alpelisib behandling. En PCR-test er således fuldt tilstrækkelig, for at identificerer patienter der kan drage nytte af behandling med alpelisib, hvorfor vi mener omkostningen for en PCR test der bør anvendes i den økonomiske sammenligning.

Kommentarer til vurderingen af den indirekte sammenligning
Vi støtter Medicinrådet i, at en analyse af effekt mellem abemaciclib og alpelisib er vanskelig at foretage med de tilgængelige data.
Markedet for behandling af kræft er i konstant udvikling og 'standard of care', som danner basis for studie design/komparator, kan ændres undervejs i studieperioden for et registreringsstudie, som det gør sig gældende for SOLAR-1. Derfor finder Novartis, at den indsendte patientjusterede indirekte sammenligning, repræsenterer den bedst mulige analyse, og belyser at der ikke er forskel på effektstørrelsen imellem de to præparater, når det gælder behandling af ER+/HER2- PIK3CA muteret metastatisk brystkræft.
Vi anerkender at der er forskelle i studiepopulationerne der er anvendt i den indirekte analyse, men det er netop dette der er forsøgt justeret for i den fremsendte indirekte sammenligning, hvilket vi mener er udført på en sådan vis, at resultatet af analysen giver et tilfredsstillende grundlag til at sidestille effekt-størrelsen af de to produkter. Yderligere bemærkes det, at der kun er et led mellem de to præparater i analysen, hvilket styrker troværdigheden af metoden.

Anmodning til Medicinrådet
I lyset af ovenstående argumenter anmoder Novartis om at Medicinrådet revurderer kategoriseringen af alpelisib til behandling af PIK3CA-muteret ER+/HER2- fremskreden brystkræft i 1. linje behandling til 'ingen klinisk merværdi' i forhold til behandling med abemaciclib. For 2. linje behandling ønsker Novartis at Medicinrådet ændrer sin kategorisering af alpelisib til 'klinisk merværdi' i forhold til fulvestrant monoterapi. Det vil øge de danske klinikeres behandlingsmuligheder, og dermed vil danske ER+/HER2- brystkræftpatienter med PIK3CA-mutation kunne få tilbudt personlig medicin.

Med venlig hilsen,

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From: Andreas Willerslev-Olsen <AWL@medicinraadet.dk>

Sent: 24. marts 2022 10:12
To: Friis Thorsen, Stine <stine.friis_thorsen@novartis.com>
Subject: alpelisib vurdering

Kære Stine

Vedhæftet finder du Medicinrådet vurdering af alpelisib som blev godkendt d. 23/3-2022.

Du er velkommen til at skrive hvis du har nogle spørgsmål.

Mvh
Andreas

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Medicinrådet

Medicinrådets vurdering vedrørende alpelisib i kombination med fulvestrant til behandling af ER+/HER2- metastatisk brystkræft

Version 1.0

Om Medicinrådet

Medicinrådet er et uafhængigt råd etableret af Danske Regioner.

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

Om vurderingsrapporten

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

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

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

Dokumentoplysninger	
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Dokumentnummer	137581
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Indholdsfortegnelse

1. Medicinrådets konklusion ... 3

2. Begreber og forkortelser ... 5

3. Introduktion ... 6

3.1 ER+/HER2- brystkræft ... 6

3.2 Alpelisib ... 9

3.3 Nuværende behandling ... 9

4. Metode ... 11

5. Resultater ... 11

5.1 Klinisk spørgsmål 1 ... 11

5.1.1 Litteratur ... 12

5.1.2 Databehandling og analyse ... 14

5.1.3 Evidensens kvalitet ... 17

5.1.4 Effektestimater og kategorier ... 17

5.1.5 Fagudvalgets konklusion vedr. klinisk spørgsmål 1 ... 25

5.2 Klinisk spørgsmål 2 ... 25

5.2.1 Litteratur ... 25

5.2.2 Databehandling og analyse ... 27

5.2.3 Evidensens kvalitet ... 27

5.2.4 Effektestimater og kategorier ... 27

5.2.5 Fagudvalgets konklusion vedr. klinisk spørgsmål 2 ... 29

6. Relation til behandlingsvejledning ... 30

7. Referencer ... 31

8. Sammensætning af fagudvalg og kontaktinformation til Medicinrådet ... 33

9. Versionslog ... 35

10. Bilag ... 36

Bilag 1: Cochrane – risiko for bias ... 36

Bilag 2: ... 38

1. Medicinrådets konklusion

Medicinrådet vurderer, at den samlede værdi af alpelisib i kombination med fulvestrant som 1. linjebehandling til patienter med ER+/HER2- PIK3CA-muteret metastatisk brystkræft ikke kan kategoriseres efter Medicinrådets metoder. Medicinrådet vurderer, at alpelisib kan have en dårligere sikkerhed end CDK4/6-hæmmerne.

Medicinrådet vurderer, at den samlede værdi af alpelisib i kombination med fulvestrant til patienter med ER+/HER2- PIK3CA-muteret metastatisk brystkræft, der er progredieret på CDK4/6-hæmmer i kombination med en aromataseinhibitor (AI), ikke kan kategoriseres efter Medicinrådets metoder. Medicinrådet vurderer, at alpelisib har en dårligere sikkerhed end fulvestrant monoterapi.

Medicinrådet bemærker, at der er meget kort progressionsfri overlevelse i 2. linjebehandling med fulvestrant monoterapi efter progression på behandling med CDK4/6-hæmmer plus AI. Det vil sige, at disse patienter inden for et kortere perspektiv overgår til kemoterapi fremfor yderligere endokrin behandling. Datagrundlaget er dog meget usikkert, og derfor er Medicinrådet ikke i stand til at konkludere, om tillægsbehandling med alpelisib øger patienternes overlevelse og/eller livskvalitet. Herudover er betydningen af resistens over for CDK4/6-hæmmere i forhold til effekten af alpelisib endnu ikke tilstrækkeligt belyst. De fleste patienter modtager AI og CDK4/6-hæmmer-behandling i 1. linje, og der er ikke data for effekten af alpelisib for denne gruppe patienter.

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MEDICINRÅDET KATEGORISERER LÆGEMIDLERS VÆRDI I EN AF FØLGENDE KATEGORIER:

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

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

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

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

2. Begreber og forkortelser

CI:	Konfidensinterval
EMA:	Det Europæiske Lægemiddelagentur (*European Medicines Agency)*
EPAR:	*European Public Assessment Report*
GRADE:	System til at vurdere evidens (*Grading of Recommendations, Assessment, Development and Evaluation*)
HR:	*Hazard ratio*
ITT:	*Intention-to-treat*
OR:	*Odds ratio*
PICO:	Population, intervention, komparator og effektmål (*Population, Intervention, Comparator and Outcome)*
PP:	*Per Protocol*
RCT:	Randomiseret kontrolleret studie *(Randomised Controlled Trial)*
RR:	Relativ risiko
SMD	*Standardized Mean Difference*

3. Introduktion

Formålet med Medicinrådets vurdering af alpelisib til ER+/HER2- metastatisk brystkræft er at vurdere den værdi, lægemidlet har sammenlignet med dansk standardbehandling.

Vurderingen er udarbejdet, fordi Medicinrådet har modtaget en endelig ansøgning fra Novartis. Medicinrådet modtog ansøgningen den 9. februar 2022.

De kliniske spørgsmål er:

Klinisk spørgsmål 1
Hvilken værdi har alpelisib i kombination med fulvestrant sammenlignet med CDK4/6-hæmmere i kombination med fulvestrant for patienter med lokalt fremskreden eller metastatisk ER+/HER2- brystkræft og mutation i PIK3CA-genet?

Klinisk spørgsmål 2
Hvilken værdi har alpelisib i kombination med fulvestrant sammenlignet med fulvestrant alene for patienter med lokalt fremskreden eller metastatisk ER+/HER2- brystkræft og mutation i PIK3CA-genet, der tidligere er progredieret på AI og en CDK4/6-hæmmer?

3.1 ER+/HER2- brystkræft

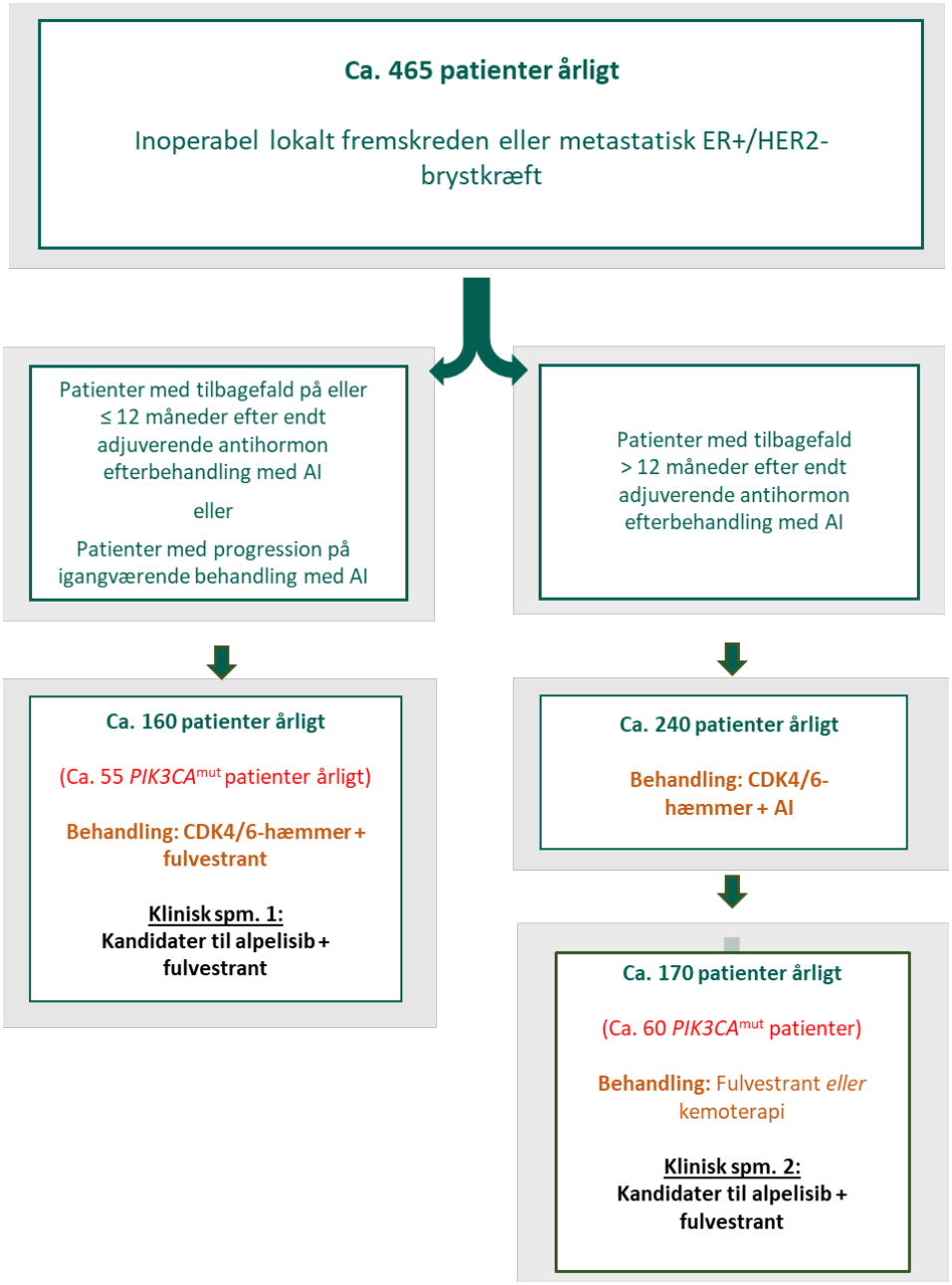
Brystkræft er den hyppigste kræftform hos kvinder i Danmark og forekommer oftest hos kvinder over 50 år. I Danmark bliver omkring 4.900 patienter årligt diagnosticeret med brystkræft, og ca. 66.000 patienter lever med diagnosen brystkræft [1,2].
Sygdommen kan opdeles i fire undertyper, afhængigt af om kræftcellerne er hormonfølsomme, dvs. om de udtrykker østrogenreceptor (ER) og/eller human epidermal vækstfaktorreceptor 2 (HER2) eller ej. I Danmark bliver omkring 3.200 patienter årligt diagnosticeret med ER+/HER2- brystkræft, dvs. at kræftcellerne udtrykker østrogenreceptorer, men ikke vækstfaktorreceptorer [3].

Der bliver årligt diagnosticeret ca. 1.000 patienter med metastatisk brystkræft (spredning til andre organer). Af dem er ca. 750 patienter med recidiv efter tidligere operation for brystkræft (ca. 350 er ER+/HER2-). Ca. 250 er nydiagnosticeret med primær metastatisk brystkræft, og heraf er ca. 65 patienter med ER+/HER2- sygdom. Det betyder, at der i Danmark årligt diagnosticeres ca. 415 patienter med metastatisk ER+/HER2- brystkræft. Der vil herudover være en kategori af patienter med primært lokal fremskreden ER+/HER2- inoperabel brystkræft, som ikke er kandidater til kurativt intenderet neoadjuverende kemoterapi og i stedet tilbydes behandling med endokrin terapi og CDK4/6-hæmmer (estimeres til ca. 50 patienter årligt).

Af de ca. 465 patienter, der således kan komme i betragtning til endokrin terapi og CDK4/6-hæmmerbehandling (415 + 50), vil nogle grundet alder og komorbiditet ikke være kandidater til CDK4/6-hæmmerbehandling, hvilket medfører, at der årligt vil være ca. 400 patienter i Danmark, som er kandidater til behandling med endokrin terapi og CDK4/6-hæmmerbehandling.

En del af patienterne vil have en mutation i *PIK3CA* (*Phosphatidylinositol-4,5-Bisphosphate 3-Kinase Catalytic Subunit Alpha)*-genet. I dansk klinisk praksis undersøger man ikke rutinemæssigt for denne mutation, men Dansk Patologisk Selskab har foretaget kvalitetssikringsprocedurer, så analysen kan blive indført nationalt med kort varsel. Internationale studier har vist, at 30-40 % af patienter med lokalt fremskreden eller metastatisk ER+/HER2- brystkræft har mutation i *PIK3CA*-genet [4,5]. Det er således forventeligt, at ca. 120-160 af de 400 patienter med metastatisk eller inoperabel ER+/HER2- brystkræft har en mutation i *PIK3CA*-genet.

I 2. linjebehandling, hvor en PI3K-hæmmer vil være aktuel, er antallet af patienter mindre, idet der vil være patienter, som har progression < 6 måneder efter opstart af endokrin behandling og dermed overgår til kemoterapi, samt nogle, der har klinisk forværring og ikke kan tilbydes alpelisib. Det betyder, at testning for *PIK3CA*-mutation vil skulle foretages på ca. 330 patienter årligt, hvoraf kun ca. 100-130 patienter (30-40 %) efterfølgende vil være kandidater til alpelisib-behandling.



Figur 1. Oversigt over behandling af patienter med ER+/HER2- brystkræft

Fagudvalget understreger, at prognosen for patienter med *PIK3CA*-mutation generelt må forventes at være væsentligt dårligere end for patienter uden. Det skyldes, at patienter med *PIK3CA*-mutationen oftere og/eller hurtigere udvikler endokrin resistens end patienter uden mutationen [6,7]. Se afsnit 2.3 for yderligere information om patienternes prognose.

3.2 Alpelisib

Alpelisib (Piqray®) har følgende indikation: *Piqray er indiceret i kombination med fulvestrant til behandling af postmenopausale kvinder, og mænd, med hormonreceptor (HR)-positiv, human epidermal vækstfaktorreceptor 2 (HER2)-negativ, lokalt fremskreden eller metastatisk brystkræft med en PIK3CA-mutation efter sygdomsprogression efter tidligere endokrin behandling som monoterapi.*

Alpelisib gives i kombination med fulvestrant.

Alpelisib gives som tablet, 300 mg doseret én gang om dagen. Fulvestrant gives som intramuskulær injektion på dag 1, 15 og 29 i den første cyklus og derefter én gang om måneden.

Alpelisib hæmmer PI3K/AKT-signaleringskaskaden. Disse signaleringskaskader er overaktive hos patienter med en mutation i *PIK3CA*-genet, hvilket medfører øget celledeling og dermed øget tumorvækst. AKT-signaleringsvejen er desuden impliceret i udvikling af resistens over for antihormonel behandling [7]. Dermed bidrager behandling med alpelisib til, at antihormonel behandling bibeholder sin virkning.

Alpelisib er ikke godkendt til andre indikationer.

3.3 Nuværende behandling

Alpelisib er det første lægemiddel, hvis virkningsmekanisme muliggør en målrettet behandlingsstrategi til patienter med ER+/HER2- brystkræft og en *PIK3CA*-mutation. Derfor fokuserer dette afsnit på den nuværende behandling for patienter med ER+/HER2- brystkræft generelt.

Af Figur 1 fremgår et overblik over behandlingen.

CDK4/6-hæmmere i kombination med aromatasehæmmer (AI) eller fulvestrant
Patienter med inoperabel lokalt fremskreden eller metastatisk ER+/HER2- brystkræft, enten på diagnosetidspunktet eller ved tilbagefald, får tilbudt CDK4/6-hæmmere i tillæg til endokrin behandling med enten AI eller fulvestrant, afhængigt af tidligere behandlinger [8]. CDK4/6-hæmmere forhindrer celledeling ved at stoppe cellecyklus [7].

Behandling efter endokrin monoterapi
Tidligere blev endokrin behandling som monoterapi benyttet som førstelinjebehandling for metastatisk sygdom, men dette er nu erstattet af CDK4/6-hæmmere i kombination med endokrin behandling [8]. Endokrin behandling som monoterapi bliver i nuværende klinisk praksis givet til patientgrupper som adjuverende behandling og i senere linjer som metastatisk behandling. Dertil kommer skrøbelige patienter, som på baggrund af forskellige medicinske og/eller compliancemæssige årsager vurderes ikke at kunne gennemføre eller tåle CDK4/6-hæmmere. Disse patienter vil ikke kunne tages i betragtning til alpelisib.

Alpelisib har indikation til patienter, som har modtaget endokrin monoterapi for ER+/HER2- brystkræft. Der findes i nuværende dansk klinisk praksis to patientgrupper, som opfylder indikationen for alpelisib:

- Patienter, som har modtaget behandling med AI som førstelinjebehandling af metastatisk sygdom, vil ved progression blive tilbudt behandling med CDK4/6-hæmmer i kombination med fulvestrant. Denne patientgruppe opstartede endokrin monoterapi, før CDK4/6-hæmmerne blev taget i brug i Danmark, og der er derfor ikke mange patienter tilbage, som har modtaget denne behandlingssekvens.
- Patienter, som får tilbagefald på eller kort tid efter adjuverende endokrin monoterapi. Disse patienter vil ligeledes blive tilbudt behandling med CDK4/6-hæmmer i kombination med fulvestrant.

Fagudvalget vurderer baseret på ovenstående, at CDK4/6-hæmmer i kombination med fulvestrant er standardbehandling efter endokrin monoterapi og dermed er komparator i klinisk spørgsmål 1.

Behandling efter CDK4/6-hæmmer i kombination med AI
EMA anerkender, at alpelisibs indikation ikke passer ind i nuværende klinisk praksis, og nævner i EPAR'en, at det er patienter, der har progredieret på en CDK4/6-hæmmer i kombination med AI, som er relevante kandidater til behandling med alpelisib i kombination med fulvestrant [9]. Dette er ligeledes fagudvalgets vurdering og anbefalingen fra internationale guidelines [10].

Ved progression på en CDK4/6-hæmmer i kombination med AI er der flere mulige behandlingsalternativer, og der er på nuværende tidspunkt en vis forskel i praksis på tværs af regioner. Fælles for tilgangen er, at behandlingen vælges på baggrund af en individuel vurdering af den enkelte patient. Behandlingsvalget afhænger af, hvornår patienterne progredierer på CDK4/6-behandlingen. Patienter, som oplever tidlig progression (dvs. under 6 måneder efter opstart af behandling), anses som at have udviklet primær endokrin resistens og forventes derfor ikke at have gavn af yderligere endokrin behandling. Disse patienter tilbydes i stedet kemoterapi. Størstedelen af patienterne oplever progression senere end 6 måneder efter opstart og formodes dermed at kunne have gavn af yderligere behandling med endokrin terapi. Disse patienter får derfor oftest tilbudt fulvestrant, men afhængigt af sygdomsudbredelse, symptomer og almen tilstand vil en mindre del af patienterne blive tilbudt kemoterapi[1]. Samlet set vurderer fagudvalget, at fulvestrant er den hyppigst benyttede behandling efter behandling med en CDK4/6-hæmmer i kombination med AI, hvorfor fulvestrant vil indgå som komparator i klinisk spørgsmål 2.

[1] Fagudvalget gør opmærksom på, at patienter, der jf. nuværende praksis tilbydes kemoterapi, formentlig vil kunne tages i betragtning til behandling med alpelisib i kombination med fulvestrant, hvis denne anbefales.

Behandlingsmål for patienter, der kan blive kandidater til alpelisib-behandling
Det er meget sjældent muligt at helbrede patienter med inoperabel lokalt fremskreden eller metastatisk brystkræft. Formålet med behandlingen med hhv. CDK4/6-hæmmere i kombination med AI/fulvestrant eller fulvestrant monoterapi er derfor at forlænge tiden til sygdomsprogression uden at påføre patienten markant flere bivirkninger, at forlænge patientens liv og om muligt at forbedre patientens livskvalitet.

Prognose for patienter, som modtager CDK4/6-hæmmere i kombination med fulvestrant (klinisk spørgsmål 1)
Overlevelsesdata for patienter, som modtager palbociclib i kombination med fulvestrant, viste en median overlevelse på ca. 35 måneder [11]. En subgruppeanalyse fra samme studie viste, at patienter med en mutation i *PIK3CA*-genet, som modtog palbociclib i kombination med fulvestrant, havde en median overlevelse på ca. 28 måneder [11].

Prognose for patienter, som modtager fulvestrant (klinisk spørgsmål 2)
Fagudvalget har ikke kendskab til direkte opgørelser over samlet overlevelse for patienter i behandling med fulvestrant monoterapi efter behandling med en CDK4/6-hæmmer i kombination med AI. Der foreligger en metaanalyse for effekten af CDK4/6-hæmmere på samlet overlevelse for patienter med ER+/HER2-, men denne giver kun information vedr. den relative overlevelse [12].

Med forbehold for ovenstående overvejelser vurderer fagudvalget, at prognosen for patienter i klinisk spørgsmål 1 og 2 er nogenlunde sammenlignelig. Selvom de to patientpopulationer er forskellige steder i behandlingskaskaden, er det fælles for begge populationer, at det næste behandlingstrin er kemoterapi, hvorfra prognosen typisk forværres.

4. Metode

Medicinrådets protokol for vurdering vedrørende alpelisib til behandling af ER+/HER2- lokalt fremskreden eller metastatisk brystkræft med PIK3CA-mutation beskriver sammen med *Håndbog for Medicinrådets proces og metode vedr. nye lægemidler og indikationsudvidelser*, hvordan Medicinrådet vil vurdere lægemidlets værdi for patienterne.

5. Resultater

5.1 Klinisk spørgsmål 1

Hvilken værdi har alpelisib i kombination med fulvestrant sammenlignet med CDK4/6-hæmmere i kombination med fulvestrant for patienter med lokalt fremskreden eller metastatisk ER+/HER2- brystkræft og mutation i PIK3CA-genet?

5.1.1 Litteratur

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

Ansøger har søgt litteratur med søgestrengen fra protokollen og har udvalgt fire fuldtekstartikler.

Der findes ikke studier, hvor alpelisib i kombination med fulvestrant er sammenlignet direkte med CDK4/6-hæmmere i kombination med fulvestrant. Derfor har Medicinrådet angivet en søgestreng i protokollen, så ansøger kunne finde studier til en indirekte sammenligning. Ansøger har søgt litteratur med søgestrengen specificeret i protokollen og identificeret to studier, der rapporterede fra relevant intervention/komparator og population. Dertil har ansøger udvalgt to ekstra studier, så der i alt er fire fuldtekstartikler til at adressere klinisk spørgsmål 1. Publikationerne fremgår i Tabel 1.

Tabel 1. Oversigt over litteratur

Reference	Klinisk forsøg	NCT-nummer	Intervention/komparator
Alpelisib for PIK3CA-Mutated, Hormone Receptor-Positive Advanced Breast Cancer, André, F., et al. N Engl J, 2019 (5)	SOLAR-1	NCT02437318	alpelisib + fulvestrant vs. placebo + fulvestrant
MONARCH 2: Abemaciclib in Combination With Fulvestrant in Women With HR+/HER2- Advanced Breast Cancer Who Had Progressed While Receiving Endocrine Therapy, Sledge, G. W., Jr., et al., J Clin Oncol, 2017 (16)	MONARCH-2	NCT02107703	abemaciclib + fulvestrant vs. placebo + fulvestrant
Fulvestrant plus palbociclib versus fulvestrant plus placebo for treatment of hormone-receptor-positive, HER2-negative metastatic breast cancer that progressed on previous endocrine therapy (PALOMA-3): final analysis of the multicentre, double-blind, phase 3 randomised controlled trial	PALOMA-3	NCT01942135	palbociclib + fulvestrant vs. placebo + fulvestrant
Phase III Randomized Study of Ribociclib and Fulvestrant in Hormone Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative Advanced Breast Cancer: MONALEESA-3. Slamon DJ et al., JCO, 2018 (8)	MONALEESA-3	NCT02422615	ribociclib + fulvestrant vs. placebo + fulvestrant

SOLAR-1
SOLAR-1 er et randomiseret dobbeltblindet, multicenter, placebokontrolleret fase III-studie af alpelisib i kombination med fulvestrant til mænd og postmenopausale kvinder med HR+/HER2- metastatisk brystkræft, som progredierede på eller efter AI-behandling. Patienterne blev randomiseret 1:1 til at modtage enten alpelisib i kombination med fulvestrant eller placebo i kombination med fulvestrant. Inkluderede patienter var mænd og postmenopausale kvinder, som havde lokalt bekræftet HR+/HER2- metastatisk brystkræft med tilstrækkeligt tumorvæv til central analyse af PIK3CA-mutationsstatus.

Patienterne havde enten målbar sygdom (mindst én målbar læsion i henhold til RECIST 1.1 eller en eller flere overvejende lytiske knoglelæsioner, en (ECOG) performancescore på 0 eller 1 (på en skala til 5) og tilstrækkelig organ- og knoglemarvsfunktion.

Den mediane opfølgningstid i SOLAR-1 for den PIK3CA-muterede kohorte SOLAR-1 fra randomisering til data cut-off (23. april 2020) var 42,4 måneder (33,1 til 55,7 måneder).

MONARCH-2
MONARCH-2 er et randomiseret, dobbeltblindet, multicenter, placebokontrolleret fase III-studie af abemaciclib i kombination med fulvestrant over for placebo i kombination med fulvestrant til kvinder med HR+/HER2- metastatisk brystkræft.

Patienterne blev randomiseret 2:1 mellem de to arme og ved følgende stratificeringsfaktorer: sygdomsart (viscerale metastaser vs. knoglemetastaser vs. andre metastaser) og resistens over for endokrin terapi (primær resistens vs. sekundær resistens). Viscerale metastaser refererer til lunge-, lever-, pleura- eller peritoneal-involvering på randomiseringstidspunktet. Kvalificerede patienter skulle have progredierende sygdom, mens de modtog neoadjuverende eller adjuverende endokrin terapi, ≤ 12 måneder efter adjuverende endokrin terapi, eller mens de modtog endokrin terapi for metastatisk brystkræft. Patienterne måtte ikke have modtaget mere end én endokrin terapi eller nogen tidligere kemoterapi for metastatisk brystkræft (16).

Den mediane opfølgningstid i MONARCH-2 var 47,7 måneder.

PALOMA-3
PALOMO-3 er et randomiseret, dobbeltblindet, placebokontrolleret fase III-studie af palbociclib i kombination med fulvestrant over for placebo i kombination med fulvestrant. Randomiseringen var stratificeret efter, om patienterne havde viscerale metastaser, om de var præ-, peri- eller postmenopausale, og om de havde responderet på tidligere endokrin behandling. Primære endepunkt var PFS hos kvinder med ER+/HER2- metastatisk brystkræft, hvis sygdom er progredieret efter tidligere endokrin terapi. Præ- og perimenopausale kvinder modtog terapi med goserelin under studiet. De inkluderede patienter havde brystkræft og histologisk eller cytologisk bekræftelse af tilbagevendende lokal eller fjern sygdomsprogression under eller inden for 12 måneder efter afslutning af adjuverende endokrin terapi, eller mens de modtog endokrin terapi eller inden for én måned efter modtagelse af endokrin terapi for metastatisk brystkræft. Både præmenopausale og postmenopausale patienter, som havde en performancestatus på 0-1 og målbar sygdom eller knoglesygdom med en lytisk læsion, var kvalificerede. Én

tidligere linje med kemoterapi i avanceret indstilling var tilladt, men der var ingen grænse for antallet af tidligere linjer af endokrin terapi i metastatisk brystkræft. (17).

Den mediane opfølgningstid i PALOMA-3 fra randomisering til data cut-off (13. april 2018) var 44,8 måneder.

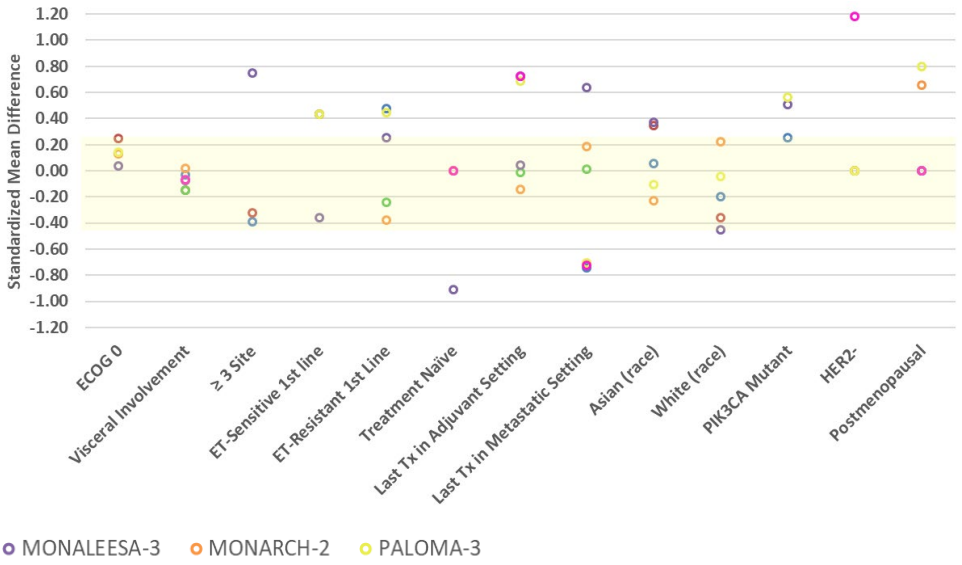
MONALEESA-3
MONALEESA-3 er et randomiseret, dobbeltblindet, multicenter, placebokontrolleret fase III-studie af ribociclib i kombination med fulvestrant til behandling af postmenopausale kvinder og mænd med ER+/HER2- metastatisk brystkræft, som ikke havde modtaget nogen – eller kun én linje endokrin terapi for fremskreden brystkræft. Patienterne blev randomiseret 2:1 til enten ribociclib eller placebo ud over fulvestrant som 1. eller 2. linjebehandling. Kvalificerede patienter inkluderede mænd og postmenopausale kvinder ≥ 18 år med histologisk eller cytologisk bekræftet ER+/HER2- metastatisk brystkræft. Patienterne havde en ECOG-performancestatus på 0 eller 1 og målbar sygdom i henhold til RECIST 1.1 eller mindst én overvejende lytisk knoglelæsion. Overkrydsning mellem de to grupper var ikke tilladt.

Den mediane opfølgningstid i MONALEESA-3 var 39,4 måneder (minimum 35,8 måneder).

5.1.2 Databehandling og analyse

Som beskrevet i protokollen til vurdering af alpelisib er 1. linjebehandling for patienter med metastatisk ER+/HER2- brystkræft blevet opdateret i dansk klinisk praksis med indførelsen af CDK4/6-hæmmere i kombination med endokrin terapi til patienter, der får tilbagefald efter endt adjuverende behandling. Det betyder, at komparatorarmen i SOLAR-1 med placebo i kombination med fulvestrant ikke svarer til dansk klinisk praksis længere. Som beskrevet i protokollen er ansøger derfor nødt til at lave en indirekte sammenligning mellem alpelisib i kombination med fulvestrant over for CDK4/6-hæmmer i kombination med fulvestrant.

Ansøger har valgt at lave en indirekte sammenligning vha. Buchers metode for effektmålene PFS og OS. Ansøger har suppleret den indirekte sammenligning med en analyse af sammenligneligheden af studierne på baggrund af baselinekarakteristika af de relevante forsøgsarme. Det har ansøger gjort ved først at identificere baselinekarakteristika med en forskel på ≥0,25 i standardiseret gennemsnit (standardized mean difference, SMD) alpelisib + fulvestrant-armen i SOLAR-1.



Figur 2. SMD for baselinekarakteristika for komparatorstudier (MONARCH-2, PALOMA-3, MONALEESA-3) vs. SOLAR-1

For baselinekarakteristika, hvor SMD overskred 0,25, kigger ansøger efter hazard ratios (HR) for progressionsfri overlevelse (PFS) og samlet overlevelse (OS) for undergrupper defineret af pågældende baselinekarakteristikum.

Idet HR var tilgængeligt for en relevant undergruppe defineret af et baselinekarakteristikum med en SMD på 0,25 eller mere, beregner ansøger forholdet mellem HR for intervention og komparator i hvert forsøg for hver undergruppe vs. en referent undergruppe. Konfidensintervaller og p-værdier for dette mål for effektmodifikation beregnes under antagelse af, at HR'erne i undergrupperne var uafhængige, og at logaritmen til ratioen var normalfordelt.

Ansøger undersøger også for proportional hazard ved at plotte Schoenfeld residualer og finder, at proportional hazard ikke er en urimelig antagelse.

Estimerede HR'er for PFS og OS fra SOLAR-1 er baseret på den endelige OS-analyse med data cut-off den 23. april 2020.

Den indirekte sammenligning er foretaget i henhold til Medicinrådets metoder, men der gælder stærke antagelser i analysen om stor sammenlignelighed af studierne for at kunne foretage en simpel indirekte sammenligning med Buchers metode.

Fagudvalget har tidligere vurderet sammenligneligheden af MONARCH-2, PALOMA-3 og MONALEESA-3 og kom bl.a. frem til, at der måtte være en større andel af patienter, som var ET-resistente, i og med at flere patienter i PALOMA-3 og MONARCH-2 tidligere havde modtaget behandling med AI for metastatisk sygdom. Det bør medføre, at flere patienter hurtigere vil svigte på behandling med fulvestrant og altså en dårligere PFS og OS hos patienter i PALOMA-3 og MONARCH-2 sammenlignet med MONALEESA-3.

Tilsvarende viser baselinekarakteristika, at 31 % af patienterne i PALOMA-3 tidligere har modtaget kemoterapi for fremskreden sygdom. Fagudvalget har vurderet, at det betyder, at patienterne har haft metastatisk sygdom i længere tid. Derfor forventer fagudvalget, at patienterne responderer dårligere på behandlingen med palbociclib i kombination med fulvestrant, eller at de har et korterevarende respons.

Medicinrådet understreger, at et fravær af statistisk signifikant effektmodifikation ikke betyder, at der ingen effektmodifikation er, men derimod, at studierne ikke har statistisk styrke til at identificere effektmodifikatorer. Dette fremgår også af de meget brede konfidensintervaller for de udregnede effektmodifikatorer (se Tabel 10 i Bilag 2). Det betyder, at den indirekte sammenligning med stor sandsynlighed er påvirket af forskelle i patientpopulationerne og dermed biased.

Datagrundlaget tillader ikke, at effekten af alpelisib kategoriseres efter Medicinrådets metoder. Medicinrådet sammenligner alpelisib og komparator i en narrativ sammenligning og fremlægger de indirekte sammenligninger til perspektivering. I den indirekte sammenligning skal der tages forbehold for, at der er stærke antagelser vedrørende analysen, som ikke nødvendigvis er til stede. Samtidig bemærker Medicinrådet de meget brede konfidensintervaller for de udregnede HR'er, der indikerer stor unøjagtighed ved denne sammenligning.

Baselinekarakteristika

Tabel 2. Karakteristika for kohorten af patienter i SOLAR-1 med PIK3CA mutation

Subgroup		No. of patients
All subjects		341
Lung/liver metastases	Yes	170
	No	171
Bone-only disease	Yes	77
	No	264
Prior CDK4/6 inhibitor treatment	Yes	20
	No	321
ER status	Positive	339
PgR status	Positive	252
	Negative	84
ER and PgR status	Both positive	250
	Positive - negative	84
Line of advanced anticancer treatment	First line	177
	Second line	161
Endocrine status	Primary resistance	45
	Secondary resistance	246
	Sensitive	39
ECOG status	0	225
	1	114

Helt overordnet vurderer fagudvalget, at studiepopulationerne fra de fire inkluderede studier tilhører den samme gruppe af patienter som den danske patientpopulation, der er relevant i forhold til klinisk spørgsmål 1 – altså gruppen af patienter med ER+/HER2- brystkræft, der får tilbagefald på eller kort tid efter endt adjuverende behandling. Den danske patientpopulation er karakteristeret ved at have en god performancestatus og langsomt progredierende sygdom, samt ved at patienterne er nået til 1. eller 2. linjebehandling for metastatisk brystkræft.

Henover de fire arme fra SOLAR-1, MONARCH-2, PALOMA-3 og MONALEESA-3 er der forskelle i baselinekarakteristika. Som beskrevet i afsnit 5.1.2 har ansøger udvalgt karakteristika, hvor forskellen på det standardiserede gennemsnit (SMD) er større end 0,25. Fx er der forskelle i menopausestatus, tidligere behandling, antal og placering af metastaser og performancestatus imellem de relevante behandlingsarme i studierne.

I Figur 2 ses eksempler på baselinekarakteristika, hvor forskellen på det standardiserede gennemsnit er større end 0,25. Ansøger tester for signifikant effektmodifikation, men som tidligere beskrevet er studierne ikke dimensioneret til at identificere effektmodifikatorer, og derfor ses der også meget brede konfidensintervaller på eventuelle effektmodifikationer (se Tabel 10 i Bilag 2).

Fagudvalget vurderer, at studierne rapporterer på den samme gruppe af patienter, men at der er forskelle i baselinekarakteristika, som bidrager med væsentlig usikkerhed til sammenligningen af effekt på tværs af studierne.

5.1.3 Evidensens kvalitet

Da vurderingen af alpelisib i kombination med fulvestrant er baseret på en narrativ sammenligning med CDK4/6-hæmmere i kombination med fulvestrant, kan Medicinrådet ikke anvende GRADE til at vurdere kvaliteten af evidensen. Medicinrådet har vurderet studierne ved Cochrane risk of bias tool 2.0. Overordnet er det vurderet, at risikoen for bias er lav.

Vurdering af risikoen for bias ved de enkelte studier fremgår af bilag 1.

5.1.4 Effektestimater og kategorier

Datagrundlaget tillader ikke, at effekten af alpelisib kategoriseres efter Medicinrådets metoder. Fagudvalget sammenligner alpelisib og komparator i en narrativ sammenligning, hvor der perspektiveres til den tidligere omtalte indirekte analyse (afsnit 5.1.2). Nedenfor ses effektestimater, som indgår i den kvalitative sammenligning, de aggregerede kategorier, den samlede kategori og den samlede kvalitet af evidensen for klinisk spørgsmål 1.

Tabel 3. Resultater for klinisk spørgsmål 1

Effektmål	Alpelisib + fulvestrant (SOLAR-1)	Abemaciclib + fulvestrant (MONARCH-2)	Palbociclib + fulvestrant (PALOMA-3)	Ribociclib + fulvestrant (MONALEESA-3)
Samlet overlevelse (OS)	39,3 mdr. (95 % CI: 34,1; 44,9) *PIK3CA-muteret kohorte*	46,7 mdr. (95 % CI: ikke rapporteret)	34,9 mdr. (95 % CI: 28,8; 40,0)	53,7 mdr. (95 % CI: 46,9; NR)
Livskvalitet	Global health status/QoL (LS mean change from baseline) -3,5 (95 % CI: -8,02; -1,02) *PIK3CA-muteret kohorte*	-	EORTC QLQ-C30 Global QoL 66,1 (95 % CI: 64,5; 67,7)	EORTC QLQ-C30 Global QoL 65,5 (95 % CI: 46,4; 84,6)
Bivirkninger	Uønskede hændelser ≥ grad 3: 76 % *PIK3CA-muteret kohorte*	Uønskede hændelser ≥ grad 3: 61 %	Uønskede hændelser ≥ grad 3: 73 %	Uønskede hændelser ≥ grad 3: 78 %
Stabilisering eller forbedring af symptomer	11,0 mdr. (95 % CI: 7,5; 14,5) *PIK3CA-muteret kohorte*	15,0 mdr. (95 % CI: 9,4; NA) *PIK3CA-muteret kohorte*	9,5 mdr. (95 % CI: 5,7; 11,2) *PIK3CA-muteret kohorte*	16,4 mdr. (95 % CI: 11,0; 19,1) *PIK3CA-muteret kohorte*
Konklusion				
Samlet kategori for lægemidlets værdi	Kan ikke kategoriseres efter Medicinrådets metoder			
Kvalitet af den samlede evidens	Meget lav			

CI = konfidensinterval, HR = Hazard Ratio, OR = Odds Ratio, RR = relativ risiko.

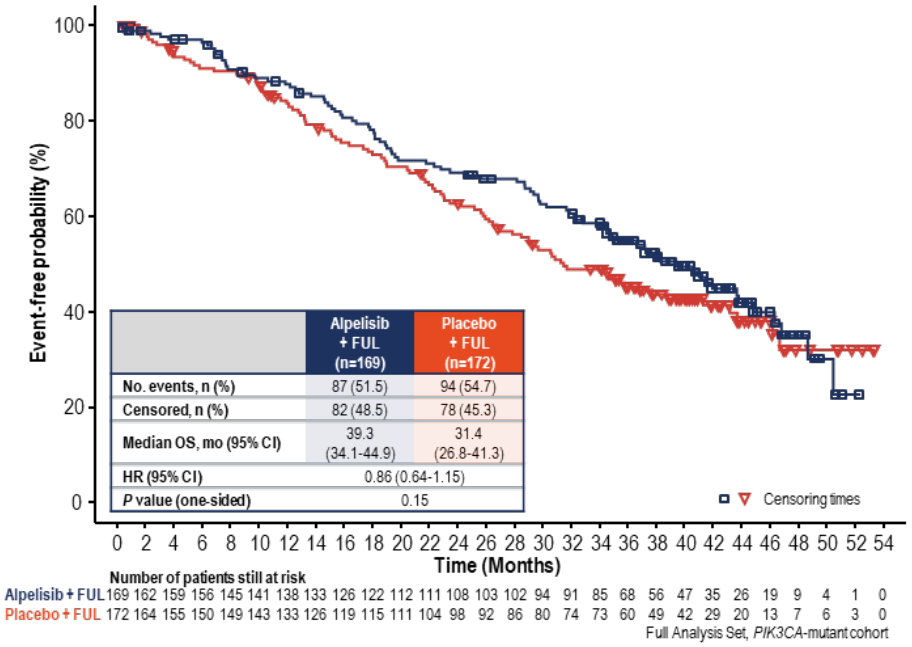
Samlet overlevelse (OS)

Samlet overlevelse er defineret som tiden fra randomisering til død, uafhængigt af årsag. Som beskrevet i protokollen er effektmålet OS kritisk for vurderingen af lægemidlets værdi for patienterne, fordi det er afgørende for patienterne, om behandlingen forlænger deres liv. Fagudvalget ønskede effektmålet opgjort som median OS. Fagudvalget vurderede, at en forskel i median OS på 5 måneder eller mere er klinisk relevant.

Den endelige OS-analyse for den PIK3CA-muterede kohorte blev udført efter data cut-off den 23. april 2020, hvor 181 hændelser havde fundet sted – med en median opfølgningstid på 30,8 måneder. Her viste alpelisib i kombination med fulvestrant ingen signifikant forskel til placebo i kombination med fulvestrant. Median OS: 39,3 vs. 31,4 måneder, HR 0,86 (95 % CI: 0,64; 1,15), se Figur 3.

I MONARCH-2 er den mediane OS i ITT-populationen 46,7 måneder for abemaciclib plus fulvestrant vs. 37,3 måneder for placebo plus fulvestrant, HR 0,757 (95 % CI: 0,61; 0,95).

Til sammenligning er den samlede overlevelse for ITT-populationerne i placeboarmene i de tre komparatorstudier: 28,0 måneder (PALOMA-3: placebo + fulvestrant), 37,3 måneder (MONARCH-2: placebo + fulvestrant) og 41,5 måneder (MONALEESA-3: placebo + fulvestrant).



Figur 3. Kaplan-Meier-estimater for OS i PIK3CA-muteret kohorte fra SOLAR-1 (data cut-off den 23. april 2020), ITT-population

Den indirekte sammenligning med Buchers metode viser ikke nogen statistisk signifikant relativ forskel i OS mellem alpelisib i kombination med fulvestrant ogCDK4/6-hæmmerne abemaciclib, palbociclib og ribociclib i kombination med fulvestrant, se Tabel 4.

Tabel 4. Resultater på HR for OS for den indirekte sammenligning ved Buchers metode

Komparator	HR (95 % CI) for alpelisib plus Fulvestrant vs.:
Palbociclib + fulvestrant 500 mg	1,17 (95 % CI: 0,69; 1,99)
Abemaciclib + fulvestrant 500 mg	1,12 (95 % CI: 0,76; 1,65)
Alpelisib + fulvestrant 500 mg	
Ribociclib + fulvestrant 500 mg	0,92 (95 % CI: 0,51; 1,68)
Fulvestrant 500 mg	0,87 (95 % CI: 0,64; 1,17)

Fagudvalget vurderer, at alpelisib i kombination med fulvestrant ikke kan kategoriseres på baggrund af Medicinrådets metoder vedr. samlet overlevelse, idet datagrundlaget er for usikkert, og der er meget brede konfidensintervaller i den indirekte sammenligning.

Helbredsrelateret livskvalitet
Som beskrevet i protokollen anser fagudvalget livskvalitet som et kritisk effektmål, da det er et patientrelevant effektmål, som ud over at give indblik i sygdomsbyrden kan indikere, om bivirkningerne ved lægemidlet påvirker patienternes livskvalitet. Fagudvalget ønsker, jf. protokollen, effektmålet belyst ved et valideret spørgeskema og finder, at den mindste klinisk relevante forskel er forskellen i ændring svarende til den validerede mindste klinisk relevante forskel for det involverede livskvalitetsspørgeskema. Mht. EORTC QLQ-C30 betragter fagudvalget en forskel på 10 point mellem alpelisib i kombination med fulvestrant og komparator som klinisk relevant.

Ansøger har sammenlignet helbredsrelateret livskvalitet mellem MONARCH-2 og SOLAR-1 og dermed abemaciclib i kombination med fulvestrant over for alpelisib i kombination med fulvestrant. Her var der ingen overordnet statistisk signifikant ændring fra baseline i EORTC QLQ-C30 og global sundhedsstatus/QoL-score hos patienter behandlet med alpelisib eller abemaciclib i kombination fulvestrant over for placebo plus fulvestrant i de to forsøg.

Fagudvalget vurderer, at alpelisib i kombination med fulvestrant ikke kan kategoriseres på baggrund af Medicinrådets metoder vedr. helbredsrelateret livskvalitet. Fagudvalget bemærker dog, at der i subskalaen for social funktion blev observeret en forværring for patienter behandlet med alpelisib i kombination med fulvestrant, og at nogle EORTC QLQ-C30-symptomscorer såsom diarré, kvalme og opkast blev forværret hos patienter behandlet med alpelisib plus fulvestrant vs. placebo plus fulvestrant. Sidstnævnte er forventeligt med udgangspunkt i den gastrointestinale toksicitet, der er observeret ved behandling med alpelisib i kombination med fulvestrant.

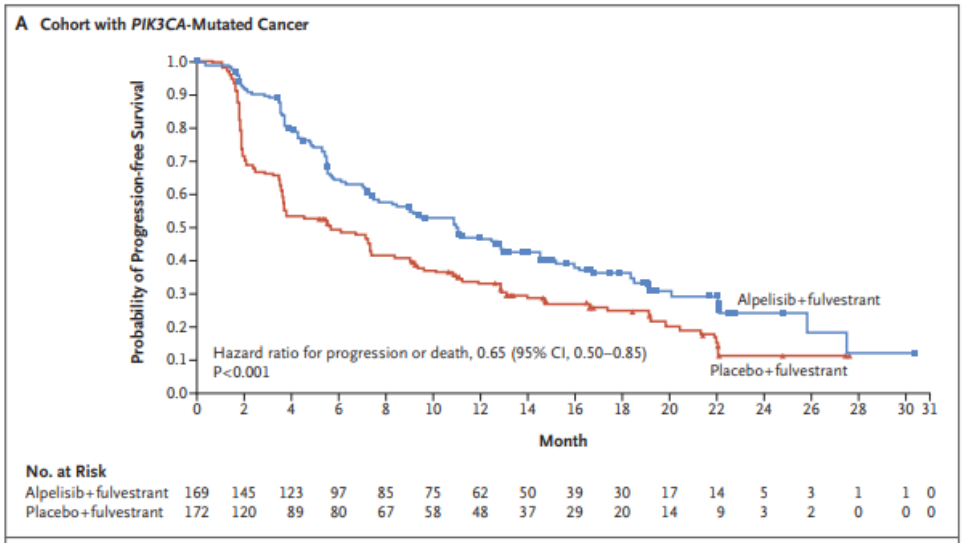
Stabilisering og forbedring af symptomer (PFS)

Fagudvalget ønsker at belyse andelen af patienter, som opnår stabilisering og forbedring af symptomer ved progressionsfri overlevelse (PFS). PFS bliver anvendt til at vurdere, hvor lang tid der går, inden patienternes sygdom udvikler sig, og er defineret som tiden fra studierandomisering til første dokumentation af progression i henhold til RECIST v1.1 [13] eller dødsfald. Fagudvalget forventer ud fra kendskab til relevant litteratur, at median PFS ved standardbehandling er mere end 6 måneder [14]. Jf. *Magnitude of Clinical Benefit Scale* (MCBS) er den mindste klinisk relevante forskel derfor 3 måneder.

I kohorten med PIK3CA-mutation i SOLAR-1 var den mediane opfølgningstid fra randomisering til data cut-off 20,0 måneder (10,7-33,3 måneder). Median PFS var 11,0 måneder (95 % CI: 7,5-14,5) i alpelisib + fulvestrant-gruppen sammenlignet med 5,7 måneder (95 % CI: 3,7-7,4) i placebo + fulvestrant-gruppen, HR 0,65 (95 % CI: 0,50; 0,85).

I MONARCH-2 er den mediane PFS i en subpopulation af *PIK3CA*-muterede patienter 15,0 måneder (95 % CI: 9,4; NA) for abemaciclib plus fulvestrant (n=58) vs. 5,7 måneder (95 % CI: 3,8; 15,0) for placebo plus fulvestrant (n=38), HR 0,46 (95 % CI: 0,24; 0,78).

Til sammenligning er PFS for de *PIK3CA*-muterede patienter i placeboarmene i de tre komparatorstudier: 3,6 måneder i PALOMA-3 (placebo + fulvestrant), 5,7 måneder i MONARCH-2 (placebo + fulvestrant) og 11,1 måneder i MONALEESA-3 (placebo + fulvestrant).



Figur 1. Investigator-bedømt PFS ved 20 måneders median opfølgning i PIK3CA-muteret kohorte (SOLAR-1)

Den indirekte sammenligning med Buchers metode viser ikke nogen statistisk signifikant relativ forskel i PFS imellem alpelisib i kombination med fulvestrant og CDK4/6-hæmmerne abemaciclib, palbociclib og ribociclib i kombination med fulvestrant, se Tabel 5.

Tabel 5. Resultater på HR for PFS for den indirekte sammenligning ved Buchers metode

Komparator	HR (95 % CI) for alpelisib plus fulvestrant vs.:
Abemaciclib + fulvestrant 500 mg	1,31 (95 % CI: 0,73; 2,35)
Palbociclib + fulvestrant 500 mg	1,25 (95 % CI: 0,73; 2,15)
Alpelisib + fulvestrant 500 mg	-
Ribociclib + fulvestrant 500 mg	0,99 (95 % CI: 0,59; 1,63)
Fulvestrant 500 mg	0,60 (95 % CI: 0,47; 0,78)

Fagudvalget vurderer, at alpelisib i kombination med fulvestrant ikke kan kategoriseres på baggrund af Medicinrådets metoder vedr. progressionsfri overlevelse, idet datagrundlaget er for usikkert, og der er meget brede konfidensintervaller i den indirekte sammenligning.

Bivirkninger

Som beskrevet i protokollen er behandlingsmålet at forlænge patienternes liv. Fagudvalget finder, at bivirkninger er et vigtigt effektmål, da det belyser, hvor godt patienterne tolererer alpelisib sammenlignet med komparator. Effektmålet er vigtigt, da det er fagudvalgets vurdering, at patienterne er relativt villige til at risikere bivirkninger for at kunne opnå en eventuel forlængelse i overlevelse. Fagudvalget ønsker, jf. protokollen, effektmålet belyst ved forskellen i andelen af grad 3-4 bivirkninger, hvor den mindste klinisk relevante forskel er 5 %-point, og ved en kvalitativ sammenligning af bivirkningsprofilen.

Bivirkninger grad 3-4

I SOLAR-1 oplever 76 % af patienterne behandlet med alpelisib plus fulvestrant en grad ≥ 3 uønsket hændelse. I MONARCH-2, PALOMA-3 og MONALEESA-3 er det henholdsvis 61 %, 73 % og 78 %, der oplever en grad ≥ 3 uønsket hændelse. Her skal igen tages forbehold for forskelle i opfølgningstid og studiepopulationer.

Fagudvalget kan med afsæt i ovenstående kvalitative sammenligning ikke vurdere, om alpelisib medfører flere eller færre bivirkninger af grad 3-4.

Kvalitativ gennemgang af bivirkningsprofil

Fagudvalget har kvalitativt gennemgået bivirkningsprofilerne for alpelisib i kombination med fulvestrant med henblik på at vurdere bivirkningernes type og reversibilitet som supplement til den kvantitative opgørelse over bivirkninger.

Tabel 6. Ansøgers oversigt over uønskede hændelser for alpelisib plus fulvestrant

	SOLAR-1 Alpelisib + fulvestrant n=284		SOLAR-1 Placebo + fulvestrant n=287		BYLieve Alpelisib + fulvestrant n=127	
Median opfølgningstid, måneder			**15,8**		**19,5**	
Uønskede hændelser, %	**Alle grader**	**Grad 3-4**	**Alle grader**	**Grad 3-4**	**Alle grader**	**Grad 3-4**
Hyperglykæmi	282 (99,3)	216 (76)	264 (92,0)	102 (35,5)	76 (70 %)	36 (29 %)
Diarré	181 (63,7)	104 (36,6)	28 (9,8)	1 (0,6)	74 (59 %)	7 (6 %)
Kvalme	164 (57,7)	19 (6,7)	45 (15,7)	1 (0,3)	58 (46 %)	0 (0 %)
Nedsat appetit	127 (44,7)	7 (2,5)	64 (22,3)	1 (0,3)	36 (29 %)	1 (1 %)
Udslæt	101 (35,6)	2 (0,7)	30 (10,5)	1 (0,3)	36 (29 %)	12 (19 %)
Opkast	101 (35,6)	28 (9,9)	17 (5,9)	1 (0,3)	30 (27 %)	2 (2 %)
Vægttab	77 (27,1)	2 (0,7)	28 (9,8)	1 (0,3)	16 (13 %)	2 (2 %)
Træthed	76 (26,8)	11 (3,9)	6 (2,1)	0	37 (29 %)	1 (1 %)
Stomatitis	70 (24,6)	7 (2,5)	18 (6,3)	0	37 (27 %)	2 (2 %)
Asteni	69 (24,3)	10 (3,5)	49 (17,1)	3 (1,0)	0 (0 %)	0 (0 %)
Alopeci	58 (20,4)	5 (1,8)	37 (12,9)	0	16 (13 %)	0 (0 %)

Seponeringsrater	**Alpelisib + fulvestrant** **n=284**	**Placebo + fulvestrant** **n=287**	**Alpelisib + fulvestrant** **n=127**
n (%)	71 (25 %)	12 (4,2 %)	26 (21 %)

Fagudvalget bemærker, at behandling med alpelisib i kombination med fulvestrant er forbundet med flere gastrointestinale bivirkninger end fulvestrant alene og sammen med CDK4/6-hæmmerne palbociclib og ribociclib. Behandling med abemaciclib medfører en

betydelig forekomst af grad 3-4 diarré. Fagudvalget bemærker også, at de ville have forventet, at denne tungere gastrointestinale toksicitet ville være afspejlet i SOLAR-1-opgørelsen over helbredsrelateret livskvalitet.

Behandling med alpelisib er også forbundet med hyperglykæmi og i mange tilfælde af grad 3-4, se Tabel 6. Ca. halvdelen af patienterne i alpelisib plus fulvestrant-armen i SOLAR-1 havde behov for insulin til behandling af deres hyperglykæmi. Derudover er der observeret udslæt hos over halvdelen af patienterne behandlet med alpelisib i kombination med fulvestrant, hvoraf ca. 20 % var af grad 3. Fagudvalget bemærker, at en høj andel på 25 % af patienterne i SOLAR-1 stopper behandling med alpelisib plus fulvestrant på baggrund af uønskede hændelser.

Tabel 7. Ansøgers oversigt over uønskede hændelser for CDK4/6-hæmmere plus fulvestrant

	PALOMA-3 n=345		MONALEESA-3 n=483		MONARCH-2 n=441	
Median opfølgningstid, måneder	**8,9**		**15,8**		**19,5**	
Uønskede hændelser, %	**Alle grader**	**Grad 3-4**	**Alle grader**	**Grad 3-4**	**Alle grader**	**Grad 3-4**
Neutropeni	80,8	64,6	69,6	53,4	46,0	26,5
Kvalme	32,5	0,0	45,3	1,4	45,1	2,7
Træthed	39,1	2,3	31,5	1,7	39,9	2,7
Diarré	21,4	0,0	29,0	0,6	86,4	13,4
Alopeci	16,8	0,0	18,6	0,0	15,6	0,0
Opkast	16,8	0,3	26,7	1,4	25,9	0,9
Artralgi	14,2	0,3	24,0	0,6	11,6	0,2
Leukopeni	49,6	27,5	28,4	14,1	28,3	8,8
Hedetur	15,4	0,0	13,3	0,0	10,4	0,0
Abdominal smerte	7,8	0,6	-	-	35,4	2,5
Infektioner	41,7	2,0	-	-	42,6	6,6

	PALOMA-3 n=345		MONALEESA-3 n=483		MONARCH-2 n=441	
Seponeringsrater	Palbociclib + fulvestrant	Placebo + fulvestrant	Ribociclib + fulvestrant	Placebo + fulvestrant	Abemaciclib + fulvestrant	Placebo + fulvestrant
N (%)	14 (4 %)	3 (2 %)	41 (8,5 %)	10 (4,1 %)	70 (15,9 %)	7 (3 %)

Til sammenligning er behandling med CDK4/6-hæmmerne i højere grad forbundet med neutropeni og leukopeni – også i svære bivirkningsgrader. Dog medfører CDK4-hæmmeren abemaciclib også gastrointestinal toksicitet, se Tabel 7.

Samlet vurdering for effektmålet bivirkninger
Baseret på ovenstående gennemgang af bivirkninger vurderer fagudvalget, at alpelisib samlet har **en værdi, som ikke kan kategoriseres** vedr. effektmålet bivirkninger. Der er ikke data til en formel sammenligning af delmålet grad 3-4 bivirkninger, som derfor ikke kan kategoriseres efter Medicinrådets metoder.

Ved gennemgang af bivirkningsprofiler er det fagudvalgets vurdering, at der er tunge gastrointestinale bivirkninger forbundet med brugen af alpelisib foruden udslæt og hyperglykæmi. Disse bivirkninger vil være belastende for patienterne, og en stor andel vil kræve behandling. Fagudvalget har dog en formodning om at profylakse, tidlig diagnostik, behandling og dosismodifikation kan mindske disse bivirkninger [15].

5.1.5 Fagudvalgets konklusion vedr. klinisk spørgsmål 1

Fagudvalget vurderer, at den samlede værdi af alpelisib i kombination med fulvestrant som 1. linjebehandling til patienter med ER+/HER2- *PIK3CA*-muteret metastatisk brystkræft ikke kan kategoriseres efter Medicinrådets metoder. Fagudvalget vurderer, at alpelisib kan have en dårligere sikkerhed end CDK4/6-hæmmerne. Det er baseret på en narrativ gennemgang af bivirkningsprofiler og punktestimater på svære og hyppige uønskede hændelser.

5.2 Klinisk spørgsmål 2

Hvilken værdi har alpelisib i kombination med fulvestrant sammenlignet med fulvestrant alene for patienter med lokalt fremskreden eller metastatisk ER+/HER2- brystkræft og mutation i PIK3CA-genet, der tidligere er progredieret på AI og en CDK4/6-hæmmer?

5.2.1 Litteratur

Nedenfor beskriver og vurderer Medicinrådet den litteratur, som ansøger har anvendt som datagrundlag for klinisk spørgsmål 2.

Tabel 8. Oversigt over studier

Reference	Klinisk forsøg	NCT-nummer	Intervention/komparator
Alpelisib for PIK3CA-Mutated, Hormone Receptor-Positive Advanced Breast Cancer, André, F., et al. N Engl J, 2019 (5)	SOLAR-1	NCT02437318	alpelisib + fulvestrant vs. placebo + fulvestrant
Alpelisib plus fulvestrant in PIK3CA-mutated, hormone receptor-positive advanced breast cancer after a CDK4/6 inhibitor (BYLieve): one cohort of a phase 2, multicenter, open-label, non-comparative study, Rugo HS et al., Lancet Oncol, 2021 (14)	BYLieve, Fase II, multicenter, open-label, tre-kohorte, non-komparativ, ikke-randomiseret og open label	NCT03056755	**Tidligere CDK4/6 + aromatase:** alpelisib 500 mg oral + fulvestrant 500 mg **Tidligere CDK4/6 + fulvestrant:** alpelisib 300 mg oral + letrozole **Tidligere systemisk kemoterapi eller endokrin terapi:** alpelisib 300 mg oral + fulvestrant 500 mg

SOLAR-1

SOLAR-1 er et randomiseret dobbeltblindet, multicenter, placebokontrolleret fase III-studie af alpelisib i kombination med fulvestrant til mænd og postmenopausale kvinder med HR+/HER2- metastatisk brystkræft, som progredierede på eller efter AI-behandling. Patienterne blev randomiseret 1:1 til at modtage enten alpelisib i kombination med fulvestrant eller placebo i kombination med fulvestrant. Inkluderede patienter var mænd og postmenopausale kvinder, som havde lokalt bekræftet HR+/HER2- metastatisk brystkræft med tilstrækkeligt tumorvæv til central analyse af PIK3CA-mutationsstatus.

Patienterne havde enten målbar sygdom (mindst én målbar læsion i henhold til RECIST 1.1 eller en eller flere overvejende lytiske knoglelæsioner, en (ECOG) performancescore på 0 eller 1 (på en skala til 5) og tilstrækkelig organ- og knoglemarvsfunktion.

Den mediane opfølgningstid i SOLAR-1 for den PIK3CA-muterede kohorte SOLAR-1 fra randomisering til data cut-off (23. april 2020) var 42,4 måneder (33,1 til 55,7 måneder).

BYLieve

Et open-label, ikke-sammenlignende, multicenter, tre-kohorte fase II-forsøg til vurdering af effektiviteten og sikkerheden af alpelisib plus fulvestrant eller letrozol hos patienter med ER+/HER2- metastatisk brystkræft med en bekræftet PIK3CA-mutation bestemt ved lokal eller central laboratorietest af tumorvæv eller plasma. Kohorte A (n=127) består af patienter, der har modtaget CDK4/6-hæmmerbehandling i kombination med en aromatasehæmmer. Kvalificerede patienter var kvinder og mænd ≥ 18 år, der havde en ECOG-performancestatus på 2 eller mindre, som havde progredieret på/efter tidligere behandlinger og ikke var modtagelige for kurativt intenderet terapi. Median opfølgningstid er 11,7 måneder.

5.2.2 Databehandling og analyse

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

Ansøger har narrativt gennemgået resultaterne for de 20 patienter i SOLAR-1, som har modtaget behandling med CDK4/6-hæmmere og derfor er relevante i klinisk spørgsmål 2. Derudover beror datagrundlaget på BYLieve, som er et åbent ikke-sammenlignende fase II-studie. Medicinrådet bemærker derfor, at datagrundlaget for klinisk spørgsmål 2 er meget usikkert.

5.2.3 Evidensens kvalitet

Da vurderingen af alpelisib i kombination med fulvestrant er baseret på en narrativ sammenligning med fulvestrant alene, kan Medicinrådet ikke anvende GRADE til at vurdere kvaliteten af evidensen. Medicinrådet har vurderet randomiserede kontrollerede forsøg ved Cochrane risk of bias tool 2.0. Overordnet er det vurderet, at for risikoen for de inkluderede randomiserede kontrollerede forsøg er lav.

Vurdering af risikoen for bias ved de enkelte studier fremgår af Bilag 1.

5.2.4 Effektestimater og kategorier

Datagrundlaget tillader ikke, at effekten af alpelisib kategoriseres efter Medicinrådets metoder. Fagudvalget sammenligner alpelisib og komparator i en narrativ sammenligning.

Samlet overlevelse (OS)
Samlet overlevelse er defineret som tiden fra randomisering til død, uafhængigt af årsag. Som beskrevet i protokollen er effektmålet OS kritisk for vurderingen af lægemidlets værdi for patienterne, fordi det er afgørende for patienterne, om behandlingen forlænger deres liv. Fagudvalget ønskede effektmålet opgjort som median OS. Fagudvalget vurderede, at en forskel ift. median OS på 5 måneder er klinisk relevant.

Resultater for OS er ikke rapporteret for BYLieve-studiet endnu, og der er ingen OS-data for populationen (n=20) i SOLAR-1, der har modtaget CDK4/6-hæmmerbehandling.

Helbredsrelateret livskvalitet
Som beskrevet i protokollen anser fagudvalget livskvalitet som et kritisk effektmål, da det er et patientrelevant effektmål, som ud over at give indblik i sygdomsbyrden kan indikere, om bivirkningerne ved lægemidlet påvirker patienternes livskvalitet.

Der er ingen data på helbredsrelateret livskvalitet fra BYLieve.

I SOLAR-1 er der ingen statistisk signifikant forskel mellem alpelisib + fulvestrant over for placebo + fulvestrant. Fagudvalget bemærker dog, at der i subskalaen for social funktion blev observeret en forværring for patienter behandlet med alpelisib i kombination med fulvestrant, og at nogle EORTC QLQ-C30-symptomscorer såsom diarré, kvalme og opkast blev forværret hos patienter behandlet med alpelisib plus fulvestrant vs. placebo plus

fulvestrant. Sidstnævnte er forventeligt med udgangspunkt i den gastrointestinale toksicitet, der er observeret ved behandling med alpelisib i kombination med fulvestrant.

Stabilisering og forbedring af symptomer (PFS)
Fagudvalget ønsker at belyse andelen af patienter, som opnår stabilisering og forbedring af symptomer ved progressionsfri overlevelse (PFS). PFS bliver anvendt til at vurdere, hvor lang tid der går, inden patienternes sygdom udvikler sig, og er defineret som tiden fra studierandomisering til første dokumentation af progression i henhold til RECIST v1.1 [13] eller dødsfald. 2. linje endokrin behandling er den sidste mulige standardbehandling, der ikke er kemoterapi, for patienter med metastatisk ER+/HER2- brystkræft. Fagudvalget forventer ud fra kendskab til relevant litteratur, at median PFS ved standardbehandling er mere end 6 måneder [14]. Jf. MCBS er den mindste klinisk relevante forskel derfor 3 måneder.

I SOLAR-1 er den mediane progressionsfri overlevelse for patienter, der tidligere har modtaget CDK4/6-hæmmerbehandling og behandles med placebo plus fulvestrant, 1,8 måneder (95 % CI: 1,7; 3,6) og 5,5 måneder (95 % CI: 1,6; 16,8) for patienter i alpelisib plus fulvestrant. HR for progression eller død er 0,48 (95 % CI: 0,17; 1,36).

I BYLieve er den mediane progressionsfri overlevelse for den relevante population 7,3 måneder (95 % CI: 5,6; 8,3)

Fagudvalget vurderer, at alpelisib i kombination med fulvestrant ikke kan kategoriseres efter Medicinrådets metoder vedr. progressionsfri overlevelse, idet datagrundlaget er meget usikkert.

Bivirkninger
Som beskrevet i protokollen er behandlingsmålet at forlænge patienternes liv. Fagudvalget finder, at bivirkninger er et vigtigt effektmål, da det belyser, hvor godt patienterne tolererer alpelisib sammenlignet med komparator. Effektmålet er vigtigt, da det er fagudvalgets vurdering, at patienterne er relativt villige til at risikere bivirkninger for at kunne opnå en eventuel forlængelse i overlevelse. Fagudvalget ønsker, jf. protokollen, effektmålet belyst ved forskellen i andelen af grad 3-4 bivirkninger, hvor den mindste klinisk relevante forskel er 5 %-point, og ved en kvalitativ sammenligning af bivirkningsprofilen.

Bivirkninger grad 3-4
I SOLAR-1 oplever 76 % af patienterne behandlet med alpelisib plus fulvestrant en grad ≥ 3 uønsket hændelse. Ved fulvestrant-behandling alene oplever 36 %en grad ≥ 3 uønsket hændelse. Det giver en absolut forskel på 40 %-point (95 % CI: 33,1; 47,9), der dermed er højere end den mindste klinisk relevante forskel på 5 %-point.

I BYLieve i kohorte A oplever 67 % af patienterne en grad ≥ 3 uønsket hændelse.

Fagudvalget vurderer, at tillægsbehandling med alpelisib medfører flere bivirkninger af grad 3-4 end behandling med fulvestrant alene. Dette stemmer også overens med fagudvalgets forventninger og erfaringer med fulvestrant som havende en mild bivirkningsprofil.

Kvalitativ gennemgang af bivirkningsprofil
Fagudvalget har kvalitativt gennemgået bivirkningsprofilerne for alpelisib i kombination med fulvestrant med henblik på at vurdere bivirkningernes type og reversibilitet som supplement til den kvantitative opgørelse over bivirkninger.

Som tidligere beskrevet i afsnit 5.1.4 under bivirkninger for klinisk spørgsmål 1 er behandling med alpelisib bl.a. forbundet med gastrointestinal toksicitet, hyperglykæmi og udslæt. Fagudvalget bemærker, at forekomsten af hyperglykæmi samt diarré, kvalme og opkastning er lidt mindre i BYLieve-studiet. Med forbehold for, at der her er tale om punktestimater, vurderer fagudvalget, at håndteringen af bivirkninger har været bedre og tidligere end i SOLAR-1, jf. tidligere omtalte reference[15].

Samlet vurdering for effektmålet bivirkninger
Baseret på ovenstående gennemgang af bivirkninger vurderer fagudvalget, at alpelisib samlet har en **værdi, som ikke kan kategoriseres** vedr. effektmålet bivirkninger. Der er ikke data til en formel sammenligning af delmålet grad 3-4 bivirkninger, som derfor ikke kan kategoriseres efter Medicinrådets metoder.

Ved sammenligning med fulvestrant monoterapi vurderer fagudvalget dog, at bivirkningerne ved alpelisib plus fulvestrant er hyppigere og sværere. Ved gennemgang af bivirkningsprofilen er det fagudvalgets vurdering, at der er tunge gastrointestinale bivirkninger forbundet med brugen af alpelisib foruden udslæt og hyperglykæmi. Disse bivirkninger vil være belastende for patienterne, og en stor andel vil kræve behandling. Fagudvalget bemærker dog, at det er beskrevet, hvordan hyperglykæmi og udslæt især kan håndteres bedre ved tidlig identifikation, behandling og dosismodifikationer[15].

5.2.5 Fagudvalgets konklusion vedr. klinisk spørgsmål 2

Fagudvalget vurderer, at den samlede værdi af alpelisib i kombination med fulvestrant til patienter med ER+/HER2- PIK3CA-muteret metastatisk brystkræft, der er progredieret på CDK4/6-hæmmer i kombination med AI, samlet har en **værdi, der ikke kan kategoriseres** efter Medicinrådets metoder. Fagudvalget vurderer, at alpelisib har en **dårligere sikkerhed** end fulvestrant monoterapi. Det er baseret på en narrativ gennemgang af bivirkningsprofiler og punktestimater på svære og hyppige uønskede hændelser.

Fagudvalget bemærker, at der er meget kort progressionsfri overlevelse i 2. linjebehandling med monoterapi fulvestrant efter progression på behandling med CDK4/6-hæmmer plus AI. Det vil sige, at disse patienter inden for et kortere perspektiv overgår til kemoterapi fremfor yderligere endokrin behandling. Datagrundlaget til klinisk spørgsmål 2 er dog meget usikkert, og derfor er fagudvalget ikke i stand til at konkludere, om tillægsbehandling med alpelisib øger patienternes overlevelse og/eller livskvalitet. Herudover er betydningen af resistens over for CDK4/6-hæmmere ift. effekten af alpelisib endnu utilstrækkeligt belyst. Da de fleste patienter har modtaget AI og CDK4/6-hæmmer behandling i 1. linje og der ikke er data for det, er det usikkert hvordan effekten af alpelisib i denne gruppe vil være.

6. Relation til behandlingsvejledning

Der findes en behandlingsvejledning vedrørende CDK4/6-hæmmerne abemaciclib, ribociclib og palbociclib. Her tages ikke stilling til *PIK3CA* mutationsstatus.

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8. Sammensætning af fagudvalg og kontaktinformation til Medicinrådet

Medicinrådets fagudvalg vedrørende brystkræft

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

Sammensætning af fagudvalg	
Formand	**Indstillet af**
Hanne Melgaard Nielsen *Overlæge*	Lægevidenskabelige Selskaber
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Guri Spiegelhauer *Sygeplejerske*	Dansk Sygepleje Selskab
Marianne Johansson *Patient/patientrepræsentant*	Danske Patienter

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9. Versionslog

Versionslog		
Version	**Dato**	**Ændring**
1.0	23. marts 2022	Godkendt af Medicinrådet.

10. Bilag

Bilag 1: Cochrane – risiko for bias

Vurdering af risiko for bias ved Cochrane risk of bias tool 2.0.

Tabel 9. Vurdering af risiko for bias: Alpelisib for PIK3CA-Mutated, Hormone Receptor-Positive Advanced Breast Cancer, André, F., et al. N Engl J, 2019; NCT02437318

Bias	Risiko for bias	Uddybning
Risiko for bias i randomiserings-processen	**Lav**	
Effekt af tildeling til intervention	**Lav**	
Manglende data for effektmål	**Lav**	
Risiko for bias ved indsamlingen af data	**Lav**	
Risiko for bias ved udvælgelse af resultater, der rapporteres	**Lav**	
Overordnet risiko for bias	**Lav**	

Tabel 10. Vurdering af risiko for bias

Bias	Risiko for bias	Uddybning
Risiko for bias i randomiserings-processen	**Lav**	Medicinrådet bibeholder tidligere vurdering af risiko for bias for MONARCH-2, PALOMA-3, MONALEESA-3 fra: Medicinrådets behandlingsvejledning vedr. vedrørende CDK4/6-hæmmere til ER+/HER2- lokalt fremskreden eller metastatisk brystkræft
Effekt af tildeling til intervention	**Lav**	Ibid.
Manglende data for effektmål	**Lav**	Ibid.
Risiko for bias ved indsamlingen af data	**Lav**	Ibid.
Risiko for bias ved udvælgelse af resultater, der rapporteres	**Lav**	Ibid.
Overordnet risiko for bias	**Lav**	Ibid.

- MONARCH 2: Abemaciclib in Combination With Fulvestrant in Women With HR+/HER2- Advanced Breast Cancer Who Had Progressed While Receiving Endocrine Therapy, Sledge, G. W., Jr., et al., J Clin Oncol, 2017 (16);
- Fulvestrant plus palbociclib versus fulvestrant plus placebo for treatment of hormone-receptor-positive, HER2-negative metastatic breast cancer that progressed on previous endocrine therapy (PALOMA-3): final analysis of the multicentre, double-blind, phase 3 randomised controlled trial
- Phase III Randomized Study of Ribociclib and Fulvestrant in Hormone Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative Advanced Breast Cancer: MONALEESA-3. Slamon DJ et al., JCO, 2018 (8)

Bilag 2:

Tabel 11. Ansøgers oversigt over potentielle effektmodifikatorer mellem studiepopulationerne i SOLAR-1, MONARCH-2, PALOMA-3 og MONALEESA-3

Trial	HR with Characteristic (95% CI)	HR without Characteristic (95% CI)	Effect Modification (95% CI)	p-value
Patients with PIK3CA mutant cancer vs. those without PIK3CA mutant cancer				
PALOMA-3 (28)	0,48 (0,30, 0,78)	0,45 (0,31, 0,64)	1,07 (0,59, 1,94)	0,83
SOLAR-1 (5)	0,65 (0,50, 0,85)	0,85 (0,58, 1,25)	0,76 (0,48, 1,22)	0,26
MONALEESA-3 (8)	0,75 (0,52, 1,08)	0,67 (0,49, 0,91)	1,12 (0,69, 1,81)	0,64
MONARCH-2 (15)	0,46 (0,27, 0,78)	0,68 (0,42, 1,09)	0,68 (0,33, 1,38)	0,28
Postmenopausal patients vs. pre-menopausal patients				
PALOMA-3 (28)	0,45 (0,34, 0,59)	0,50 (0,29, 0,87)	0,90 (0,49, 1,66)	0,74
MONARCH-2 (25)	0,58 (0,46, 0,73)	0,42 (0,25, 0,70)	1,38 (0,79, 2,43)	0,26
Last therapy in (neo)adjuvant setting vs. last therapy in advanced/metastatic setting				
SOLAR-1 (13)	0,71 (0,49, 1,03)	0,61 (0,42, 0,89)	1,16 (0,69, 1,97)	0,57
PALOMA-3 (28)	0,55 (0,32, 0,92)	0,43 (0,32, 0,57)	1,28 (0,70, 2,33)	0,42
One previous line of therapy for metastatic disease vs. two previous lines of therapy for metastatic disease				
PALOMA-3 (28)	0,42 (0,29, 0,60)	0,46 (0,31, 0,69)	0,91 (0,53, 1,57)	0,74
One previous line of therapy for metastatic disease vs. three or more previous lines of therapy for metastatic disease				

Trial	HR with Characteristic (95% CI)	HR without Characteristic (95% CI)	Effect Modification (95% CI)	p-value
PALOMA-3 (28)	0,42 (0,29, 0,60)	0,61 (0,30, 1,24)	0,69 (0,31, 1,53)	0,36
First-line with PIK3CA mutation vs. second-line with PIK3CA mutation				
MONALEESA-3 (data on file)	0,70 (0,41, 1,21)	0,53 (0,25, 1,09)	1,33 (0,53, 3,31)	0,54
SOLAR-1 (data on file)	0,58 (0,40, 0,85)	0,62 (0,44, 0,87)	0,95 (0,57, 1,59)	0,84
Bone-only metastases vs. not bone-only metastases				
SOLAR-1 (13)	0,62 (0,33, 1,18)	0,66 (0,49, 0,88)	0,94 (0,47, 1,89)	0,86
MONALEESA-3 (8)	0,38 (0,23, 0,61)	0,66 (0,52, 0,83)	0,58 (0,34, 0,99)	0,05
Visceral metastases vs. no visceral metastases				
PALOMA-3 (28)	0,47 (0,34, 0,63)	0,43 (0,28, 0,67)	1,09 (0,64, 1,86)	0,74
Lung or liver metastases vs. no lung or liver metastases				
SOLAR-1 (13)	0,62 (0,44, 0,89)	0,69 (0,47, 1,01)	0,90 (0,53, 1,51)	0,69
MONALEESA-3 (8)	0,65 (0,48, 0,86)	0,56 (0,42, 0,76)	1,16 (0,77, 1,76)	0,48
< 3 metastatic sites vs. ≥ 3 metastatic sites				
MONALEESA-3 (8)	0,59 (0,45, 0,77)	0,62 (0,44, 0,87)	0,94 (0,61, 1,46)	0,79
ECOG performance status 0 vs. ECOG performance status 1-2				
MONALEESA-3 (8)	0,56 (0,43, 0,73)	0,63 (0,45, 0,89)	0,89 (0,58, 1,37)	0,59

Trial	HR with Characteristic (95% CI)	HR without Characteristic (95% CI)	Effect Modification (95% CI)	p-value
MONARCH-2 (25)	0,49 (0,37, 0,64)	0,66 (0,48, 0,90)	0,74 (0,49, 1,13)	0,16

Application for the assessment of Piqray(R) for postmenopausal women, and men, with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer with a PIK3CA mutation

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Contents

1 Basic information 4

2 Abbreviations 7

3 Summary 9

4 Literature search 11
4.1 Relevant studies 12
4.2 Main characteristics of included studies 13

5 Clinical question 1 15
5.1 Presentation of relevant studies 15
5.2 Results per study 15
5.2.1 SOLAR-1 15
5.2.2 Comparator study: MONARCH-2 (abemaciclib + fulvestrant) 26
5.2.3 Comparator study: PALOMA-3 (palbociclib + fulvestrant) 29
5.2.4 Comparator study: MONALEESA-3 (ribociclib + fulvestrant) 31

5.3 Comparative analyses and indirect treatment comparison 34
5.3.1 Overview 34
5.3.2 PFS and OS in Included Studies 36
5.3.3 Indirect Treatment Comparison using the Bucher Method 36
5.3.4 Included studies 37
5.3.5 Patient characteristics of the Identified Studies 39
5.3.6 Treatment Effect Modifiers 40
5.3.7 Proportional Hazards Assumption 42
5.3.8 Results of ITC of HRs for PFS and OS Using Bucher Method 44
5.3.9 Summary of the indirect treatment comparison 48
5.3.10 Adverse Events 49
5.3.11 HRQoL 49

6 Clinical question 2 50
6.1 BYLieve 50
6.2 Summary of clinical efficacy and safety of alpelisib in current indication 55

7 Other considerations 55
7.1 PIK3CA testing 55
7.2 Candidate patient population 56
7.3 Supplementary health economic analysis 57
7.3.1 Inclusion of chemotherapy patients in the budget impact analysis. 57

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7.4 Patients with visceral metastasis (or others who may not be considered for treatment with fulvestrant) 57
7.4.1 Visceral Metastasis 57
7.4.1 Endocrine Resistance 57

8 Economic comparison – this has been moved to the technical document 58

9 Budget impact – this has been moved to the technical document 58

10 Discussion and conclusion 58

11 References 60

12 Appendix A 63
12.1 Literature search 63
12.2 Main characteristics of included studies 64
12.3 Results per study 94

13 Appendix B - Systematic Literature Review 114

14 Appendix C - Plots of Schoenfeld Residuals 115

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1 Basic information

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Overview of the pharmaceutical	
Proprietary name	Piqray®
Generic name	Alpelisib
Marketing authorization holder in Denmark	Novartis Healthcare A/S Edvard Thomsens Vej 14, 3.sal DK-2300 Copenhagen S DENMARK
ATC code	L01EM03
Pharmacotherapeutic group	Antineoplastic agents, other antineoplastic agents.
Active substance(s)	Alpelisib, an α-specific class-I phosphatidylinositol-3-kinase (PI3Kα) inhibitor.

Overview of the pharmaceutical	
Pharmaceutical form(s)	**50-mg:** Light pink, round, curved film-coated tablet with bevelled edges, imprinted with "L7" on one side and "NVR" on the other side. Approximate diameter: 7.2 mm. **150-mg:** Pale red, ovaloid, curved film-coated tablet with bevelled edges, imprinted with "UL7" on one side and "NVR" on the other side. Approximate size: 14.2 mm (length); 5.7 mm (width). **200-mg:** Light red, ovaloid, curved film-coated tablet with bevelled edges, imprinted with "YL7" on one side and "NVR" on the other side. Approximate size: 16.2 mm (length); 6.5 mm (width).
Mechanism of action	Piqray(R) (alpelisib) is a new molecular entity and acts as an inhibitor of the alpha (α) subunit of the class I Phosphatidyl-Inositol-3-kinase (PI3Kα). Gain of function mutations in the gene encoding the catalytic α subunit of PI3K (PIK3CA) lead to activation of PI3Kα and AKT signaling, cellular transformation and the generation of tumors in *in vitro* and *in vivo* (breast cancer cell lines and xenograft models, including models of breast cancer). Here, alpelisib inhibited PI3K/AKT downstream signaling targets and reduced tumor growth. (1)
Dosage regimen	Recommended dose is 300 mg alpelisib/day (2x 150 mg film-coated tablets) taken once daily on a continuous basis. Depending on the dose prescribed, the number of tablets to take is as follows: • 300 mg dose: two 150 mg tablets • 250 mg dose: one 200 mg tablet and one 50 mg tablet • 200 mg dose: one 200 mg tablet
Therapeutic indication relevant for assessment (as defined by the European Medicines Agency, EMA)	Alpelisib is indicated in combination with fulvestrant for the treatment of postmenopausal women, and men, with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer with a PIK3CA mutation after disease progression following endocrine therapy as monotherapy (2)
Other approved therapeutic indications	No
Will dispensing be restricted to hospitals?	No, alpelisib is administrated as tablets daily and can be taken by the patient at home. Fulvestrant is given as an intramuscular injection.
Combination therapy and/or co-medication	Fulvestrant. Alpelisib should be co-administered with fulvestrant. The recommended dose of fulvestrant is 500 mg administered intramuscularly on days 1, 15 and 29, and once monthly thereafter.

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Overview of the pharmaceutical	
Packaging – types, sizes/number of units, and concentrations	**Piqray(R) 50 mg and 200 mg film-coated tablets:** Packs containing 28 film-coated tablets (14 of 50 mg and 14 of 200 mg) or 56 film-coated tablets (28 of 50 mg and 28 of 200 mg). Multipacks containing 168 film-coated tablets (3x 56, each comprising 28 tablets of 50 mg and 28 tablets of 200 mg). **Piqray(R) 150 mg film-coated tablets:** Packs containing 28 or 56 film-coated tablets (150 mg). Multipacks containing 168 (3x 56) film-coated tablets (150 mg). **Piqray(R) 200 mg film-coated tablets:** Packs containing 14 or 28 film-coated tablets (200 mg). Multipacks containing 84 (3x 28) film-coated tablets (200 mg).
Orphan drug designation	No

2 Abbreviations

aBC	Advanced Breast Cancer
AI	Aromatase inhibitor
AKT	Protein kinase B
BC	Breast Cancer
CDK	Cyclin-dependent kinase
CGDB	Clinicogenomics
CR	Complete response
ctDNA	Circulating tumor DNA
DBCG	Danish Breast Cancer Group
EMA	European Medicines Agency
EORTC-QLQ-BR23	European Organization for Research and Treatment of Cancer Quality-of-life Questionnaire-Breast 23 module
EORTC-QLQ-C30	European Organization for Research and Treatment of Cancer Quality-of-life Questionnaire-Core 30
EPAR	European Public Assessment Report
EQ-5D	EuroQol-5-Dimention
EQ-5D 5L	EuroQol 5-Dimension 5 Level
ER	Estrogen receptor
ET	Endocrine therapy
EUnetHTA	European Network for Health Technology Assessment
FDA	The Food and Drug Administration
FMI	Flatiron Health-Foundation Medicine
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
HR	Hazard Ratio
HR+	Hormone Receptor positive
HER2	Human epidermal growth factor receptor 2
HER2-	Human epidermal growth factor receptor 2 negative
HTA	Health Technology Assessment
ITC	Increased time to chemotherapy
i.m	Intramuscular
IPD	individual patient data
IQWIG	The Institute for Quality and Efficiency in Healthcare
ITCs	Indirect treatment comparisons
ITT	Intention-to-treat
NICE	The National Institute for Health and Care Excellence
ORR	Overall response rate
OS	Overall survival
PCR	Polymerase chain reaction
PFS	Progression-free survival
PH	Proportional hazards
PI3K	Phosphoinositide 3-kinase
PICO	Population, Intervention, Comparison and Outcome

PIK3CA	Phosphatidylinositol-4,5-Bisphosphate 3-Kinase Catalytic Subunit Alpha
PgR	Progesteron receptor
PH	Proportional hazards
PK	Pharmacokinetics
PP	Per Protocol
RCT	Randomized controlled trials
RECIST 1.1	Response Evaluation Criteria in Solid tumors version 1.1
SAE	Serious adverse events
SMD	Standardized Mean Difference

3 Summary

Unmet need for patients eligible for alpelisib treatment. The PI3kinase alpha-specific inhibitor alpelisib (Piqray®) is the first precision medicine targeting a specific mutation within this patient population which suffer from an incurable disease with a poor prognosis. Currently available therapies in Denmark fail to address the unmet need for patients with advanced or metastatic breast cancer whose tumors harbor one or more phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (PIK3CA) mutations. Presumably, these patients will be treated with cyclin-dependent kinase (CDK4/6) inhibitors initially; however, there are no clear treatment options after patients progress on a CDK4/6 inhibitor. In addition, patients with hormone receptor-positive (HR+) Human epidermal growth factor receptor 2 negative (HER2-) advanced breast cancer (aBC) and PIK3CA mutation represents a high unmet need, due to a higher degree of endocrine resistance and overall shorter progression free survival (PFS)/worse prognosis (3). Indeed, resistance to ET (even in combination with CDK4/6 inhibitor) is common, leading to disease progression and the need for subsequent-line therapy (4). Data also show that this patient population present a resistance to chemotherapy and a worse outcome (5). These findings are consistent with studies showing that the activation of the PI3K/protein kinase pathway B (AKT) pathway could mediate chemoresistance in breast cancer (6). Based on data from prospective subgroup analysis in several of the CDK4/6 studies, it has also been demonstrated that median PFS consistently is decreased in the PIK3CA-mutant patients compared to the wildtype population regardless of therapy (7-9). Alpelisib is the first approved treatment specifically targeting patients with PIK3CA mutations in breast cancer and the only predominantly α-selective PI3K inhibitor to confirm a favorable risk:benefit profile in a randomized phase III study. (5)

As previously discussed with the Medicines Council, the current treatment option for this patient population (HR+/HER2- aBC; progressing on an endocrine treatment) includes a combination of CDK4/6 inhibitor and fulvestrant in line with recommendations stated in international guidelines. However, as the registrational CDK4/6 inhibitor trials (MONALEESA-3 (NCT02422615), PALOMA-3 (NCT01942135), MONARCH-2 (NCT02107703) did not specifically target or stratify for PIK3CA mutations, the SOLAR-1 trial, investigating Piqray® (alpelisib) in combination with fulvestrant, is currently the only registrational phase III trial powered to demonstrate a significant clinical benefit in this population. Furthermore, patients with lung or liver metastases (constituting the majority of HR+/HER2- aBC patients), being more aggressive and challenging to treat (10), had a 14 months prolongation in OS improvement (11). SOLAR-1 also showed an increased time to chemotherapy (TTC) in the alpelisib arm, which is of particular interest in PIK3CA mutated patients, as these patients are suggested to develop a resistance to chemotherapy (3). Observations from SOLAR-1 and BYLieve are consistent, and data shows that alpelisib plus fulvestrant is an active treatment option with manageable tolerability for patients with HR+/HER2-, PIK3CA mutated aBC. (5, 11, 12).

In accordance with the protocol received from the Medicines Council, we report the findings of an indirect treatment comparison (ITC). The hazard ratios (HRs), for progression free survival (PFS), and overall survival (OS) were found using the Bucher method with the best available data for conducting the ITCs. The analysis showed no significant differences between CDK4/6 treatment and alpelisib, with all confidence intervals crossing one for both PFS and OS. This analysis is subject to a number of limitations based on differences in patient populations across randomized controlled trials (RCTs). Specifically, lack of data for subgroups of patients with PIK3CA mutation from MONARCH-2, pre-stratification of the subgroup of interest and lack of patient level data. The analysis suggests that access to individual patient data (IPD) are necessary to construct linked evidence networks for both PFS and OS in

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patients with PIK3CA mutated, HR+/HER2-aBC for each of the comparators of interest in order to perform a meaningful comparison.

The indirect treatment comparison provides estimates of relative efficacy of alpelisib plus fulvestrant versus CDK 4/6 + fulvestrant treatment for postmenopausal women with PIK3CA-mutated, HR+/HER2-aBC who have received prior treatment with an aromatase inhibitor (AI) and have not received more than one prior endocrine therapy (ET) for advanced disease. This may be used to form the basis for an economic evaluation. However, given the multiple potentially serious limitations in the ITCs due to differences in the patient populations of the trials contributing to the evidence network, results of these ITCs are potentially biased and careful consideration should be given to how they should be used in the context of any such evaluations.

As the ITC suggested no difference in relative efficacy between alpelisib and relevant comparators, the economic comparison solely compared on costs. The costs included were the following: adverse events, test costs, costs related to initiation of therapy, follow up costs and drug costs. When comparing treatment with alpelisib + fulvestrant to abemaciclib + fulvestrant for treatment of HR+/HER2- PIK3CA mutated aBC in the first line, the incremental cost difference between the two were approximately DKK 35 000, favoring the latter. When comparing alpelisib + fulvestrant to mono-therapy fulvestrant and chemotherapy in the post CDK4/6 setting the incremental cost difference was approximately DKK 131 000.

In conclusion, alpelisib is a novel treatment specifically targeting the PIK3CA mutation, which provides a new treatment option for a group of advanced breast cancer patients with a high medical need. The incremental cost of introducing alpelisib is considered reasonable for a precision medicine.

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4 Literature search

Novartis have performed a systematic literature review (SLR) based on two search strings provided by The Medicines Council (PubMed by MEDLINE and CENTRAL by Cochrane Library). Both searches were conducted on May 22nd, 2021. The search terms, inclusion and exclusion criteria are presented in Appendix A in Table A1. Further, Prisma diagram presenting the number of publications that were included after each round of review is available in Appendix B. A list of reason for exclusion after full text review is available in Appendix B.

Publications included for data extraction were added to an extraction grid in Microsoft Excel®. Information for each included article was extracted by a single individual in the first instance, with a second individual independently verifying the extracted information and checking that no relevant information had been missed. Any discrepancies or missing information identified by the second individual were discussed until a consensus was reached.

In total, publications reporting on 7 unique studies (EMERALD, SOLAR-1, PALOMA-2, PALOMA-3, MONALEESA-3, MONARCH-2, MONARCH-3) were included in the full text review. Of these, only two studies (SOLAR-1 and PALOMA-3), reported through 11 publications, investigated the intervention and population of interest. This demonstrates the limited data available on the PIK3CA mutant subgroup and the difficulties in discussing and comparing between similar populations and compounds.

Despite the literature search result, we have decided to include three additional studies to the list of relevant studies for this application. This was done to be able to discuss the unmet medical need in the PIK3CA mutation subgroup and to compare alpelisib with abemaciclib as directed in the Medicines Council Protocol. The first study included is the registration study MONARCH-2 (NCT02107703), and though no data on PIK3CA mutated patients were reported in the initial study, the study met the criteria of investigating abemaciclib as the comparator for alpelisib. However, we have identified and included an abstract on post-analyses from MONARCH-2 reporting the clinical outcomes of patients with PIK3CA mutations in circulating tumor DNA, which gives us an opportunity to compare among the populations of interest (13). MONALEESA-3 (NCT02422615) is the second study included to the list of relevant studies. MONALEESA-3 is reporting on + CDK4/6 treatment with fulvestrant and can provide insights into data using this as add on therapy. The study is Novartis sponsored and we have access to subgroup data and a subsequent analysis which is included in the ITC. This enables a more accurate basis for comparison. Since there are limited data available from patients who possess PIK3CA mutations and who have been treated with alpelisib after progression on CDK4/6 + AI (the population of interest), data from the phase II trial BYLieve (NCT03056755) is included to give insight into the clinical benefit in post-CDK4/6 treated patients. Therefore, the five studies (SOLAR-1, MONARCH-2, PALOMA-3, MONALEESA-3 and BYLieve) will be the basis of this application.

4.1 Relevant studies

Table 1. Relevant studies included in the assessment.

Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)	Relevant for clinical question <x>*
Alpelisib for PIK3CA-Mutated, Hormone Receptor-Positive Advanced Breast Cancer, André, F., et al. N Engl J, 2019 (5)	SOLAR-1	NCT02437318	Start: July 23, 2015 Estimated study completion: July 1, 2022	1/2
MONARCH 2: Abemaciclib in Combination With Fulvestrant in Women With HR+/HER2- Advanced Breast Cancer Who Had Progressed While Receiving Endocrine Therapy, Sledge, G. W., Jr., et al., J Clin Oncol, 2017 (14)	MONARCH-2	NCT02107703	Start: July 22, 2014 Completion: February 14, 2017	1
Palbociclib in Combination with Fulvestrant in Women With Hormone Receptor-Positive/HER2-Negative Advanced Metastatic Breast Cancer: Detailed Safety Analysis From a Multicenter, Randomized, Placebo-Controlled, Phase III Study (PALOMA-3). Verma S., Oncologist, 2016	PALOMA-3	NCT01942135	Start: September 26, 2013 Completion: February 28, 2022	1

Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)	Relevant for clinical question <x>*
Phase III Randomized Study of Ribociclib and Fulvestrant in Hormone Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative Advanced Breast Cancer: MONALEESA-3. Slamon DJ et al., JCO, 2018 (8)	MONALEESA-3	NCT02422615	Actual Study Start Date: June 9, 2015 Actual Primary Completion Date: November 3, 2017 Estimated Study Completion Date: February 19, 2020	1
Alpelisib plus fulvestrant in PIK3CA-mutated, hormone receptor-positive advanced breast cancer after a CDK4/6 inhibitor (BYLieve): one cohort of a phase 2, multicenter, open-label, non-comparative study, Rugo HS et al., Lancet Oncol, 2021 (12)	BYLieve	NCT03056755	Start: August 14, 2017 Estimated study completion: July 15, 2022	2

*when multiple clinical questions are defined in the protocol

4.2 Main characteristics of included studies

In this section, a brief description of each of the included studies will be listed. For full details on in- and exclusion criteria and study design, see Appendix A.

SOLAR-1

A phase III randomized double-blind, multicenter, placebo-controlled study of alpelisib in combination with fulvestrant for men and postmenopausal women with HR+/HER- aBC which progressed on or after AI treatment. Patients were randomized 1:1 to receive either alpelisib in combination with fulvestrant (treatment arm B) or placebo in combination with fulvestrant (treatment arm A). Eligible patients were men and postmenopausal women who had locally confirmed HR+/HER2- aBC, who had adequate tumor tissue for central analysis of PIK3CA mutational status. Patients had either measurable disease (at least one measurable lesion according to the Response Evaluation Criteria in Solid tumors version 1.1. (RECIST 1.1) or one or more predominantly lytic bone lesions, an Eastern Cooperative Oncology Group (ECOG) performance-status score of 0 or 1 (on a scale to 5) and adequate organ and bone marrow function. (5) A detailed description of the inclusion and exclusion criteria, the

method of analyses, the follow-up time, and the baseline characteristics can be seen in the Appendix A in Table A2a.

MONARCH-2

A phase III randomized, double-blind, multicenter, placebo-controlled study of abemaciclib in combination with fulvestrant for women with HR+/HER2- locally advanced or metastatic breast cancer. Patients were randomized 2:1 between the 2 arms and were randomized using the following stratification factors: nature of disease (visceral metastases versus bone only metastases versus other) and sensitivity to ET (primary resistance versus secondary resistance). The presence of visceral metastases refers to lung, liver, pleural, or peritoneal involvement at the time of randomization. Eligible patients were required to have disease that progressed while receiving neoadjuvant or adjuvant ET, ≤12 months after adjuvant ET, or while receiving ET for aBC. Patients must not have received more than one ET or any prior chemotherapy for aBC (14). A detailed description of the inclusion and exclusion criteria, the method of analyses, the follow-up time, and the baseline characteristics can be seen in Appendix A in Table A2b.

PALOMA-3

A phase III, randomized, double blind, placebo controlled clinical trial with the primary objective of demonstrating the superiority of palbociclib in combination with fulvestrant over fulvestrant alone in prolonging PFS in women with HR+/HER2- metastatic breast cancer, whose disease has progressed after prior ET. The safety between the two treatment arms was also compared. During study treatment, pre- and perimenopausal women had to receive therapy with goserelin. Eligible patients had breast cancer and histologic or cytologic confirmation of recurrent local or distant disease progression during or within 12 months of completion of adjuvant ET, or while receiving ET, or within 1 month after receiving ET metastatic breast cancer. Both premenopausal and postmenopausal patients who had an ECOG performance status of 0–1 and measurable disease, or bone-only disease with a lytic lesion, were eligible. One prior line of chemotherapy in the advanced setting was allowed, but there was no limit on the number of prior lines of ET in the metastatic breast cancer setting. (15). A detailed description of the inclusion and exclusion criteria, the method of analyses, the follow-up time, and the baseline characteristics can be seen in Appendix A in Table A2c.

MONALEESA-3

A phase III, randomized, double-blind, multicenter, placebo-controlled study of ribociclib in combination with fulvestrant for the treatment of postmenopausal women and men with HR+/HER2-, aBC who have received no or only one line of ET for advanced breast cancer. Patients were randomly assigned in a 2:1 ratio to receive either ribociclib or placebo in addition to fulvestrant as first-line or second-line treatment. Eligible patients included men and postmenopausal women ≥18 years of age at trial entry, with histologically or cytologically confirmed HR+, HER2- aBC (metastatic or locoregionally recurrent disease not amenable to curative treatment). Patients had an ECOG performance-status score of 0 or 1 (on a 5-point scale) and measurable disease according to RECIST 1.1, or at least one predominantly lytic bone lesion. Crossover between the two groups was not permitted. (8). A detailed description of the inclusion and exclusion criteria, the method of analyses, the follow-up time, and the baseline characteristics can be seen in Appendix A in Table A2d.

BYLieve
A phase II, open-label, non-comparative, multicenter, three-cohort trial to assess the efficacy and safety of alpelisib plus fulvestrant or letrozole in patients with HR+/HER2- aBC with a confirmed PIK3CA mutation determined by local or central laboratory testing of tumor tissue or plasma. Eligible patients were women and men ≥18 years of age, who had an ECOG performance status of 2 or less and who have progressed on or after prior treatments and not amenable to curative therapy. (12). A detailed description of the inclusion and exclusion criteria, method of analyses, follow-up time, and baseline characteristics can be seen in the Appendix A in Table A2e.

5 Clinical question 1

What is the value of alpelisib in combination with fulvestrant compared to CDK4 / 6 inhibitors in combination with fulvestrant in patients with locally advanced or metastatic ER + / HER2- breast cancer and mutation in the PIK3CA gene?

Population of relevance:
Patients currently eligible for treatment with CDK4 / 6 inhibitors in combination with fulvestrant, i.e.:

- Patients with locally advanced or metastatic ER+ / HER2- breast cancer and mutation in the PIK3CA gene who have received endocrine monotherapy as first-line treatment for metastatic disease.

- Patients with locally advanced or metastatic ER + / HER2- breast cancer and mutation in the PIK3CA gene relapse at or shortly after the end of endocrine monotherapy as adjuvant therapy.

5.1 Presentation of relevant studies

Below is a brief summary of the studies that are used in the assessment of this clinical question.

5.2 Results per study

5.2.1 SOLAR-1

SOLAR-1 introduction: SOLAR-1 is the registration trial for alpelisib in first- and second-line treatment of postmenopausal women and men with HR+/HER2- aBC with or without the PIK3CA mutation (2, 5). The trial enrolled patients in 34 countries (including Denmark) at 198 trial sites (of which 4 are Danish) into two cohorts on the basis of tumor-mutation status of the PI3Kα gene (i.e. PIK3CA-mutated vs. not PIK3CA-mutated (proof of concept population)). Here we only report efficacy data on the PIK3CA mutated population, in line with the current indication. For complete overview, safety data is reported on the Intention-to-treat (ITT) (mutated and the wild type (proof of concept) population) (16).

Efficacy
Progression-free survival (PFS): In the cohort with PIK3CA-mutated HR+/HER2- aBC, the median duration of follow-up from randomization to data cut-off was 20.0 months (range, 10.7-33.3 months). The median PFS was 11.0 months (95% confidence interval [CI]: 7.5-14.5) in the alpelisib + fulvestrant group, as compared to 5.7

months (95% CI: 3.7-7.4) in the placebo + fulvestrant group (hazard ratio for progression or death [HR] 0.65; 95% CI: 0.50-0.85; p<0.001) (Figure 1). (5).

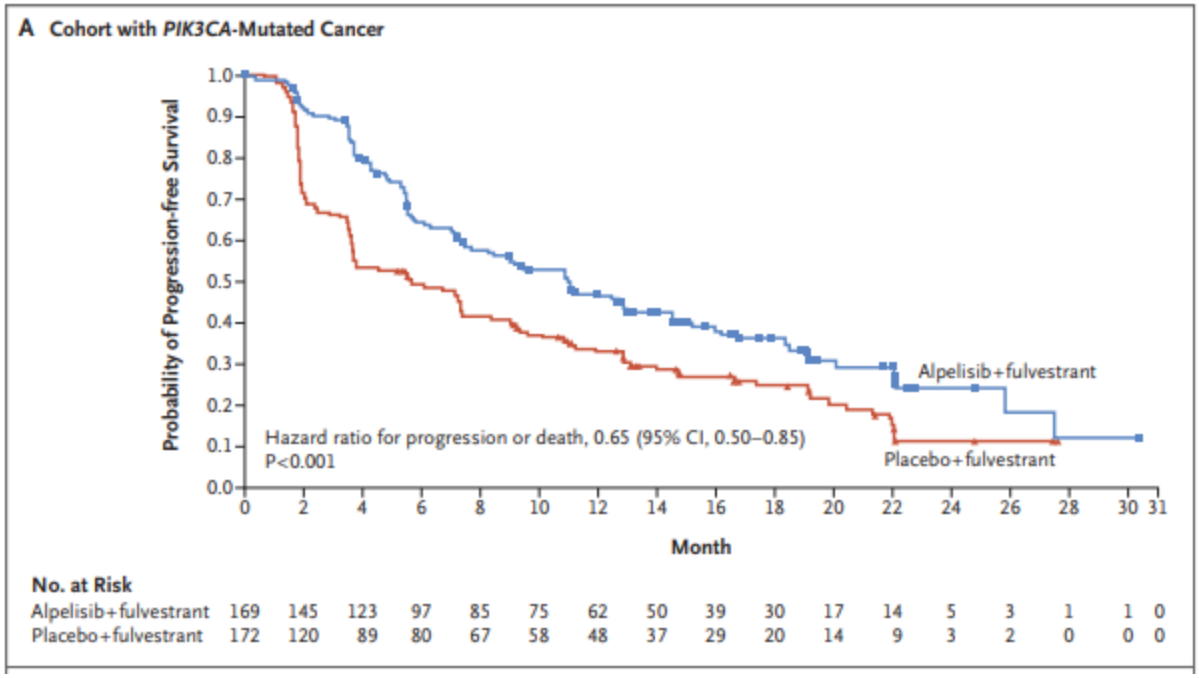


Figure 1. PFS at 20 months of median follow-up based on local assessment in SOLAR-1 (5), in the cohort of patients with PIK3CA-mutated cancer (Panel A). The gene PIK3CA encodes for the alpha isoform of phosphatidylinositol 3-kinase (PI3Kα). Symbols indicate censored data.

As illustrated in Figure 2, forest plot analyses of PFS according to stratification criteria and important demographic and prognostic factors showed consistent benefit of treatment with alpelisib + fulvestrant across pre-specified subgroups, irrespective of presence or absence of lung/liver metastases.

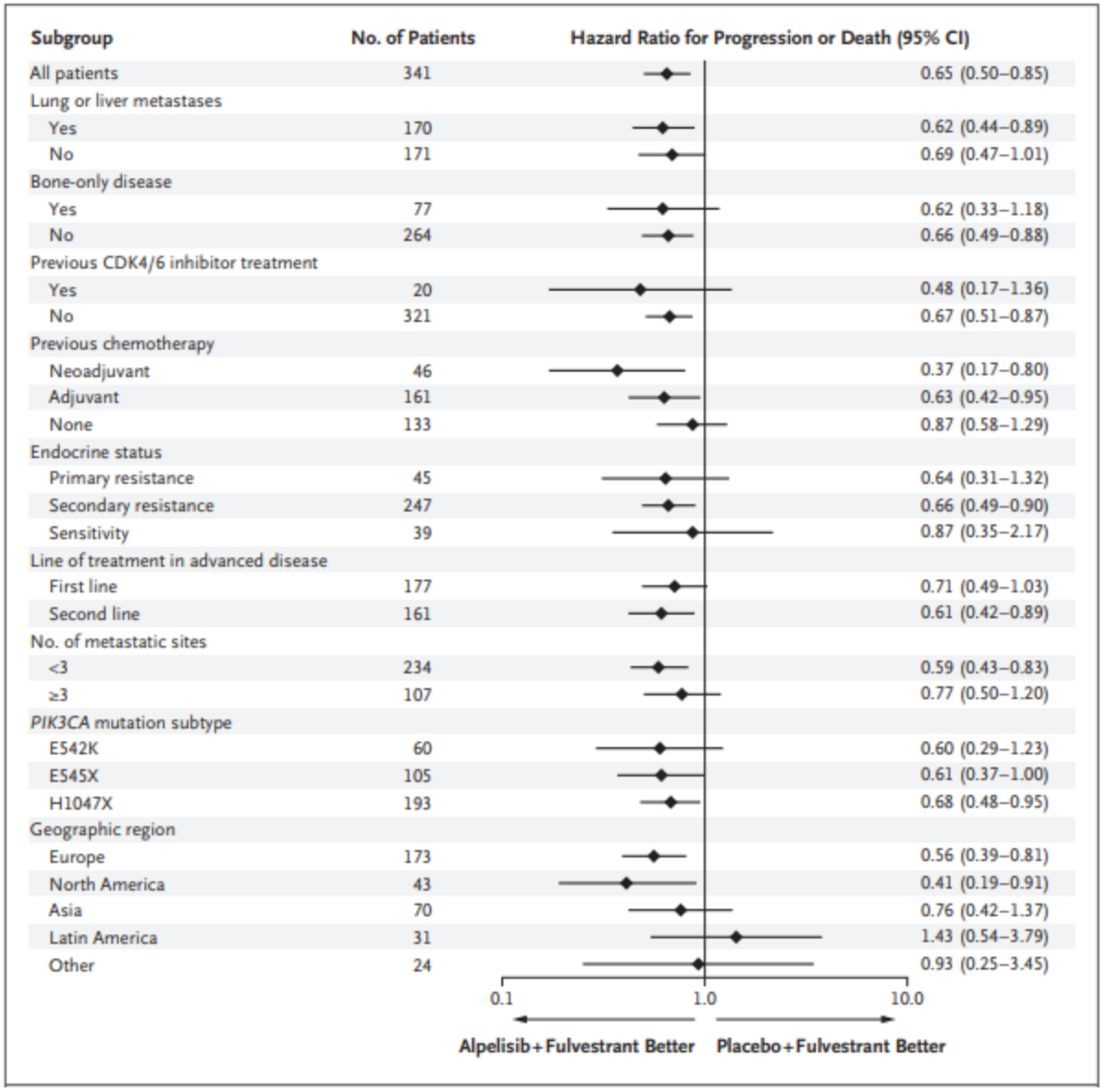


Figure 2. Pre-specified PFS subgroup analyses in SOLAR-1, PIK3CA-mutated cohort. Forest plot of hazard ratio with 95% confidence interval for PFS based on local investigator's assessment from subgroup analysis. Confidence intervals have not been adjusted for multiplicity. Inferences drawn from the confidence intervals may not be reproducible. The previous chemotherapy subgroup was based on the last line of chemotherapy received. Patients may have received chemotherapy in the context of both neoadjuvant and adjuvant therapy. Patients may have had more than one PIK3CA mutation. There were multiple subtypes of E545 and H1047 mutations. (5).

Visceral disease: Of 341 patients with PIK3CA mut, 193 (56.6%) had visceral metastasis. Tumor responses were improved with alpelisib vs placebo in patients with or without visceral metastasis. The majority (n=170; 88.1%) of patients with visceral metastasis had lung and/or liver metastases and median PFS was 9.0 vs 3.7 months in the alpelisib (n=84) vs PBO (n=86) arms (HR 0.62; 95% CI, 0.44-0.89). PFS HRs (95% CI) for alpelisib vs placebo in patients with presence of liver metastases (alpelisib, n=49; PBO, n=54) or lung involvement (alpelisib, n=57; PBO, n=68) were 0.58 (0.37-0.90) and 0.65 (0.42-1.01), respectively. PFS HRs (95% CI) for alpelisib vs placebo in patients

without lung and/or liver metastases (alpelisib, n=85; PBO, n=86) and in patients with bone-only metastases (alpelisib, n=42; PBO, n=35) were 0.69 (0.47-1.01) and 0.62 (0.33-1.18), respectively. Median PFS for patients with bone-only metastases in the ALP vs PBO arms was 19.1 vs 13.0 months. Conclusions: Treatment benefit from alpelisib + fulvestrant was maintained across patient subgroups analysed, including patients with visceral metastasis and bone-only metastases, and was consistent with the benefit observed in the PIK3CA-mutated cohort in SOLAR-1 (1, 5).

POST-CDK4/6 population: In SOLAR-1 20 patients received a prior CDK4/6 inhibitor before inclusion in the study. This population is relevant for Clinical question 2, therefor this population will be further described in section 6. As SOLAR-1 study was recruiting at a time where limited CDK4/6 inhibitors were available and not yet standard of care, the actual number of participants who had prior treatment with CDK4/6 inhibitors was 20 participants. (5).

Endocrine-resistant population: PFS results for the subgroup of endocrine resistant patients (HR=0.64; 95% CI: 0.49, 0.85, n=292) and endocrine sensitive patients (HR=0.87; 95% CI: 0.35, 2.17, n=39) were in favor of the alpelisib plus fulvestrant treatment. The number of endocrine sensitive patients with a PIK3CA mutation was limited (n=39) and should be interpreted with caution (5).

Circulating tumor DNA: Benefit in alpelisib-treated patients using circulating tumor DNA (ctDNA) for PIK3CA mutational information was furthermore confirmed (17) with HR of 0.55 (10.9 months vs 3.7 months in alpelisib vs placebo-treated patients harbouring a PIK3CA mutation) (Figure 3) - allowing non-invasive (liquid) biopsies to be used for treatment decisions within this patient population (2).

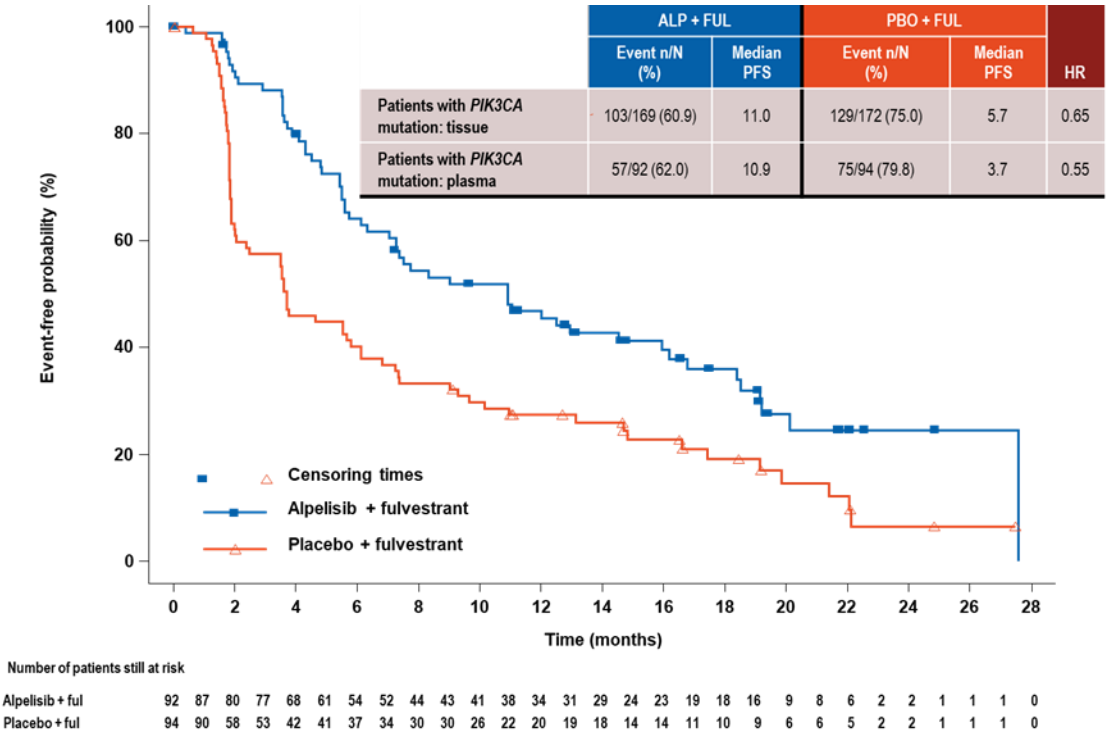


Figure 3: Locally Assessed PFS by Tissue or Plasma ctDNA-determined Mutation Status (5)

Other clinical responses: Overall response rates (ORR) among all PIK3CA-mutated patients were greater with alpelisib + fulvestrant than with placebo + fulvestrant (26.6% vs. 12.8%), and clinical benefit rate (CBR) was also greater with alpelisib + fulvestrant (61.5% vs. 45.3%). Among patients with measurable disease at baseline, ORR were 35.7% in the alpelisib + fulvestrant group and 16.2% in the placebo + fulvestrant group; with CBR of 57.1% and 44.1% in the alpelisib + fulvestrant group and placebo + fulvestrant groups, respectively (2, 5).

Overall survival – interim analyses 1 and 2: OS results were not mature at the time of the first interim analysis (data cut-off date June 12, 2018), with 92 deaths (40 in the alpelisib group and 52 in the placebo group) – corresponding to 52% of the planned OS events for the final analysis (5) . At this time-point, median OS was not yet reached in the alpelisib + fulvestrant group, vs 26.9 months in the placebo + fulvestrant group. The study remained blinded for follow-up of OS after the first data-cut. The second interim OS analysis in the PIK3CA mutant cohort was conducted using a data cut-off date of 30th of September 2019 and was based on 153 deaths corresponding to an 86.0% information fraction. The pre-specified O'Brien Fleming stopping boundary (p value ≤0.0117) was not crossed at this analysis. There were 69 events (40.8%) reported in the alpelisib plus fulvestrant arm, compared to 84 events (48.8%) in the placebo plus fulvestrant arm. A median OS difference of 9.4 months in favour of the patients receiving alpelisib plus fulvestrant was observed, which at the cut off point for this interim analysis was not statistically significant at the required p value of ≤0.0117 (HR=0.77, 95% CI: 0.56-1.06, one sided p value=0.06) (1, 2).

Overall survival – Final Overall Survival analysis and other updated analyses: Final OS analysis for the mutated cohort was performed upon a data cut-off on April 23rd, 2020, when 181 events had occurred – with a median time between randomization to OS event or censoring being 30.8 months. Here, alpelisib + fulvestrant demonstrated a 7.9-month improvement in median OS: 39.3 vs 31.4 months (HR 0.86; 95% CI: 0.64, 1.15) (Figure 4), although the analysis did not cross the pre-specified O'Brien-Fleming efficacy boundary (1-sided p≤0.0161). Of note, patients with lung and/or liver metastases demonstrated a 14.4-month increase in median OS; 37.2 vs 22.8 months (HR 0.68; 95% CI: 0.46, 1.00) (Figure 5) (11).

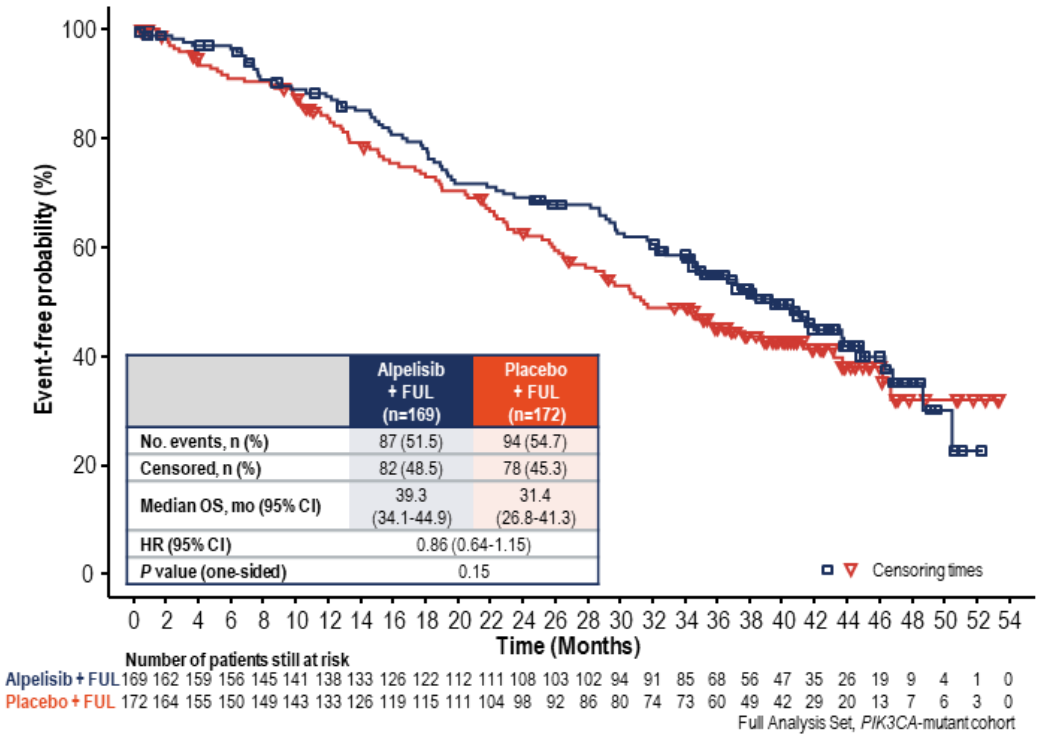


Figure 4: Plot of Kaplan-Meier estimate of OS in the PIK3CA mutated cohort at final OS analysis (data cut-off April 23, 2020), ITT population. Reprinted from the 2020 ESMO oral presentation by Professor André. (11)

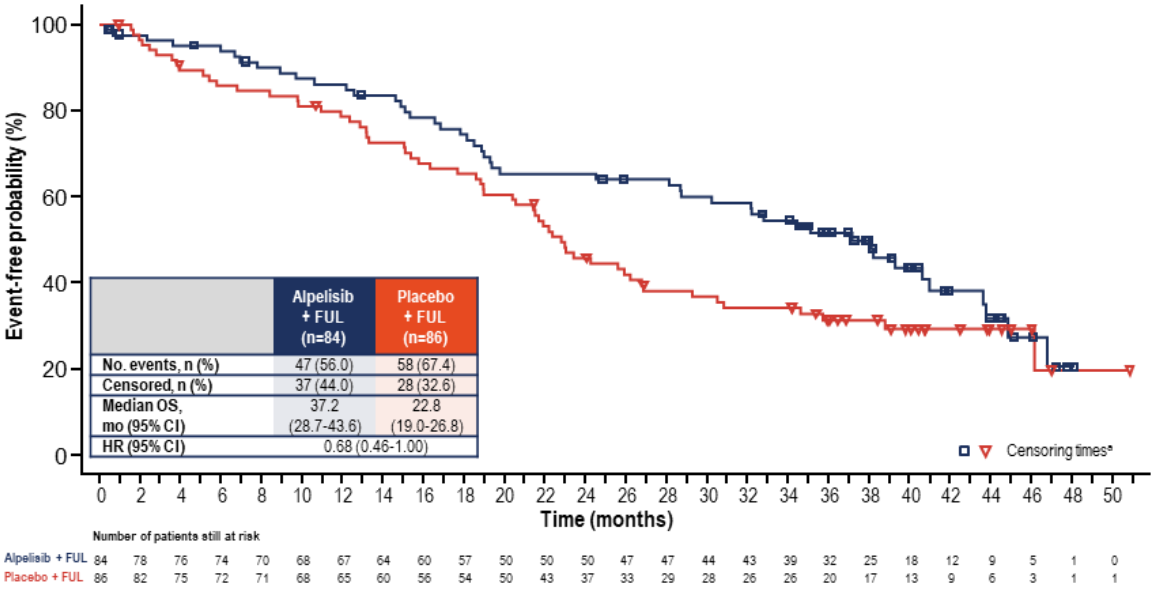


Figure 5: Plot of Kaplan-Meier estimate of OS in the PIK3CA mutated cohort at final OS analysis (data cut-off April 23, 2020), patients with lung and/or liver metastases. Reprinted from the 2020 ESMO oral presentation by Professor André. (11)

In patients with a PIK3CA mutation in ctDNA, which may be indicative of greater disease burden (and provides a more up-to-date view on ongoing disease compared to primary tumor mutational analysis), a 9.2-month increase in median OS was observed in the alpelisib vs placebo arms (34.4 vs 25.2 months, respectively; HR 0.74; 95% CI: 0.51, 1.08) (11).

Moreover, a post-hoc exploratory analysis demonstrated that TTC was prolonged in the alpelisib treated group; with a median TTC delay of 8.5 months observed for patients in the alpelisib + fulvestrant arm (23.3 months [15.2-28.4] vs 14.8 months [10.5-22.6]; HR 0.72 [95% CI: 0.54, 0.95]) (11).

Taken together, SOLAR-1 demonstrated statistically significant and clinically meaningful PFS difference between the two arms. Moreover, an 8-month clinically meaningful OS benefit was also observed in this patient population, which had a worse prognosis due to presence of a PIK3CA mutation. Improved OS was also observed in alpelisib treated patients with harder-to-treat disease, such as patients with visceral involvement - showing an incremental OS benefit of more than 14 months compared to fulvestrant monotherapy (11).

Duration of drug exposure in SOLAR-1: In the overall population (mutant + non-mutant), the median duration of exposure to study treatment was longer in the alpelisib plus fulvestrant group (8.2 months) compared to the placebo plus fulvestrant treatment group (5.6 months). In the alpelisib plus fulvestrant treatment group, exposure to fulvestrant was longer than alpelisib (median 8.2 versus 5.5 months), reflecting that some subjects who discontinued alpelisib for reasons other than disease progression continued treatment with fulvestrant. In the placebo plus fulvestrant treatment group, the duration of exposure to both study drugs was similar (with a median of 5.6 months for both placebo and fulvestrant. In SOLAR-1, the mean drug exposure was 8.0 months for alpelisib and 10.0 month for fulvestrant in the alpelisib + fulvestrant arm (IQR: 1.7 – 12.9). (Data on File)

Safety: In the safety population (284 patients in the alpelisib group and 287 in the placebo group), adverse events of any grade that occurred in at least 35% of the patients in either group were hyperglycaemia (63.7% in the alpelisib group and 9.8% in the placebo group, respectively), diarrhoea (57.7% and 15.7%, respectively), nausea (44.7% and 22.3%), decreased appetite (35.6% and 10.5%), and rash (35.6% and 5.9%) or maculopapular rash (in 14.1% and 1.7%) (18). See table 2 for details.

Table 2. Adverse events in SOLAR-1. Most frequently reported adverse events (≥20% incidence of any grade event in either treatment group) in the safety population[a] (18)

AE, n(%)	Alpelisib plus fulvestrant (n=284)					Placebo plus fulvestrant (n=287)				
	Any grade	Grade 1	Grade 2	Grade 3	Grade 4	Any grade	Grade 1	Grade 2	Grade 3	Grade 4
Any AE	282 (99.3)	12 (4.2)	54 (19.0)	183 (64.4)	33 (11.6)	264 (92.0)	69 (24.0)	92 (32.1)	87 (30.3)	15 (5.2)
Hyperglycaemia[b]	181 (63.7)	32 (11.3)	45 (15.8)	93 (32.7)	11 (3.9)	28 (9.8)	19 (6.6)	7 (2.4)	1 (0.3)	1 (0.3)
Diarrhoea	164 (57.7)	93 (32.7)	52 (18.3)	19 (6.7)	0	45 (15.7)	30 (10.5)	14 (4.9)	1 (0.3)	0
Nausea	127 (44.7)	90 (31.7)	30 (10.6)	7 (2.5)	0	64 (22.3)	49 (17.1)	14 (4.9)	1 (0.3)	0
Decreased appetite	101 (35.6)	75 (26.4)	24 (8.5)	2 (0.7)	0	30 (10.5)	21 (7.3)	8 (2.8)	1 (0.3)	0
Rash[c]	101 (35.6)	48 (16.9)	25 (8.8)	28 (9.9)	0	17 (5.9)	14 (4.9)	2 (0.7)	1 (0.3)	0
Vomiting	77 (27.1)	64 (22.5)	11 (3.9)	2 (0.7)	0	28 (9.8)	18 (6.3)	9 (3.1)	1 (0.3)	0

Decreased weight	76 (26.8)	34 (12.0)	31 (10.9)	11 (3.9)	0	6 (2.1)	1 (0.3)	5 (1.7)	0	0
Stomatitis	70 (24.6)	39 (13.7)	24 (8.5)	7 (2.5)	0	18 (6.3)	15 (5.2)	3 (1.0)	0	0
Fatigue	69 (24.3)	36 (12.7)	23 (8.1)	10 (3.5)	0	49 (17.1)	36 (12.5)	10 (3.5)	3 (1.0)	0
Asthenia	58 (20.4)	25 (8.8)	28 (9.9)	5 (1.8)	0	37 (12.9)	29 (10.1)	8 (2.8)	0	0

AEs (adverse events) were graded per the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03.

[a] AEs reported as a single preferred term regardless of relationship to study medication.

[b] Hyperglycaemia is reported in the table as a preferred term. Hyperglycaemia adverse event of special interest (AESI) (preferred terms listed in (18) supplementary Table S1) was reported in 187 (65.8%) patients in the alpelisib plus fulvestrant group [grade>3, n=108 (38.0%)] and in 30 (10.5%) of those randomly assigned to receive placebo plus fulvestrant [grade ≥3, n=2 (0.7%)].

[c] Rash is reported in the table as a preferred term. Rash AESI (preferred terms listed in (18) supplementary Table S1) was reported in 153 (53.9%) of patients in the alpelisib plus fulvestrant group [grade>3, n=57 (20.1%)] and in 24 (8.4%) of those randomly assigned to receive placebo plus fulvestrant [grade ≥3, n=1 (0.3%)].

Grade 3-4 adverse events were reported by 76% of patients in the alpelisib plus fulvestrant arm compared to 35.5% of patients in the placebo plus fulvestrant arm, with treatment-related grade 3 and 4 adverse events being 66.9% vs 11.8%, respectively. Hyperglycaemia (37% vs. 1%) and diarrhoea (7% vs. 0.7%) were the most frequent grade 3-4 adverse events in the alpelisib group (1). Serious adverse events (SAE) were reported by 36.6% of patients treated with alpelisib plus fulvestrant and 18.8% of those that received placebo plus fulvestrant. In the alpelisib arm most of the SAEs were considered treatment-related (22.5% vs. 1.7%, experimental and control arm, respectively). Among patients receiving alpelisib plus fulvestrant, more treatment discontinuations (26.1% vs. 5.6%) and dose modifications (79.2% vs. 23%) were reported (DCO 30 Sep 2019)(1, 19). The most frequent adverse events leading to treatment discontinuation of alpelisib in > 2% were hyperglycaemia (6%), rash (4.2%), diarrhoea (2.8%), and fatigue (2.5%). The most frequent adverse events leading to dose reduction in > 2% of the patients receiving alpelisib plus fulvestrant were hyperglycaemia (29%), rash (9%), diarrhoea (6%), stomatitis (3.5%) and mucosal inflammation (2.1%). The most common adverse events including laboratory abnormalities (all grades, incidence ≥ 20%) were glucose increased, creatinine increased, diarrhoea, rash, lymphocyte count decreased, GGT (gamma-glutamyl transferase) increased, nausea, ALT increased, fatigue, haemoglobin decreased, lipase increased, decreased appetite, stomatitis, vomiting, weight decreased, calcium decreased, glucose decreased, a PTT (activated partial thromboplastin time) prolonged, and alopecia. SAE occurred in 99 patients (34.9%) receiving alpelisib plus fulvestrant and 48 (16.7%) receiving placebo plus fulvestrant. SAE in > 2% of patients receiving alpelisib plus fulvestrant included hyperglycaemia (10%), rash (3.5%), diarrhoea (2.8%), acute kidney injury (2.5%), abdominal pain (2.1%), and anaemia (2.1%). Deaths and SAEs have been investigated in a pooled set combining data from SOLAR-1 and two phase Ib studies, X2101 and X1101. A review of the deaths did not identify any worrisome pattern. Most deaths were due to disease progression. Out of the pooled safety analysis of 725 patients, there was only one doubtful case of alpelisib-related death, an event of thrombotic microangiopathy reported in one patient in SOLAR-1. However, other contributing factors not related to study treatment were also present in that patient. (1, 20).

A recent publication focusing on the time course and management of key adverse events (hyperglycaemia, rash and diarrhoea) in SOLAR-1 could demonstrate a lower frequency of, and more importantly, a decrease in discontinuations of study treatment due to these adverse events after a study amendment providing more detailed adverse event management information as well as recommendation of prophylactic medication towards

e.g. rash and diarrhoea The data cut-off from April 23rd, 2020 – equivalent to median follow-up of 42.4 months - did not reveal any new safety signals and the safety profile therefore remains consistent (18).

Quality of life / Patient-reported outcomes: Patient-reported outcomes (PROs) provide further insights into the benefit-risk profile of alpelisib from a patient perspective and enable an evaluation of whether the observed efficacy benefit of alpelisib plus fulvestrant versus placebo plus fulvestrant in SOLAR-1 was achieved at the expense of a deterioration in QoL. QoL was investigated using PROs, including HRQoL and cancer-related pain. These were collected using the EORTC QLQ-C-30 (Global health/QoL, functional subscales and symptoms), EQ-5D-5L (index values), and BPI-SF (worst pain item, pain severity index, and pain interference indices) questionnaires. Patient-reported outcomes data were collected at screening, every 8 weeks for 18 months, then every 12 weeks thereafter until progression, at the end of treatment, and during follow-up for efficacy. At baseline, ≥93% of patients completed the EORTC QLQ C-30, EQ-5D-5L, and BPI-SF questionnaires. At each post-baseline visit, completion rates ranged from 75% to 100%. (21).

PRO results: Based on previously established criteria, there was no clinically meaningful overall change from baseline in EORTC QLQ-C30 global health status/QoL score in patients treated with either alpelisib plus fulvestrant or placebo plus fulvestrant (Fig. 6**Error! Reference source not found.**). Similarly, no statistical difference was o bserved in terms of Time to 10% Deterioration, TTD, for EORTC QLQ-C30 physical, emotional, and social functioning subscale scores (Figure 6). However, there was deterioration in the social functioning subscale in patients treated with alpelisib plus fulvestrant. Some EORTC QLQ-C30 symptom scores, such as diarrhoea and nausea/vomiting, were worsened in patients treated with alpelisib plus fulvestrant. This is expected given that gastrointestinal toxicities are commonly observed with alpelisib plus fulvestrant treatment. (21).
Changes from baseline in EORTC QLQ-C30 Global Health Status/QoL scale score over time were estimated from a repeated measurement model that included terms for treatment, stratification factors, time, treatment-by-time interaction, and baseline score; to ensure the model provided stable estimates, data were cut when patient numbers were 10 in each treatment arm. This analysis only included assessments up to the time point at which there were at least 10 patients in each of the treatment groups. Time to deterioration in Global Health Status/QoL and Physical, Emotional, and Social functioning was defined as a worsening in score by ≥ 10% compared with baseline with no later improvement above this threshold during the treatment period or death because of any cause, as supported by EORTC QLQ-C30 interpretation guidelines 26 and previous PRO analyses in patients with HR1, HER22 ABC (Fig 6). (21)

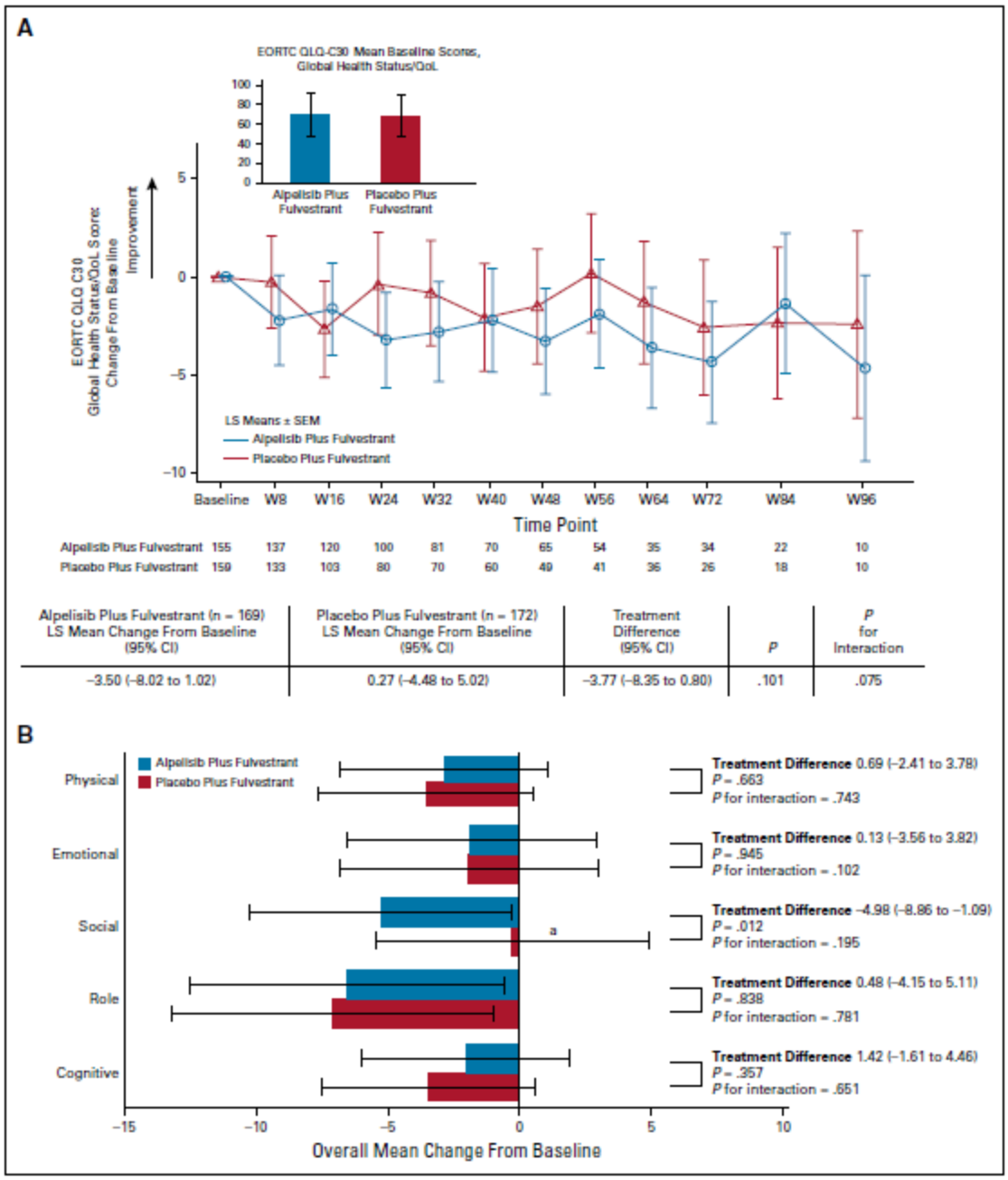


Figure 6. (A) Changes from baseline in EORTC QLQ-C30 Global Health Status/QoL scale score and (B) overall mean change from baseline in EORTC QLQ-C30 functioning subscale scores, PIK3CA-mutant cohort. In (A), error bars for mean baseline scores indicate 6 SD; error bars for LS means change from baseline indicate 6 SEM. Changes. 0 indicate improvement from baseline. In (B), error bars indicate 95% CIs; a indicates P, .05 for treatment difference. EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life of Cancer Patients questionnaire; LS, least squares; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; QoL, quality of life; W, week.(21)

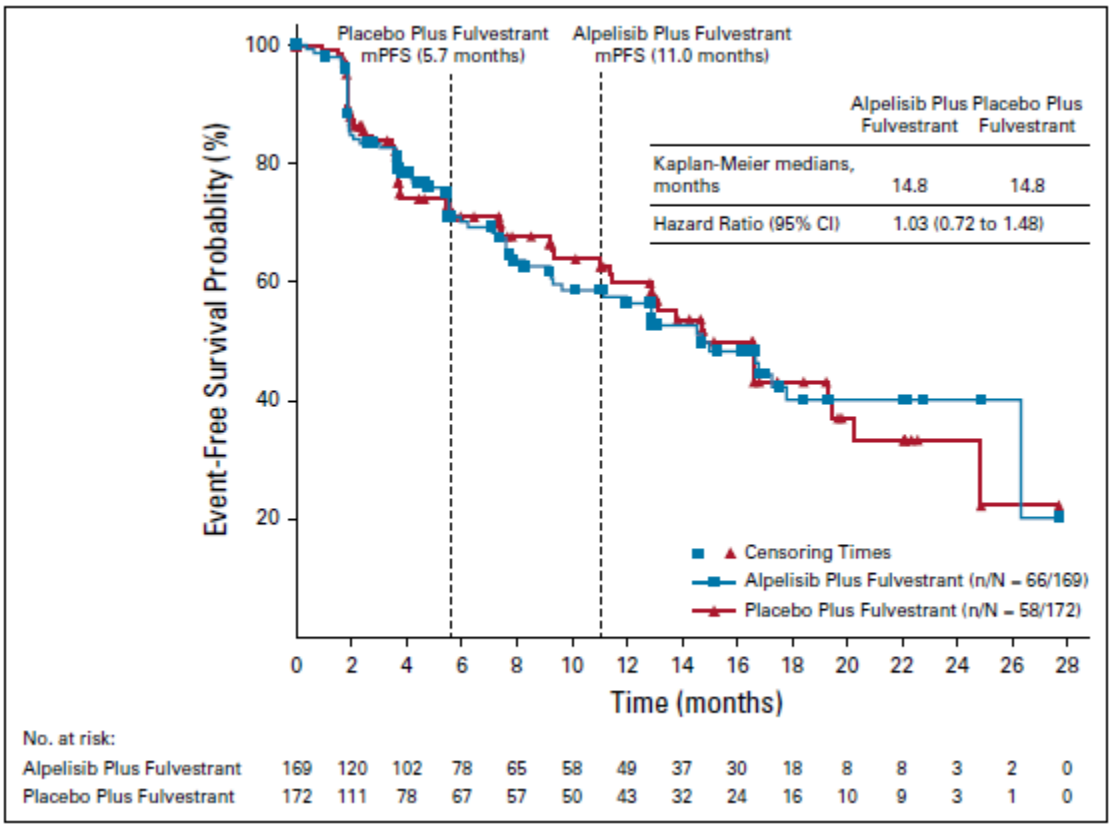


Figure 6. Time to 10% deterioration in European Organization for Research and Treatment of Cancer Global Health Status/quality of life scale score, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha–mutant cohort. Data include all randomly assigned patients in the phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha–mutant cohort. mPFS, median progression-free survival. (21).

The results from the TTD analyses were also consistent with the observed mean changes and did not demonstrate differences between the two treatment arms over 28 months (HR, 1.03; 95% CI, 0.72 to 1.48; (Fig. 7) (23).

To summarize, the analyses of secondary PRO variables of interest generally showed no clinically meaningful differences between the alpelisib plus fulvestrant and placebo plus fulvestrant arms. In conclusion, the updated analysis reported, that patients with HR+/HER2- PIK3CA-mutated ABC treated with alpelisib plus fulvestrant did not experience a significant decline in their overall HRQoL, measured as Global Health Status/QoL. Symptom scores for diarrhea, appetite loss, nausea or vomiting, and fatigue favored the placebo arm, which was expected as these are known AEs of alpelisib in clinical trials. Physical, Emotional, Cognitive, and Role functioning scores were similar to those observed in the placebo group. Collectively, these data indicate that while there were some changes in subscale and symptom scores, overall QoL and functioning were maintained in patients with HR+/HER2- aBC with

PIK3CA-mutated tumors who were treated with alpelisib plus fulvestrant in the SOLAR-1 study, with no meaningful differences versus placebo plus fulvestrant (21).

5.2.2 Comparator study: MONARCH-2 (abemaciclib + fulvestrant)

MONARCH-2 introduction: MONARCH-2 is the EMA registration trial for abemaciclib in combination with fulvestrant in first line treatment of HR+/HER2- aBC. The global Phase III, double-blind study was designed to evaluate the efficacy and safety of abemaciclib, in combination with fulvestrant, in patients with advanced (locoregionally recurrent or metastatic) breast cancer, who had progressed while receiving neoadjuvant or adjuvant endocrine therapy (ET), ≤ 12 months from the end of adjuvant ET, or while receiving first-line ET for metastatic disease (14).

Between August 2014 and December 2015, 669 patients were randomly assigned 2:1, to receive abemaciclib plus fulvestrant (n = 446) or placebo plus fulvestrant (n = 223). The study met its primary endpoint of improving PFS. Primary efficacy results are summarized in Table 3 and Figure 8 (14).

Table 3. MONARCH 2: Summary of abemaciclib efficacy data (Investigator assessment, intent-to-treat population) (22)

	Abemaciclib + fulvestrant	**Placebo + fulvestrant**
Progression-free survival	**N=446**	**N=223**
Investigator assessment, number of events (%)	222 (49.8)	157 (70.4)
Median [months] (95% CI)	16.4 (14.4, 19.3)	9.3 (7.4, 12.7)
Hazard ratio (95% CI) and p-value	0.553 (0.449, 0.681), p=0.0000001	
Independent radiographic review, number of events (%)	164 (36.8)	124 (55.6)
Median [months] (95% CI)	22.4 (18.3, NR)	10.2 (5.8, 14.0)
Hazard ratio (95% CI) and p-value	0.460 (0.363, 0.584); p <.000001	
Objective response rate[b] [%] (95% CI)	35.2 (30.8, 39.6)	16.1 (11.3, 21.0)
Duration of response [months] (95%CI)	NR (18.05, NR)	25.6 (11.9, 25.6)
Objective response for patients with measurable disease[a]	**N=318**	**N=164**
Objective response rate[b] [%] (95% CI)	48.1 (42.6, 53.6)	21.3 (15.1, 27.6)
Complete response, (%)	3.5	0
Partial response, (%)	44.7	21.3
Clinical benefit rate[c] **(measurable disease)** [%] (95% CI)	73.3 (68.4, 78.1)	51.8 (44.2, 59.5)

[a] Measurable disease defined per RECIST version 1.1
[b] Complete response + partial response
[c] Complete response + partial response + stable disease for ≥ 6 months
N=number of patients; CI=confidence interval; NR=not reached.

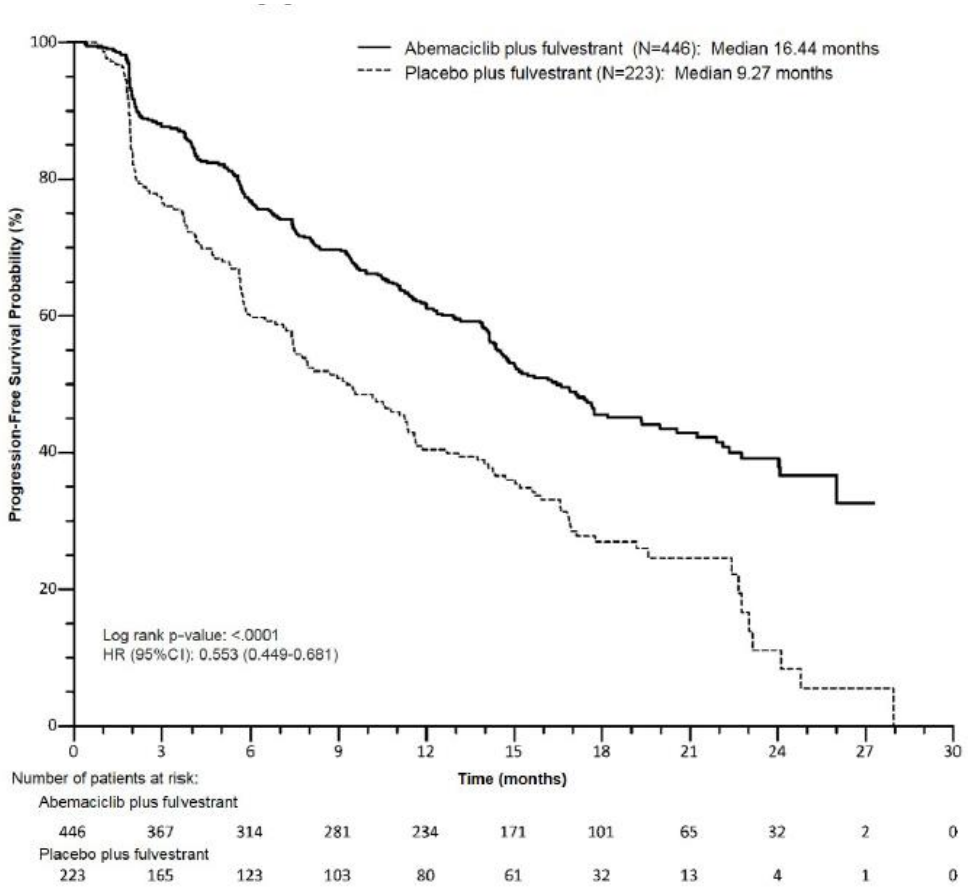


Figure 7. MONARCH 2: Kaplan-Meier plot of progression-free survival (Investigator assessment, intent-to-treat population) (14).

Median progression-free survival: A blinded central analysis demonstrated consistent PFS results. PFS was significantly prolonged in the abemaciclib plus fulvestrant arm (HR of 0.553 [95% CI 0.449, 0.681]); median PFS was 16.4 months versus 9.3 months in the placebo plus fulvestrant arm. These results correspond to a clinically meaningful reduction in the HR of 44.7% and a 7.2 months improvement in median PFS for patients treated with abemaciclib plus fulvestrant. Abemaciclib plus fulvestrant prolonged progression-free survival with neither a clinically meaningful nor significant detriment to health-related quality of life. A series of prespecified subgroup PFS analyses showed consistent results across patient subgroups including age (<65 or ≥65 years), race, geographic region, disease site, endocrine therapy resistance, presence of measurable disease, progesterone receptor status, and menopausal status. A reduction in the risk of disease progression or death was observed in patients with visceral disease, (HR of 0.481 [95% CI: 0.369, 0.627]), median PFS 14.7 months versus 6.5 months; in patients with bone-only disease (HR of 0.543 [95% CI: 0.355, 0.833]); patients with measurable disease (HR of 0.523 [95% CI: 0.412, 0.644]). In patients who were pre/perimenopausal, the hazard ratio was 0.415 (95% CI: 0.246, 0.698); in patients who were progesterone receptor negative, the HR was 0.509 (95% CI: 0.325, 0.797). In a sub-population with locally advanced or metastatic disease that had not received prior endocrine therapy, the PFS was also consistent. In the MONARCH-2 trial, abemaciclib + fulvestrant significantly improved PFS compared to placebo with a median of 16.4 months vs 9.3 months, (HR: 0.553) (14) and see section with data overview tables, Table 14.

Overall survival (OS): Analysis in the ITT population showed a statistically significant improvement in patients receiving Abemaciclib plus fulvestrant compared with those receiving placebo plus fulvestrant. Overall survival was significantly improved with a median OS of 46.7 months for abemaciclib plus fulvestrant and 37.3 months for placebo plus fulvestrant (HR of 0.757 [CI:0.606-0.945]). The OS results are summarized in Table 15. (23).

Subgroup Analysis of Patients with Visceral Metastases: In MONARCH-2 54.9% and 57.4% of patients had visceral disease in the abemaciclib + fulvestrant group and fulvestrant plus placebo group respectively. The median PFS was 14.7 v 6.5 months for abemaciclib + fulvestrant group and fulvestrant plus placebo group respectively (HR of 0.471 [CI:0.371-0.598]) supplement, (23). In patients with visceral disease, the median overall survival (OS) was 40.3 months vs 32.2 months in the abemaciclib plus fulvestrant and fulvestrant plus placebo arms, respectively (HR of 0.675 [CI:0.511-0.891]) (23). See section with data overview tables, Table 16.

Exploratory Analysis of Patients with PIK3CA mutation: In an exploratory analysis of MONARCH-2 patients with PIK3CA-mutated tumors had shorter PFS compared with those with wild-type tumors in both the abemaciclib-plus-fulvestrant (mutated, 15 months; wild type, 20 months) and the placebo-plus-fulvestrant (mutated, 5.7 months; wild type, 12.7 months) arms (7). See section with data overview tables, Table 17.

Safety summary: The most common adverse events reported in the abemaciclib versus placebo arms were diarrhoea (86.4% v 24.7%), neutropenia (46.0% v 4.0%), nausea (45.1% v 22.9%), and fatigue (39.9% v 26.9%). See section with data overview tables, Table 18. For common AEs with abemaciclib in combination with fulvestrant. The safety profile of abemaciclib with fulvestrant was broadly consistent with that reported for other CDK 4 and 6 inhibitors with the exception of diarrhoea. Most diarrhoea was of low grade, occurred early in the first treatment cycle, and was managed with dose adjustment and standard anti-diarrheal medication. Other frequent, nonhematological AEs in the abemaciclib arm included nausea, fatigue, and abdominal pain. In the safety population (abemaciclib, n = 441; placebo, n = 223), the most frequent adverse events of any grade were diarrhoea, neutropenia, nausea, fatigue, and abdominal pain. These occurred at predominately grade 1 or 2 severity. SAE(SAEs) were reported in 22.4% of patients in the abemaciclib arm and 10.8% of patients in the placebo arm. SAEs possibly related to the study drug were reported in 8.8% of patients on the abemaciclib arm and 1.3% of patients on the placebo arm, with the most frequent being diarrhoea (1.4% in the abemaciclib arm v 0% in the placebo arm). There were 14 deaths (3.2%) in the abemaciclib arm (nine due to AEs) and 10 (4.5%) in the control arm (two due to AEs) reported in patients receiving therapy or within 30 days of treatment discontinuation. Of these, three deaths (0.7%) in the abemaciclib arm were determined to be related to the study treatment; two were due to sepsis in patients in whom guidance regarding granulocyte colony-stimulating factor administration and dose reduction was not followed, and one was due to viral pneumonia in a patient receiving steroids for spinal stenosis. (14)

PRO results:
Time to Sustained deterioration favoured the abemaciclib arm, compared with the control arm, in HRQoL (reflected in the global health status score) and all functional and most symptom scales on the QLQ-C30 (Fig. 9). At baseline, the EORTC QLQ-C30 global health status score and the QLQ-C30 and QLQ-BR23 functional and symptom scores were similar between study arms and comparable to established reference values for patients with recurrent or metastatic breast cancer. Change from baseline for most functional and symptom scores were similar between study arms, but four scores statistically favoured the control arm over time: appetite loss (between treatment group difference ± SE, 5.31 ± 1.43; p < .001), nausea and/or vomiting (3.42 ± 0.88; p < .001), diarrhoea (24.64 ± 1.56; p < .001), and systemic therapy side effects (5.21 ± 0.87; p < .001). (24)

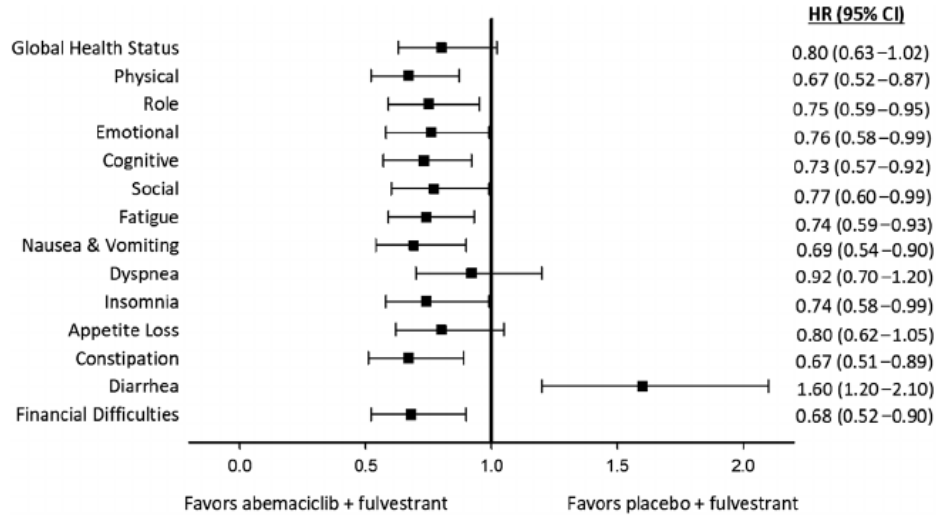


Figure 8. Forest plot of time to sustained deterioration of European Organization for Research and Treatment of Cancer Quality of Life Core 30 symptom and functioning items. Abbreviations: CI, confidence interval; HR, hazard ratio. (24)

5.2.3 Comparator study: PALOMA-3 (palbociclib + fulvestrant)

PALOMA-3 introduction: PALOMA-3 was a prospective, randomized, double-blind, placebo-controlled phase 3 study investigating the efficacy and safety of fulvestrant with or without palbociclib in women with hormone-receptor-positive, HER2-negative metastatic breast cancer whose disease had progressed after previous endocrine therapy.

Median progression-free survival: Median PFS was 9.5 months (95% CI 9.2-11.0) in the fulvestrant plus palbociclib group and 4.6 months (3.5-5.6) in the fulvestrant plus placebo group (HR 0.46, 95% CI 0.36-0.59, p<0·0001). See table 4 (25). See section with data overview tables, Table 14.

Overall survival: The differences in OS in the entire trial group were not significant. In the palbociclib-fulvestrant group median OS was 34.9 months (95% CI, 28.8 to 40.0) and 28.0 months (95% CI, 23.6 to 34.6) in the placebo-fulvestrant group (HR 0.81; 95% CI, 0.64 to 1.03; P=0.09; absolute difference, 6.9 months). (26). See section with data overview tables, Table 15.

Subgroup Analysis of Patients with Visceral Metastases: In PALOMA-3, 59% of patients it the palbociclib plus fulvestrant group and 60% in the fulvestrant plus placebo group had visceral disease. Median PFS was significantly longer in patients treated with palbociclib plus fulvestrant than with placebo plus fulvestrant in the presence of visceral metastases (9.2 months, 95% CI 7.5–11.1 versus 3.4 months, 1.9–5.1, respectively; HR 0.47; 95% CI 0.35–0.61). The median overall survival was 27.6 months (95% CI, 24.4 to 31.2) in the palbociclib plus fulvestrant group and 24.7 months (95% CI, 20.8 to 31.8) in the placebo plus fulvestrant group (HR 0.85; 95% CI, 0.64 to 1.13). (27). See section with data overview tables, Table 16.

Safety summary: The most common grade 3 or 4 adverse events were neutropenia (223 [65%] in the fulvestrant plus palbociclib group and one [1%] in the fulvestrant plus placebo group), anemia (ten [3%] and three [2%]), and leucopenia (95 [28%] and two [1%]). SAE (all causalities) occurred in 44 patients (13%) of 345 in the fulvestrant plus palbociclib group and 30 (17%) of 172 patients in the fulvestrant plus placebo group. for common AEs with palbociclib in combination with fulvestrant. (25). See section with data overview tables, Table 18.

Exploratory Analysis of Patients with PIK3CA mutation: PIK3CA mutation was detected in the plasma DNA of 129 (33%) of 395 patients for whom these data were available. Neither PIK3CA status nor hormone-receptor expression level significantly affected treatment response. In the 266 patients who had wild-type PIK3CA, median progression-free survival was 9.9 months (95% CI 9.2–13.9) in the fulvestrant plus palbociclib group and 4.6 months (3.4–7.3) in the fulvestrant plus placebo group (HR 0.45, 95% CI 0.31–0.64). In patients with a PIK3CA mutation, median progression-free survival was 9.5 months (95% CI 5.7–11.2) in the fulvestrant plus palbociclib group and 3.6 months (1.9–5.6) in the fulvestrant plus placebo group (HR 0.48, 95% CI 0.30–0.78). (25). See section with data overview tables, Table 17.

PRO results: Questionnaire completion rates were high at baseline and during treatment (from baseline to cycle 14, ≥95.8% in each group completed ≥1 question on the EORTC QLQ-C30). On treatment, estimated overall global QoL scores significantly favored the palbociclib plus fulvestrant group. The difference between treatment groups in estimated overall global QoL scores was found to be statistically significant favoring palbociclib plus fulvestrant [66.1 (95% CI: 64.5–67.7) versus 63.0 (95% CI: 60.6–65.3); P = 0.0313]. A significantly greater delay in deterioration of QoL was observed in the palbociclib plus fulvestrant versus control (median not reached; HR: 0.641; 95% CI: 0.451–0.910; 1-sided P = 0.0065;Significantly greater improvement from baseline in pain was also observed in this group (−3.3, 95% CI−5.1 to−1.5 versus 2.0, 95% CI−0.6 to 4.6; P= 0.0011). No significant differences were observed for other QLQ-BR23 functioning domains, breast or arm symptoms. Treatment with palbociclib plus fulvestrant significantly delayed deterioration in global QoL(P<0.025) (Figure 9) and pain (P< 0.001) compared with fulvestrant alone. Conclusion: Palbociclib plus fulvestrant allowed patients to maintain good QoL in the endocrine resistance setting while experiencing substantially delayed disease progression. (28)

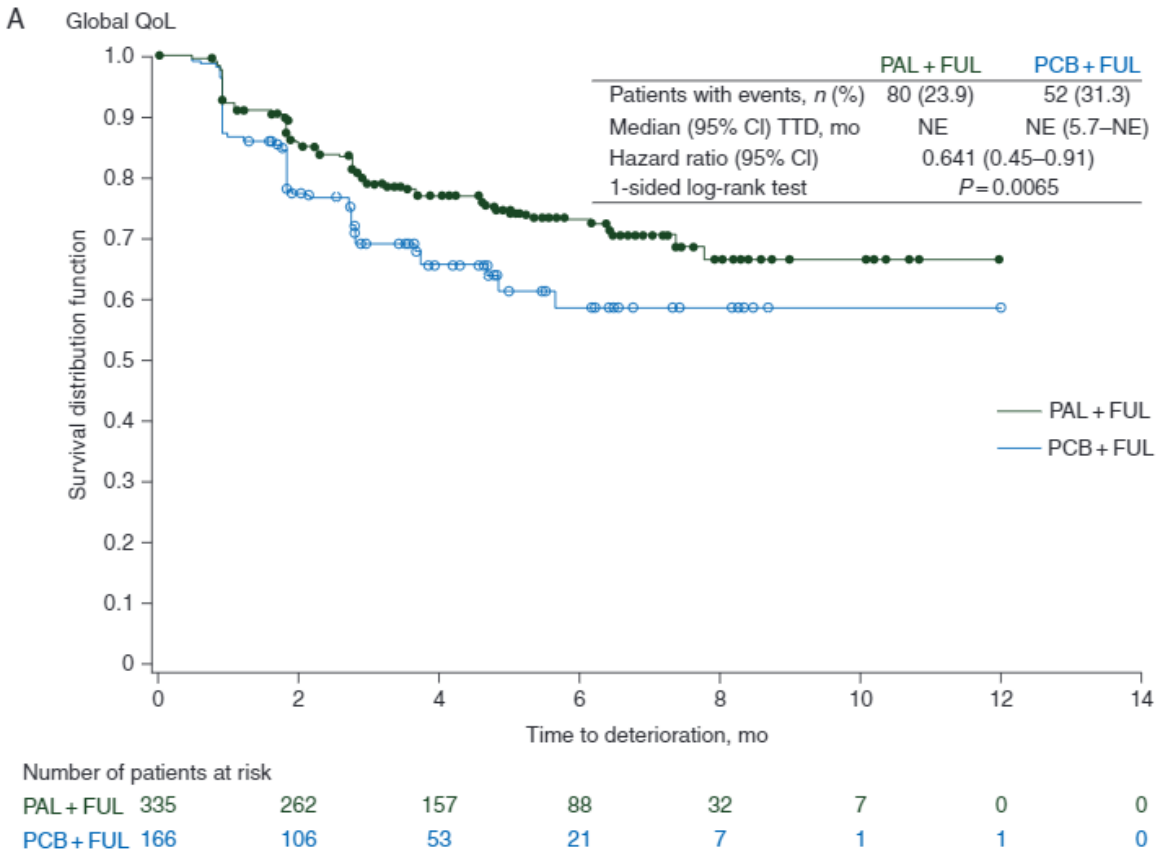


Figure 9. Time to deterioration in global QoL (A) in the PRO analysis set. Kaplan–Meier curves of European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 items (EORTC QLQ-C30) scores for the patient-reported outcomes analysis population. CI, confidence interval; NE, not estimable; TTD, time to deterioration; PRO, patient-reported outcomes; QoL, quality of life. Circles and pluses indicate patients censored. (28)

5.2.4 Comparator study: MONALEESA-3 (ribociclib + fulvestrant)

MONALEESA-3 introduction: MONALEESA-3 was a randomized double-blind, placebo controlled, multicenter phase III clinical study assessing the safety and efficacy of ribociclib in combination with fulvestrant versus fulvestrant in combination placebo, in the treatment of men and postmenopausal women with HR+/HER2- aBC who had received no or only one line of prior endocrine treatment. (8).

Progression free survival: Median progression-free survival was significantly improved with ribociclib plus fulvestrant versus placebo plus fulvestrant: 20.5 months (95% CI, 18.5 to 23.5 months) versus 12.8 months (95% CI, 10.9 to 16.3 months), respectively (HR 0.593; 95% CI, 0.480 to 0.732; P < .001). Consistent treatment effects were observed in patients who were treatment naïve in the advanced setting (HR 0.577; 95% CI, 0.415 to 0.802), as well as in patients who had received up to one line of prior endocrine therapy for advanced disease (HR 0.565; 95% CI, 0.428 to 0.744). Among patients with measurable disease, the overall response rate was 40.9% for the ribociclib plus fulvestrant arm and 28.7% for placebo plus fulvestrant. See Table 14 (8).

Overall Survival: A significant overall survival benefit was seen with ribociclib plus fulvestrant over placebo plus fulvestrant. The estimated overall survival at 42 months was 57.8% (95% CI, 52.0 to 63.2) in the ribociclib group and 45.9% (95% CI, 36.9 to 54.5) in the placebo group, for a 28% difference in the Hazard Rate (HR 0.72; 95% CI, 0.57 to 0.92; P=0.00455). At the time of this analysis, the median overall survival in the ribociclib group was not reached; the median overall survival in the placebo group was 40.0 months (95% CI, 37.0 to, could not be estimated). See Table 15(29).

Subgroup Analysis of Patients with Visceral Metastases: In MONALEESA-3, 60.5% of patients in the ribociclib + fulvestrant group and 60.7% of patients in the fulvestrant + placebo group had visceral disease. Median PFS in patients with visceral metastases was 16.6 (13.4-19.9) months in the ribociclib plus fulvestrant group and 10.6 (5.5-12.9) months fulvestrant + placebo group, with a hazard ratio of 0.616 (95% CI, 0.487-0.779). The OS was similar across study arms and consistent with that observed in the overall population. The OS was 41 months in the ribociclib-containing arm and 39.4 months in the placebo-containing arm (HR=0.804, 95% CI, 0.596-1.083). See Table 16. (29).

Exploratory Analysis of Patients with PIK3CA mutation: A numerically shorter PFS was observed in patients with PIK3CA-altered tumors compared with patients with wild-type tumors in the same treatment arms in both the ribociclib-plus-fulvestrant (mutated, 16.4 months; wild type, 22.3 months) and placebo-plus-fulvestrant (mutated, 11.1 months; wild type, 16.69 months) groups. These data are relevant in regard to the clinical question 2. See Table 17 (29). In the updated analysis from 2021, Patients with lung or liver metastases had an mOS of 46.9 months (95% CI 38.1-NR months) with ribociclib versus 39.4 months (95% CI 29.9-44.9 months) with placebo (HR, 0.73; 95% CI 0.55-0.98)(30, 31).

Safety: Grade 3 adverse events reported in ≥ 10% of patients in either arm (ribociclib plus fulvestrant v placebo plus fulvestrant) were neutropenia (46.6% v 0%) and leukopenia (13.5% v 0%); the only grade 4 event reported in ≥ 5% of patients was neutropenia (6.8% v 0%). For common AEs with ribociclib in combination with fulvestrant. (7, 8, 29). See section with data overview tables, Table 18.

PRO results: Health/QOL scores at baseline were well balanced between treatment groups: 65.5 (±19.1) in the ribociclib group and 68.4 (±18.5) in the placebo group Figure 10. The mean standard deviation EORTC QLQ-C30 symptom scores assessed at baseline included fatigue (32.2 [±23.1] in the ribociclib group vs 30.5 [±21.4] in the placebo group), diarrhea (6.4 [±15.7] vs 6.7[±14.5]), nausea and vomiting (6.4 [±14.0] vs 7.0 [±14.7]), and pain (30.0 [±25.5] vs 27.8 [±25.9]). In general, at 8 weeks (day1 of cycle 3) and later during treatment, the EORTC QLQ-C30 symptom scores were maintained or improved slightly, irrespective of treatment. In general, patient-reported outcomes demonstrated a maintained HRQoL in the ribociclib + fulvestrant arm. Time to definitive deterioration (TTD) ≥10%, was defined as worsening of the scales score relative to baseline, with no later improvement above this threshold observed during the treatment period, or death due to any cause (32). There was a numerical trend favoring ribociclib vs placebo for TTD ≥10% in global HRQoL (median NE vs 19.4 in ribociclib + fulvestrant vs placebo + fulvestrant; HR 0.795 [0.602; 1.050]; Figure 11. In addition, global HRQoL was improved/maintained vs baseline while on treatment but worsened when treatment was stopped in both arms. Since the delayed disease progression experienced with ribociclib is associated with maintained HRQoL, it seems that AEs associated with ribociclib treatment do not have a substantial impact on HRQoL. (32)

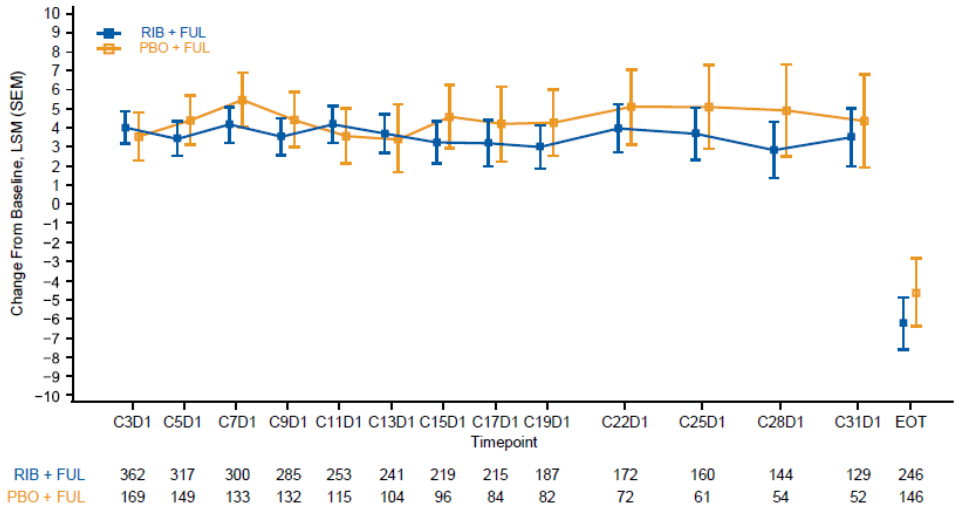


Figure 10. Change from baseline in global health status/QOL scale score of EORTC QLQ-C30. C cycle, D day, EORTC-QLQ-C30 European Organisation for Research and Treatment of Cancer core quality-of-life questionnaire, EOT end of treatment, FUL fulvestrant, HRQOL health-related quality of life, LSM least squares mean, PBO placebo, QOL quality of life, RIB ribociclib, SEM standard error of the mean. The time profile provides the average estimates for the change from baseline to the respective cycle as derived using the linear effects model. Positive changes from baseline indicate improvement in HRQOL. (32).

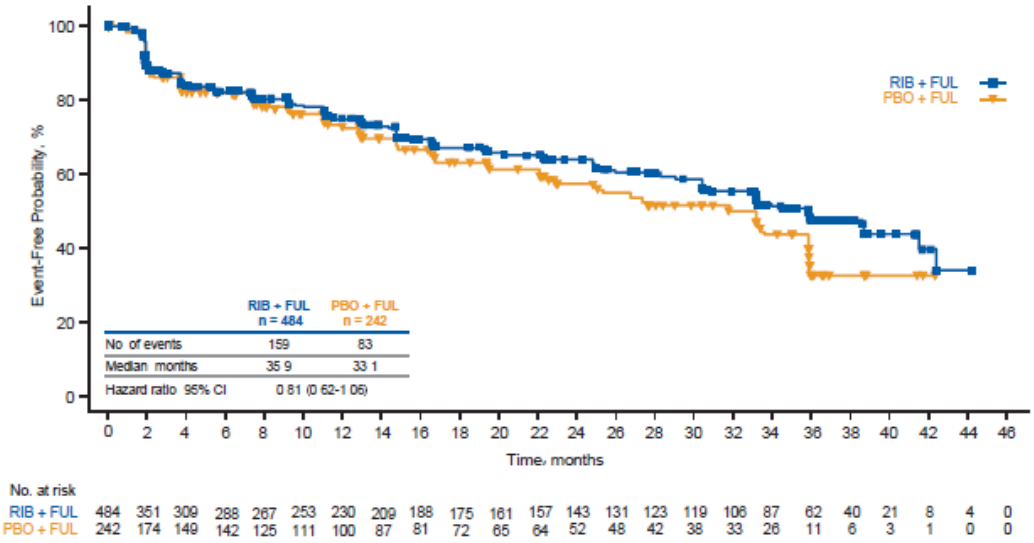


Figure 11. Time to definitive deterioration of global health status/QOL scale score of EORTC QLQ-C3 from baseline by 10%. EORTC-QLQ-C30 European Organization for Research and Treatment of Cancer core quality-of-life questionnaire, FUL fulvestrant, PBO placebo, QOL quality of life, RIB ribociclib. (32)

5.3 Comparative analyses and indirect treatment comparison

The indirect treatment comparisons (ITCs) of PFS and OS for treatments of ET-resistant patients are limited by a lack of RCTs that reported results for subgroups of patients with PIK3CA mutant disease who were receiving first- and second-line therapy. Results of the ITC on PFS or OS of RCTs of treatments for ET-resistant patients with PIK3CA mutated, HR+/HER2- aBC shows no significant differences between CDK 4/6 treatment versus alpelisib with all confidence intervals crossing 1.

In order to answer parts of the clinical question 1, an ITC was conducted assessing PFS and OS of alpelisib plus fulvestrant CDK4/6 treatments plus fulvestrant as well as fulvestrant monotherapy for men and postmenopausal women with PIK3CA-mutation, HR+/HER2- aBC who have received prior treatment with an AI and have not received more than one prior ET for advanced disease (addressing the patient population in the clinical question 1). Estimated HRs for PFS and OS from SOLAR-1 were based on the final OS analysis with data cut-off date April 23, 2020. A review of HRQoL and adverse events will follow the analysis of efficacy.

5.3.1 Overview

The analysis was conducted in two parts. First, an assessment of the feasibility of conducting the ITC was performed in which the characteristics of the trials, that might contribute to the ITC, were compared with respect to patient baseline characteristics that might introduce bias into the comparisons. Next, the ITCs of PFS and OS were conducted using information on PFS and OS from the trials in the evidence network. The ITCs were conducted first using HRs for PFS and OS using the Bucher method (33).

The assessment of feasibility entailed the following steps. First, we sought to determine whether evidence networks for PFS and OS could be constructed linking alpelisib plus fulvestrant to each of the following comparators of interest:

- Fulvestrant
- Ribociclib and fulvestrant
- Palbociclib and fulvestrant
- Abemaciclib and fulvestrant

This analysis was originally performed to include a broader selection of therapies. These are however irrelevant for the clinical question 1 and has consequently been omitted. Only abemaciclib is directly relevant for clinical question 1, but both palbociclib and ribociclib has been included to demonstrate a more comprehensive representation of the challenges related to performing and ITC.

It should be noted that in SOLAR-1, initially patients who relapsed >12 months after completing (neo)adjuvant ET with no prior ET for advanced disease (first-line ET-sensitive) were eligible. The protocol was subsequently amended on August 30, 2016 to exclude such patients. This analysis focused on the ET-resistant population and therefore excluded any patients who enrolled with ET-sensitivity who did not receive prior treatment for advanced disease. RCTs of treatments were identified from the SLR presented in Appendix B, as well as analyses of IPD from Novartis-sponsored studies, for which we had access to such data. This analysis was constructed before the protocol was

received by the Medicines Council and will not be detailed further, as the results of the SLR presented in Appendix B covers the same studies.

We conducted an assessment of the similarity assumption—that is, the extent to which the studies in the networks differ in terms of patient characteristics, that might modify the effects of treatments on PFS and OS, expressed as HRs. This process entailed two steps. First, for each trial contributing to the network, we calculated for each patient characteristic the standardized mean difference (SMD) for the trial vs. SOLAR-1. For each characteristic, the SMD was calculated as the difference in the mean value for that characteristic from the comparator RCT and SOLAR-1, divided by the pooled SD of characteristics in SOLAR-1 and the comparator RCT. Second, for those characteristics for which the SMD exceeded a threshold value of 0.25, we assessed the extent to which these factors modified the effect of treatment in each trial. The latter step required determining whether HRs for PFS or OS were reported for subgroups defined on these factors. For each trial, where such data were available, we calculated a measure of the degree to which these factors modify the effects of treatment, by calculating the ratio of the HRs for the treatment vs. control in each trial for each subgroup vs. a referent subgroup (the log of ratio can be considered as equivalent to the coefficient for an interaction term for treatment and the characteristic in the linear predictor for a Cox regression analysis). CIs and p-values for this measure of effect modification were calculated assuming that the HRs in the subgroups were independent and that the log of the ratio was distributed normally.

ITCs of PFS and OS using HRs may be biased if duration of follow-up varies across trials or if the proportional hazards (PH) is violated within trials. Additionally, projections of benefit on PFS and OS beyond the end of follow-up, based on HRs estimated from ITCs, also may be biased when non-proportionality of hazards exists in one or more trials contributing to the ITC. Accordingly, an assessment of the PH assumption also was conducted for PFS and OS for each trial contributing to the feasibility assessment by examination of Schoenfeld residuals. Schoenfeld residuals are calculated at each failure time by taking the difference of the covariate value for the patient and a weighted average covariate value of patients remaining in the risk set at that time. The scaled residuals are then obtained by multiplying the vector of unscaled residuals by the inverse of their covariance matrix. The scaled residuals can then be used as a time-dependent measure of the treatment effect. An increasing or decreasing trend in the Schoenfeld residuals can be used to detect a deviation from the PH assumption. Because the treatment group covariate is a binary variable, the scaled residuals will either appear well above or below the mean, depending on the group in which the failure occurred. In order to make the pattern of these residuals easier to visualize, a kernel-smoothed estimate was provided. In order to test the PH assumption, the slope of the scaled Schoenfeld residuals was tested using linear regression. IPD were available for Novartis-sponsored RCTs of treatments for advanced breast cancer. For SOLAR-1 and MONALEESA-3, Schoenfeld residuals were calculated using IPD for the relevant subgroups of interest. For other RCTs included in the ITCs, Schoenfeld residuals were calculated using reconstructed IPD derived from digitized Kaplan-Meier (K-M) curves for PFS and OS from study publications and an adaptation of a published algorithm for deriving such data by Guyot (34).

In addition to the assessment of similarity, assessment of the feasibility of an ITC should also consider the assumption of homogeneity (study estimates must measure the same treatment effect) and consistency (indirect evidence must be consistent with direct evidence). Homogeneity is assessed by comparing result of identical treatment comparisons within the network to determine if the observed difference can be attributed to chance alone (34). Consistency is assessed by comparing results of direct and indirect comparisons in networks with mixed treatment comparisons to determine if difference in results can be explained by chance alone. Since none of the networks

included links with multiple trials or closed loops (and hence both direct and indirect evidence), no assessment of homogeneity or consistency was required.

Published K-M survival plots for PFS and OS were digitized using WebPlotDigitizer and reconstructed survival data were derived using a published algorithm by Guyot and colleagues (34, 35).

5.3.2 PFS and OS in Included Studies

HRs and 95% CIs, duration of follow-up, median survival times, and Kaplan-Meier curves were reported for PFS and OS for all included studies. Results were collected for subgroups of patients with PIK3CA mutated cancer if available or irrespective of PIK3CA mutation status otherwise.

5.3.3 Indirect Treatment Comparison using the Bucher Method

ITCs of PFS and OS were conducted separately using a frequentists approach (i.e., Bucher method) (33). With this approach, the effect of intervention B relative to intervention A can be estimated indirectly as follows, using the direct estimators for the effects of intervention C relative to intervention A ($Effect_{AC}$) and intervention C relative to intervention B ($Effect_{BC}$):

$$Effect_{AB} = Effect_{AC} - Effect_{BC}$$

The variance of the indirect estimator $Effect_{AB}$ is the sum of the variances of the direct estimators:

$$Variance_{AB} = Variance_{AC} + Variance_{BC}$$

The corresponding two-tailed 95% confidence interval can thus be calculated as follows:

$$Effect_{AB} \pm Z_{0.975} \times Variance_{AB}^{1/2}$$

5.3.4 Included studies

Table 4: Studies Included in the indirect treatment comparison, identified in the systematic literature review

Study	Author/Year	Inclusion Criteria					
		HR Status	HER2 Status	Menopause Status	PIK3CA Mutation Status	Prior Treatment in (Neo) Adjuvant Setting	Prior Treatment for Advanced Disease
MONALEESA-3	Slamon, 2018 (8)	HR+	HER2-	Postmenopausal	N/A	Resistant or sensitive	Progressed on ET
MONARCH 2	Sledge, 2017 (14)	HR+	HER2-	Any menopause status	N/A	Resistant	Progressed on ET
PALOMA-3	Cristofanilli, 2016 (25)	HR+	HER2-	Any menopause status	N/A	Resistant	Progressed on ET
SOLAR-1	André, 2019 (5)	HR+	HER2-	Postmenopausal	Must provide tissue sample	Resistant or sensitive*	Progressed on ET

*Protocol was amended to exclude ET-sensitive first-line patients; Resistant: relapsed ≤12 months from completion of (neo)adjuvant ET and no treatment for metastatic; Sensitive: relapsed >12 months from completion of (neo)adjuvant ET and no treatment for metastatic disease.

The evidence network for the ITC of PFS for the ET-resistant subgroup of SOLAR-1 is shown in Figure 12. HRs for PFS were available from at least one publication identified by the SLRs for each of the four RCTs. HRs for PFS in a subgroup of patients with PIK3CA mutation were available from the same trials. Kaplan-Meier PFS in subgroups of patients with PIK3CA mutation have not been published for MONALEESA-3 or MONARCH-2, but Kaplan-Meier PFS for the PALOMA-3 and SOLAR-1 trials were available.

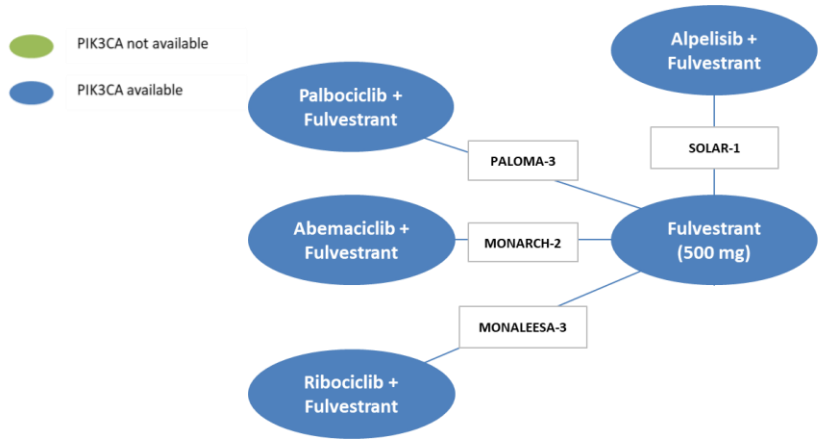


Figure 12. Evidence Network for PFS

The evidence network for the ITC of OS for the ET-resistant subgroup of SOLAR-1 is shown in Figure 13. HRs for OS were available from at least one publication identified by the SLRs for each of the four trials included in the ITC (5, 9, 25, 28). HRs for OS in a subgroup of patients with PIK3CA mutated cancer were only available in SOLAR-1. However, PALOMA-3 reported results on the PIK3CA mutated subgroup in additional publications. In MONALEESA-3 and MONARCH-2 no Kaplan-Meier OS in subgroups with PIK3CA mutation have been published (26, 36). HRs and Kaplan-Meier estimates of OS for other trials were collected for the ITT populations.

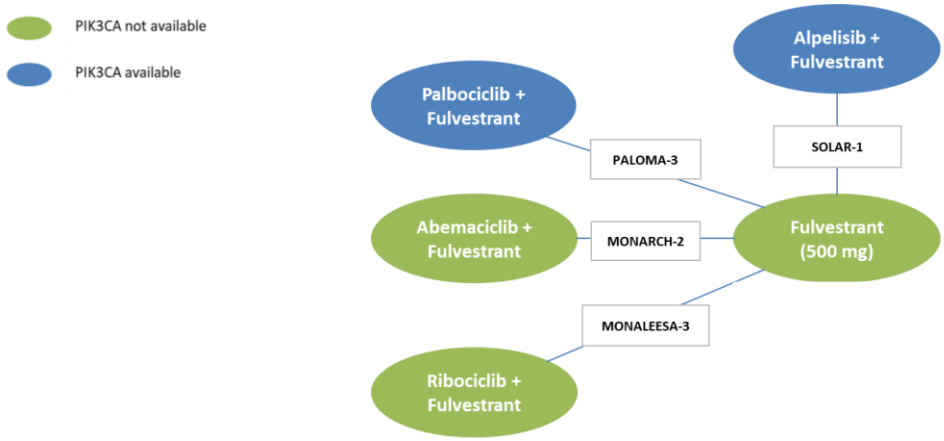


Figure 13. Evidence Network for OS

5.3.5 Patient characteristics of the Identified Studies

Patient characteristics were based on data for patients with PIK3CA mutation for the PALOMA-3 and SOLAR-1 trials. For all other trials, characteristics were based on data for all patients regardless of PIK3CA mutation status. For all the trials, 100% of patients had HR+ tumors. SOLAR-1 enrolled 1 male patient whereas no male patients enrolled in any of the other trials.

In Figure 14, we present the SMDs for ECOG performance status, visceral involvement, number of metastatic sites, timing of relapse or progression on last therapy, race, PIK3CA mutation status, HER2- status, and menopause status. As can be seen, there is broad heterogeneity, which increases the caution one must use when interpreting results. Only in the cases where individual patient level data is available, can a proper matching of patients be performed. However, it was not feasible to exclude these data points in the graph shown in Figure 14. But the data points of the three included studies are clearly visible.

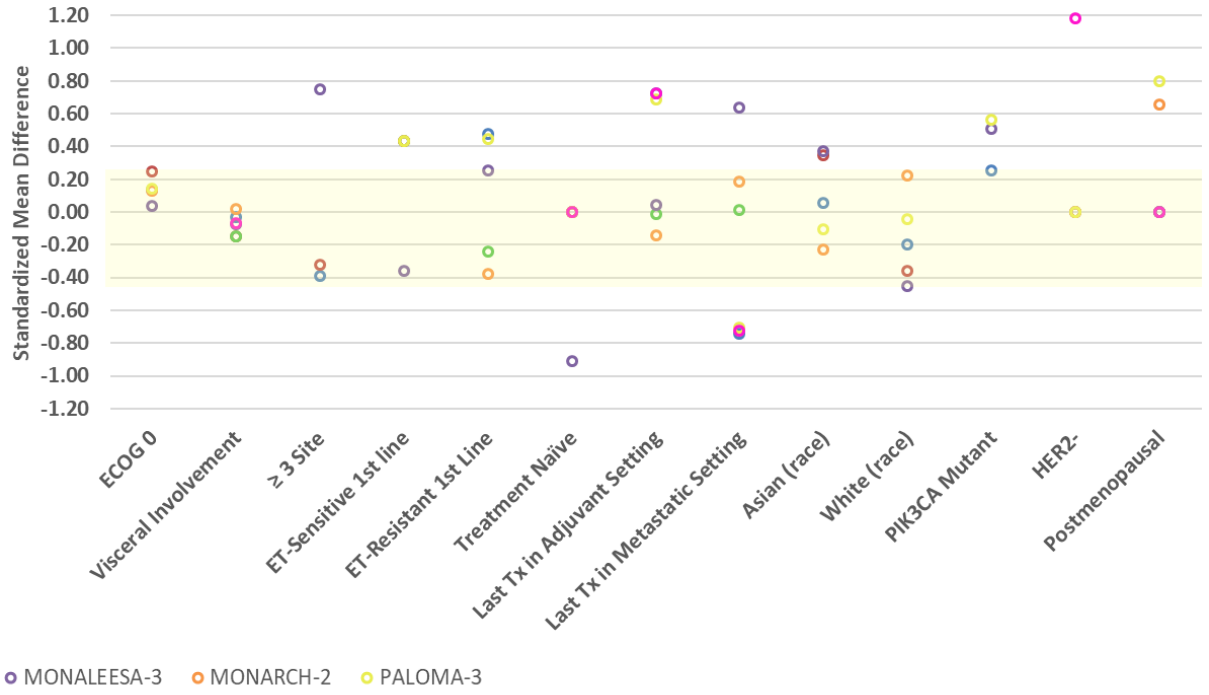


Figure 14. SMD in Baseline Characteristics for Trials Included in Feasibility Assessment vs. SOLAR-1. ET-Sensitive 1st Line: patients with relapse >12 months from completion of adjuvant ET with no treatment for advanced/metastatic disease; ET-Resistant 1st Line: patients with relapse ≤12 months from completion of adjuvant ET with no treatment for advanced/metastatic disease; Tx: treatment.

Among trials that reported PIK3CA mutation status, 42% on average had PIK3CA mutated cancer (range: 32%-60%). In PALOMA-3 and MONARCH-2, 77% and 82% of patients were postmenopausal, respectively. All other RCTs included exclusively postmenopausal patients. Across all RCTs, 60% of patients had visceral involvement (range: 55%-66%), 21% had bone-only metastases (range: 13%-25%), and 58% had 1-2 metastatic sites (range: 46%-72%). Across all trials, 38% had ECOG PS ≥1 (range: 30%-52%). Only the SOLAR-1 and MONALEESA-3 trials enrolled patients who relapsed >12 months from completion of (neo)adjuvant ET with no prior treatment for metastatic disease (i.e., first-line ET-sensitive).

5.3.6 Treatment Effect Modifiers

Estimates of the degree of effect modification for PFS for all the characteristics for which the SMD was greater than 0.25 in one or more trials is shown in Table 5.

Table 5. PFS Treatment Effect Modification

Trial	HR with Characteristic (95% CI)	HR without Characteristic (95% CI)	Effect Modification (95% CI)	p-value
Patients with PIK3CA mutant cancer vs. those without PIK3CA mutant cancer				
PALOMA-3 (28)	0.48 (0.30, 0.78)	0.45 (0.31, 0.64)	1.07 (0.59, 1.94)	0.83
SOLAR-1 (5)	0.65 (0.50, 0.85)	0.85 (0.58, 1.25)	0.76 (0.48, 1.22)	0.26
MONALEESA-3 (8)	0.75 (0.52, 1.08)	0.67 (0.49, 0.91)	1.12 (0.69, 1.81)	0.64
MONARCH-2 (13)	0.46 (0.27, 0.78)	0.68 (0.42, 1.09)	0.68 (0.33, 1.38)	0.28
Postmenopausal patients vs. pre-menopausal patients				
PALOMA-3 (25)	0.45 (0.34, 0.59)	0.50 (0.29, 0.87)	0.90 (0.49, 1.66)	0.74
MONARCH-2 (37)	0.58 (0.46, 0.73)	0.42 (0.25, 0.70)	1.38 (0.79, 2.43)	0.26
Last therapy in (neo)adjuvant setting vs. last therapy in advanced/metastatic setting				
SOLAR-1 (5)	0.71 (0.49, 1.03)	0.61 (0.42, 0.89)	1.16 (0.69, 1.97)	0.57
PALOMA-3 (25)	0.55 (0.32, 0.92)	0.43 (0.32, 0.57)	1.28 (0.70, 2.33)	0.42
One previous line of therapy for metastatic disease vs. two previous lines of therapy for metastatic disease				
PALOMA-3 (25)	0.42 (0.29, 0.60)	0.46 (0.31, 0.69)	0.91 (0.53, 1.57)	0.74
One previous line of therapy for metastatic disease vs. three or more previous lines of therapy for metastatic disease				
PALOMA-3 (25)	0.42 (0.29, 0.60)	0.61 (0.30, 1.24)	0.69 (0.31, 1.53)	0.36
First-line with PIK3CA mutation vs. second-line with PIK3CA mutation				
MONALEESA-3 (data on file)	0.70 (0.41, 1.21)	0.53 (0.25, 1.09)	1.33 (0.53, 3.31)	0.54
SOLAR-1 (data on file)	0.58 (0.40, 0.85)	0.62 (0.44, 0.87)	0.95 (0.57, 1.59)	0.84
Bone-only metastases vs. not bone-only metastases				
SOLAR-1 (5)	0.62 (0.33, 1.18)	0.66 (0.49, 0.88)	0.94 (0.47, 1.89)	0.86
MONALEESA-3 (8)	0.38 (0.23, 0.61)	0.66 (0.52, 0.83)	0.58 (0.34, 0.99)	0.05
Visceral metastases vs. no visceral metastases				
PALOMA-3 (25)	0.47 (0.34, 0.63)	0.43 (0.28, 0.67)	1.09 (0.64, 1.86)	0.74
Lung or liver metastases vs. no lung or liver metastases				
SOLAR-1 (5)	0.62 (0.44, 0.89)	0.69 (0.47, 1.01)	0.90 (0.53, 1.51)	0.69
MONALEESA-3 (8)	0.65 (0.48, 0.86)	0.56 (0.42, 0.76)	1.16 (0.77, 1.76)	0.48
< 3 metastatic sites vs. ≥ 3 metastatic sites				
MONALEESA-3 (8)	0.59 (0.45, 0.77)	0.62 (0.44, 0.87)	0.94 (0.61, 1.46)	0.79
ECOG performance status 0 vs. ECOG performance status 1-2				
MONALEESA-3 (8)	0.56 (0.43, 0.73)	0.63 (0.45, 0.89)	0.89 (0.58, 1.37)	0.59
MONARCH-2 (37)	0.49 (0.37, 0.64)	0.66 (0.48, 0.90)	0.74 (0.49, 1.13)	0.16

While the measure of effect modification was not statistically significant for one or more trials for any other characteristic, the presence of bone-only metastases vs. not bone-only metastases was consistently associated with a more favorable treatment effect (i.e., effect modification < 1.0) across the trials that reported a HR for PFS for this subgroup. Similarly, presence of visceral metastases vs. no visceral metastases was consistently associated with a

less favorable treatment effect (i.e., effect modification >1.0) across the trials that reported this subgroup. No other factors were associated with consistently positive or negative effects across multiple trials.

Presence of PIK3CA mutated cancer vs. absence of PIK3CA mutated cancer negatively impacted on the HRs in the MONALEESA-3 and PALOMA-3 trials but had a positive impact on HRs in SOLAR-1 and MONARCH-2 trials. The favorable effect in SOLAR-1 likely relates to the specific mechanism of action of alpelisib vs. that of the other therapies. The favorable effect in MONARCH-2 contrasts the negative effect in PALOMA-3 and MONALEESA-3, all of which evaluated CDK4/6 inhibitors with the same mechanism of action. The prognosis of HR+/HER2- aBC patients is generally worse if there is a PIK3CA mutation present, which is seen across the three RCT trials (PALOMA-3, MONARCH-2, MONALEESA-3). However, the PFS effect of the placebo arm observed in MONARCH-2 is exceptionally poor when compared to the placebo arm of PALOMA-3 and MONALEESA-3. This could lead to the conclusion, that the difference might be due to randomness.

Estimates of the degree of effect modification for OS for all the characteristics for which the SMD was greater than 0.25 in one or more trials is shown in Table 6.

Table 6. OS Treatment Effect Modification

Trial		HR with Characteristic (95% CI)	HR without Characteristic (95% CI)	Effect Modification (95% CI)	p-value
Patients with PIK3CA mutant cancer vs. those without PIK3CA mutant cancer					
PALOMA-3 (38)		0.74 (0.48, 1.14)	0.84 (0.59, 1.18)	0.88 (0.51, 1.53)	0.65
SOLAR-1*		0.73 (0.48, 1.10)	0.44 (0.18, 1.07)	1.66 (0.62, 4.43)	0.31
Postmenopausal patients vs. pre-menopausal patients					
PALOMA-3 (38)		0.73 (0.57, 0.95)	1.07 (0.61, 1.86)	0.68 (0.37, 1.26)	0.22
MONARCH-2 (37)		0.77 (0.61, 0.98)	0.69 (0.38, 1.25)	1.12 (0.59, 2.13)	0.73
Last therapy in (neo)adjuvant setting vs. last therapy in advanced/metastatic setting					
MONALEESA-3 (29)		0.77 (0.57, 1.04)	0.69 (0.40, 1.20)	1.12 (0.60, 2.09)	0.73
No prior therapy for metastatic disease vs. one prior line of therapy for metastatic disease					
PALOMA-3 (39)		0.70 (0.43, 1.14)	0.70 (0.43, 1.14)	0.86 (0.60, 1.22)	0.81 (0.45, 1.49)
No prior therapy for metastatic disease vs. two prior lines of therapy for metastatic disease					
PALOMA-3 (39)		0.70 (0.43, 1.14)	0.76 (0.48, 1.22)	0.92 (0.47, 1.81)	0.81
No prior therapy for metastatic disease vs. three or more prior lines of therapy for metastatic disease					
PALOMA-3 (39)		0.70 (0.43, 1.14)	0.64 (0.29, 1.40)	1.09 (0.43, 2.76)	0.85
One prior line of therapy for metastatic disease vs. two prior lines of therapy for metastatic disease					
PALOMA-3 (39)		0.86 (0.60, 1.22)	0.76 (0.48, 1.22)	1.13 (0.63, 2.03)	0.68
One prior line of therapy for metastatic disease vs. three or more prior lines of therapy for metastatic disease					
PALOMA-3 (39)		0.86 (0.60, 1.22)	0.64 (0.29, 1.40)	1.34 (0.57, 3.19)	0.50
First-line with PIK3CA mutation vs. second-line with PIK3CA mutation					
MONALEESA-3 (data on file)		1.05 (0.55, 2.02)	0.92 (0.38, 2.27)	1.14 (0.37, 3.45)	0.82
SOLAR-1 (data on file)		0.85 (0.54, 1.32)	0.75 (0.46, 1.22)	1.13 (0.58, 2.19)	0.72
Bone-only metastases vs. not bone-only metastases					
MONALEESA-3 (29)		0.60 (0.33, 1.07)	0.76 (0.58, 1.00)	0.79 (0.41, 1.51)	0.47

Trial		HR with Characteristic (95% CI)	HR without Characteristic (95% CI)	Effect Modification (95% CI)	p-value
Visceral metastases vs. no visceral metastases					
PALOMA-3 (38)		0.85 (0.64, 1.13)	0.69 (0.46, 1.04)	1.23 (0.75, 2.03)	0.41
Lung or liver metastases vs. no lung or liver metastases					
MONALEESA-3 (29)		0.81 (0.58, 1.12)	0.65 (0.45, 0.93)	1.25 (0.76, 2.03)	0.38
SOLAR-1*		0.56 (0.34, 0.95)	1.17 (0.57, 2.37)	0.48 (0.20, 1.15)	0.10
<3 metastatic sites vs. ≥ 3 metastatic sites					
MONALEESA-3 (29)		0.75 (0.54, 1.04)	0.73 (0.50, 1.05)	1.03 (0.63, 1.69)	0.91
ECOG performance status 0 vs. ECOG performance status 1-2					
MONALEESA-3 (29)		0.67 (0.48, 0.92)	0.81 (0.56, 1.19)	0.83 (0.50, 1.36)	0.46

*Based on unpublished clinical study report (Novartis, data on file)

The measure of effect modification on OS was not statistically significant for one or more trials for any other characteristic. Also, for no factors was effect modification consistently favorable or unfavorable. Interestingly, the HR for OS for alpelisib plus fulvestrant vs. placebo plus fulvestrant was less favorable in patients with PIK3CA mutation than among those without PIK3CA mutation based on the unpublished clinical study report (HR=0.73, 95%CI 0.48 to 1.10 vs. HR=0.44, 95%CI 0.18 to 1.07). As of the December 2016 data cut-off of SOLAR-1 – which was the basis of the unpublished clinical study report – OS data for the PIK3CA mutant cohort remained immature with 92 OS events observed out of 178 planned OS events (51.7% information fraction), including 40 in the alpelisib plus fulvestrant arm and 52 in the placebo plus fulvestrant arm. Among the PIK3CA non-mutant cohort of SOLAR-1, only 23 OS events were observed out of 125 planned OS events (18.4%), including 7 in the alpelisib plus fulvestrant arm and 16 for the placebo plus fulvestrant arm. As noted above, PIK3CA mutation was not a statistically significant treatment effect modifier (p=0.22). This finding must therefore be interpreted with caution due to the small numbers of OS events observed.

5.3.7 Proportional Hazards Assumption

Results of the assessment of the proportionality assumption for PFS and OS based on the test of the linearity of the Schoenfeld residuals for each of the trials and relevant subgroups included in the feasibility assessment are summarized in Table 7. The test of the PH assumption for OS was not statistically significant for any trial. A further breakdown of the PH assumption testing can be found in Appendix C.

Taken as a whole, these results suggest that the assumption of PH may be appropriate for OS and PFS. The use of a PH assumption in an ITC of these treatments would not be unreasonable. Further, testing for PHs were not feasible for MONARCH-2 nor PALOMA-3, since IPD is not available.

Table 7. Hazard Ratios for PFS and OS from Trials of HR+/HER2- Advanced Breast Cancer

					Line of Therapy			Menopause Status		PFS		OS	
Trial	Treatment	Comparator	Subgroup Description	PIK3CA Mutant	First-Line	Second-Line	Third-Line +	Pre-	Post	HR	95% CI	HR	95% CI
MONALEESA-3	Ribociclib + Fulvestrant 500 mg	Fulvestrant 500 mg	ITT Population						✓	0.59	0.49, .071	0.72	0.57, .92
MONALEESA-3	Ribociclib + Fulvestrant 500 mg	Fulvestrant 500 mg	PIK3CA+	✓	✓	✓			✓	0.61	0.39, 0.94	0.94	0.56, 1.58
MONARCH-2	Abemaciclib + Fulvestrant 500 mg	Fulvestrant 500 mg	ITT Population		✓	✓	✓	✓	✓	0.54	0.45, 0.65	0.76	0.61, 0.95
MONARCH-2	Abemaciclib + Fulvestrant 500 mg	Fulvestrant 500 mg	PIK3CA+	✓	✓	✓	✓	✓	✓	0.46	0.27, 0.78	NR	NR
PALOMA-3	Palbociclib + Fulvestrant 500 mg	Fulvestrant 500 mg	ITT Population		✓	✓	✓	✓	✓	0.46	0.36, 0.59	0.81	0.64, 1.29
PALOMA-3	Palbociclib + Fulvestrant 500 mg	Fulvestrant 500 mg	PIK3CA+	✓	✓	✓	✓	✓	✓	0.48	0.30, 0.78	0.74	0.48, 1.14
SOLAR-1	Alpelisib + Fulvestrant	Fulvestrant	PIK3CA+	✓	✓	✓			✓	0.65	0.50, 0.85	0.73	0.48, 1.10*

*Data on file, unpublished clinical study report.

5.3.8 Results of ITC of HRs for PFS and OS Using Bucher Method

Trials contributing to the ITCs of PFS, along with HRs and median survival from published papers and analyses of patient-level data, are described in Table 8. The ITCs of OS are described in Table 9. Result of the ITCs of HRs for PFS and OS using the Bucher methods are in the sections that follow.

Table 8. Sources Used in ITCs of HRs for PFS from Trials of Patients with HR+/HER2- aBC

Trial	Treatment	PIK3CA (%)	Median PFS (months)		HR (95%CI)	Source/Notes
			Treatment	Control		
MONALESSA-3	Ribociclib + Fulvestrant 500 mg	100%*	9.2	3.7	0.61 (0.39, 0.94)	Cox PH regression of MONALEESA-3 IPD. Patients were those with PIK3CA mutant disease and either relapsed ≤12 months after completion of (neo)adjuvant ET with no prior therapy for metastatic disease or had one prior line of therapy in the metastatic setting (data on file).
MONARCH-2	Abemaciclib + Fulvestrant 500 mg	NR	15.0	5.7	0.46 (0.27, 0.78)	Trial included patients receiving both first- and second-line treatment for aBC, as well pre- and postmenopausal women. At least 40% of patients were receiving second-line treatment for aBC. Approximately 80% of patients were postmenopausal. NOTE: HR and median PFS values are for the PIK3CA mutant subgroup (14) .
PALOMA-3	Palbociclib + Fulvestrant 500 mg	100%*	9.5	3.6	0.48 (0.30, 0.78)	Trial included patients receiving first-, second-, and third-line or subsequent treatment for aBC, as well pre- and postmenopausal women. Approximately 45% of patients were receiving second-line treatment for aBC; corresponding values for first-line and greater than second-line were ~25% and ~30%, respectively. Approximately 80% of patients were postmenopausal. Approximately 25% were PIK3CA mutant in the ITT population. NOTE: Both the HR and median PFS values reported here are specific to the PIK3CA mutant subgroup (25).
SOLAR-1	Alpelisib + Fulvestrant	100%*	9.2	3.8	0.60 (0.47, 0.78)	Cox PH regression of SOLAR-1 IPD. Patients were those with PIK3CA mutant disease and either relapsed ≤12 months after completion of (neo)adjuvant ET with no prior therapy for metastatic disease or had one prior line of therapy in the metastatic setting (5) .

Table 9. Sources Used in ITCs of HRs for OS from Trials of Patients with HR+/HER2- aBC

Trial	Treatment	PIK3CA (%)	Median OS (months)		HR (95%CI)	Source/Notes
			Treatment	Control		
MONALESSA-3	Ribociclib + Fulvestrant 500 mg	100%*	32.4	32.5	0.94 (0.56, 1.58)	Cox PH regression of MONALEESA-3 IPD. Patients were those with PIK3CA mutant disease and either relapsed ≤12 months after completion of (neo)adjuvant ET with no prior therapy for metastatic disease or had one prior line of therapy in the metastatic setting (data on file).
MONARCH-2	Abemaciclib + Fulvestrant 500 mg	NA	46.7	37.3	0.77 (0.61, 0.98)	Trial included patients receiving both first- and second-line treatment for aBC, as well pre- and postmenopausal women. At least 40% of patients were receiving second-line treatment for aBC. Approximately 80% of patients were postmenopausal. NOTE: HR based on the postmenopausal subgroup, PIK3CA mutation subgroup data not reported; median OS values are for the total population as these were not reported by menopause status (23).
PALOMA-3	Palbociclib + Fulvestrant 500 mg	100%*	28.6	22.2	0.74 (0.48, 1.14)	Trial included patients receiving first-, second-, and third-line or subsequent treatment for aBC, as well pre- and postmenopausal women. Approximately 45% of patients were receiving second-line treatment for aBC; corresponding values for first-line and greater than second-line were ~25% and ~30%, respectively. Approximately 80% of patients were postmenopausal. Approximately 25% were PIK3CA mutant in the ITT population. NOTE: Both the HR and median OS values reported here are specific to the PIK3CA mutant subgroup(26).
SOLAR-1	Alpelisib + Fulvestrant	100%*	34.9	30.5	0.87 (0.64, 1.17)	Cox PH regression of SOLAR-1 IPD. Patients were those with PIK3CA mutant disease and either relapsed ≤12 months after completion of (neo)adjuvant ET with no prior therapy for metastatic disease or had one prior line of therapy in the metastatic setting (data on file).

The ITCs of PFS and OS for treatments of ET-resistant patients are limited by a lack of RCTs that reported results for subgroups of patients with PIK3CA mutant disease who were receiving first- and second-line therapy. HRs for PFS and OS from PALOMA-3 were based on subgroups of patients with PIK3CA mutation, but these subgroups also include postmenopausal patients and those with more than one prior line of therapy for advanced disease. The HR for PFS in a subgroup of patients with PIK3CA mutation was available from MONARCH-2, but the HR for OS in this subgroup was not available from publications that were identified in the SLR. Differences in patient populations with respect to numbers of prior therapies received, PIK3CA mutation status, menopausal status, and HER2 status may have introduced bias to ITCs to the extent that these characteristics may have modified the treatment effects of therapies for which data were not available.

Results of the ITC on PFS of RCTs of treatments for ET-resistant patients with PIK3CA mutated, HR+/HER2- aBC based on the Bucher method are shown in Table 10. Based on the ITC of PFS, abemaciclib plus fulvestrant is the most effective treatment and fulvestrant is the least effective treatment.

Table 10. Results for HRs for PFS from the ITC Using Bucher Method

Comparator	HR (95%CI) of Comparator vs.		HR (95% CI) of Alpelisib plus Fulvestrant vs.
	Fulvestrant	Alpelisib plus Fulvestrant	
Abemaciclib + Fulvestrant 500 mg	0.46 (0.27, 0.78)	0.77 (0.42, 1.38)	1.31 (0.73, 2.35)
Palbociclib + Fulvestrant 500 mg	0.48 (0.30, 0.77)	0.80 (0.46, 1.37)	1.25 (0.73, 2.15)
Alpelisib + Fulvestrant 500 mg	0.60 (0.47, 0.78)		
Ribociclib + Fulvestrant 500 mg	0.61 (0.39, 0.94)	1.01 (0.61, 1.68)	0.99 (0.59, 1.63)
Fulvestrant 500 mg	1.00 (n/a, n/a)	1.66 (1.29, 2.15)	0.60 (0.47, 0.78)

Results of the ITC on OS of RCTs of treatments for ET-resistant patients with PIK3CA mutated, HR+/HER2- aBC based on the Bucher method are shown in Table 11. Based on the ITC of OS, palbociclib plus fulvestrant is the most effective treatment while fulvestrant is the least effective treatment.

Table 11. Results for HRs for OS from the ITC Using Bucher Method

Comparator	HR (95%CI) of Comparator vs.		HR (95% CI) of Alpelisib plus Fulvestrant vs.
	Fulvestrant	Alpelisib plus Fulvestrant	
Palbociclib + Fulvestrant 500 mg	0.74 (0.48, 1.14)	0.85 (0.50, 1.45)	1.17 (0.69, 1.99)
Abemaciclib + Fulvestrant 500 mg	0.77 (0.61, 0.98)	0.89 (0.61, 1.31)	1.12 (0.76, 1.65)
Alpelisib + Fulvestrant 500 mg	0.87 (0.64, 1.17)		
Ribociclib + Fulvestrant 500 mg	0.94 (0.56, 1.59)	1.09 (0.59, 1.98)	0.92 (0.51, 1.68)
Fulvestrant 500 mg	1.00 (n/a, n/a)	1.15 (0.85, 1.56)	0.87 (0.64, 1.17)

As can be seen from the results, the data would suggest, that there could be a difference of effect between the studies. Palbociclib has the best outcomes for OS, whereas abemaciclib has the best PFS outcomes. These data should, however, be interpreted cautiously. Firstly, one would assume correlation between PFS and OS, since the assumption of proportional of hazards holds. However, it is eminent from the data, that this is not reproduced in the ITC, which suggests a comparison might not be representative. Further, the comparison to abemaciclib and palbociclib is not

based on individual patient level data, which is another ground for caution, when interpreting the results. Lastly, the discrepancy in study populations between the trials further complicate the comparison.
As an addendum to the original analysis, the 9 and 11 patients from SOLAR-1 who previously received CDK4/6 was removed and the comparison was performed again. Since there were not any data on these patients in PALOMA-3 and MONARCH-2, this analysis could not be performed. The estimated HRs for PFS from the ITC for each population of interest are provided below.

Table 12. Results for HRs for PFS from the ITC Using Bucher Method

Comparator	HR (95%CI) of Comparator vs.		HR (95% CI) of Alpelisib plus Fulvestrant vs.
	Fulvestrant	Alpelisib plus Fulvestrant	
Alpelisib + Fulvestrant 500 mg	0.61 (0.47, 0.80)	1.00 (n/a, n/a)	1.00 (n/a, n/a)
Ribociclib + Fulvestrant 500 mg	0.61 (0.39, 0.94)	0.99 (0.60, 1.65)	1.01 (0.60, 1.68)
Fulvestrant 500 mg	1.00 (n/a, n/a)	1.63 (1.25, 2.12)	0.61 (0.47, 0.80)

HRs for OS for each comparator vs. fulvestrant and alpelisib plus fulvestrant are provided below.
Excluding endocrine resistant patients did not change the overall results of the ITC.

Table 13. Results for HRs for OS from the ITC Using Bucher Method

Comparator	HR (95%CI) of Comparator vs.		HR (95% CI) of Alpelisib plus Fulvestrant vs.
	Fulvestrant	Alpelisib plus Fulvestrant	
Alpelisib + Fulvestrant 500 mg	0.90 (0.65, 1.23)	1.00 (n/a, n/a)	1.00 (n/a, n/a)
Ribociclib + Fulvestrant 500 mg	0.94 (0.56, 1.58)	1.05 (0.57, 1.93)	0.95 (0.52, 1.75)
Fulvestrant 500 mg	1.00 (n/a, n/a)	1.11 (0.81, 1.53)	0.90 (0.65, 1.23)

5.3.9 Summary of the indirect treatment comparison

The objective of this analysis was to conduct an ITC of PFS and OS of alpelisib plus fulvestrant and other treatments for postmenopausal women with HR+/HER2- aBC with PIK3CA mutation, who have received prior treatment with an AI and not received more than one prior ET for advanced disease. The analysis was conducted in two parts. First, an assessment of the feasibility of conducting the ITC was done in which the characteristics of the trials that might contribute to the ITC were compared with respect to patient baseline characteristics that might bias the comparisons. Second, the ITCs of PFS and OS were conducted using information on PFS and OS from the trials in the evidence network.

The ITC was conducted first using HRs for PFS and OS using the Bucher method. Results of the feasibility assessment suggest that the ITC based only on published data from the RCTs included in this feasibility assessment would be limited by a lack of Kaplan-Meier PFS for subgroups of patients with PIK3CA-mutated cancer from MONARCH-2; Kaplan-Meier OS for subgroups with PIK3CA-mutated cancer were also not available for PALOMA-3 or MONARCH-2. A published HR for OS in patients with PIK3CA-mutated cancer from the MONARCH-2 trial was not identified by the SLR. Additionally, MONARCH-2 and PALOMA-3 included both pre-and postmenopausal patients and outcomes were not reported for the PIK3CA mutant subgroup by menopause status. PALOMA-3 enrolled patients with greater than one prior line of ET for advanced disease. In MONALEESA-3, patients could have relapsed > 12 months after completion of (neo)adjuvant ET with no ET for advanced disease. As noted above, information on the HR for OS for abemaciclib plus fulvestrant vs. fulvestrant in patients with PIK3CA mutation was not included in the ITC because such information was not identified in this SLR. However, such information from the MONARCH-2 trial has since been presented at the American Association of Cancer Research 2020 conference (40). Inclusion of information that was identified using a non-systematic approach would introduce potential for selection bias. As such, we did not include the HR for OS in the PIK3CA mutant subgroup from MONARCH-2 in this analysis. This could bias the results of the ITC to the extent to which PIK3CA mutation could modify the treatment effect on OS for abemaciclib plus fulvestrant. The inclusion of pre-menopausal patients in PALOMA-3 and MONARCH-2, inclusions of patients with multiple prior lines of treatment for advanced disease in PALOMA-3, and lack of data for OS in patients with PIK3CA-mutated cancer in MONARCH-2 are still present.
PIK3CA mutation status was not found to be a statistically significant treatment effect modifier, but differences in the treatment effect expressed as a HR for patients with vs. without this mutation may still be clinically meaningful. In SOLAR-1 and MONARCH-2, the treatment effect on PFS expressed as a HR was more favorable in patients with PIK3CA mutated cancer vs. patients without PIK3CA mutated cancer. This contrasts with the PALOMA-3 and MONALEESA-3 trials, in which PIK3CA mutation was associated with less favorable treatment effects on PFS.

As alluded to, conclusion on effect size should be made with great caution, due to the wide CIs. However, the results showed abemaciclib had the highest effect size for PFS, followed by palbociclib, alpelisib, ribociclib and lastly fulvestrant. The HRs of alpelisib versus the various comparators were: HR: 1.31 (95% CI 0.73, 2.35) for abemaciclib, HR: 1.25 (95% CI 0.73, 2.15) for palbociclib, HR: 0.99 (95% 0.59, 1.63) for ribociclib and HR: 0.60 (95% CI 0.47, 0.78) for fulvestrant alone, with only the latter being significant. For OS, the results ranked palbociclib, following, abemaciclib, alpelisib, ribociclib and lastly mono-therapy fulvestrant. For alpelisib versus the various comparators, the results were: HR: 1.17 (95% 0.69, 1.99) for palbociclib, HR: 1.12 (95% 0.76, 1.65), HR: 0.92 (95% CI 0.51, 1.68) for ribociclib and HR: 0.87 (95% CI 0.64, 1.17) for fulvestrant with no significant differences, when compared to all four treatments. When using patient level data, the HRs for PFS were 1.01 (95% CI 0.60, 1.68) for ribociclib and HR: 0.61 (95% CI 0.47, 0.80) for fulvestrant mono-therapy. For OS, the analysis showed a HR of 0.95 (95% CI 0.52, 1.75) for ribociclib and HR: 0.90 (95% CI 0.65, 1.23) for mono-therapy with fulvestrant.

In summary, results of this analysis suggest that access to IPD from Novartis-sponsored trials are necessary to construct linked evidence networks for both PFS and OS in patients with PIK3CA mutated, HR+/HER2-aBC for each of the comparators of interest. However, such an analysis is subject to a number of limitations due to differences in patient populations across RCTs. Specifically, data for subgroups of patients with PIK3CA mutation in PALOMA-3 and MONARCH-2. While this analysis did not show statistically significant effect modification from these factors, not all trials included in the feasibility assessment reported HRs for subgroups of patients with vs. without each of the

aforementioned characteristics. The potential limitations above notwithstanding, ITCs of HRs for PFS and OS were conducted using the Bucher method and the best available data for conducting the ITCs. For PFS, abemaciclib plus fulvestrant was numerically most effective. Palbociclib plus fulvestrant was found to be numerically more effective with respect to OS.

This analysis provides estimates of relative efficacy of alpelisib plus fulvestrant versus other CDK4/6 and fulvestrant for postmenopausal women with PIK3CA-mutated, HR+/HER2-aBC who have received prior treatment with an AI and have not received more than one prior ET for advanced disease that may be used in economic evaluations of these treatments. However, given the multiple potentially serious limitations in the ITCs due to differences in the patient populations of the trials contributing to the evidence network, results of these ITCs are potentially biased and careful consideration should be given to how they should be used in the context of any such evaluations. When conducting economic evaluations based on these assumptions, consideration should be given if a class effect concerning efficacy is to be assumed across all CDK 4/6 inhibitors using the same ET backbone in similar populations. Even though the results across studies (e.g. MONALEESA-2, PALOMA-3 and MONARCH-3) are similar, there is no direct head-to-head data concerning efficacy available.

Adverse events and HRQoL was not included in the ITC and as such any comparison should be made with caution. However, and attempt has been made to set the findings of SOLAR-1 and MONARCH-2 side by side in order to answer the remaining parts of clinical question 1.

5.3.10 Adverse Events

An overview of adverse events experienced by patients receiving CDK4/6 or alpelisib in combination with fulvestrant or fulvestrant alone is provided under the section addressing clinical question two in Table 18 and Table 19.

5.3.11 HRQoL

Comparing the PRO between MONARCH-2 and SOLAR-1 and thereby abemaciclib and alpelisib, there was no clinically meaningful overall change from baseline in EORTC QLQ-C30 global health status/QoL score in patients treated with either alpelisib or abemaciclib plus fulvestrant or placebo plus fulvestrant in the two trials respectively. However, in SOLAR-1, some EORTC QLQ-C30 symptom scores, such as diarrhoea and nausea/vomiting, were worsened in patients treated with alpelisib plus fulvestrant (21). In MONARCH-2, four scores statistically favoured the control arm over time: appetite loss (between treatment group difference ± SE, 5.31 ± 1.43; $p < .001$),nausea and/or vomiting (3.42 ± 0.88; $p < .001$), diarrhoea(24.64 ± 1.56; $p < .001$), and systemic therapy side effects (5.21 ± 0.87; $p < .001$) (24). Comparing these two without adjustments provides little clinical meaning. It would appear they both incurred a worsening of some symptoms, when compared to fulvestrant mono-therapy, and comparing them naively, they appear to have a similar impact on HRQoL. However, any attempt at quantifying whether there is a meaningful difference between the two would be futile.

6 Clinical question 2

What value does alpelisib have in combination with fulvestrant compared to fulvestrant alone in patients with locally advanced or metastatic ER + / HER2- breast cancer and mutation in the PIK3CA gene?

Population of relevance:
Patients with locally advanced or metastatic ER + / HER2- breast cancer and mutation in the PIK3CA gene who relapse upon treatment with a CDK4 / 6 inhibitor in combination with AI. Intervention: Alpelisib (300 mg as a tablet, dosed once a day) in combination with fulvestrant (500 mg as an intramuscular injection on days 1, 15 and 29 of the first cycle and then once a month). Comparator: Fulvestrant (500 mg as intramuscular injection on days 1, 15 and 29 of the first cycle and then once a month).

Results per study
We did not identify any studies on efficacy of fulvestrant monotherapy in PIK3CA mutated patients in the post-CDK4/6 setting, which could be used to verify the results in SOLAR-1 and BYLieve. As a consequence, only the post CDK4/6 population in SOLAR-1 and BYLieve is described in this section.

SOLAR-1 POST-CDK4/6 population: Among the 20 patients with prior CDK4/6 inhibitor treatment included in SOLAR-1, the HR was 0.48 (95% CI: 0.17-1.36); median PFS was prolonged by 3.7 months in favor of alpelisib treated patients - from 1.8 months (95% CI: 1.7- 3.6) in the comparator arm to 5.5 months (95% CI: 1.6, 16.8) in the alpelisib plus fulvestrant arm (36). The relative PFS treatment effect for patients with prior CDK4/6 inhibitor treatment is consistent with updated results for the overall study population using a data cut-off date of 30 Sep 2019 (HR=0.64; 95% CI: 0.50-0.81) where median PFS was prolonged by 5.3 months, from 5.7 months (95% CI: 3.7-7.4) in the placebo plus fulvestrant arm to 11.0 months (95% CI: 7.5-14.5) in the alpelisib plus fulvestrant arm. (1, 2, 36).

6.1 BYLieve

BYLieve introduction: As stated in the protocol, there is limited data available in the post-CDK 4/6 inhibitor setting. It is also stated in the protocol, that the applicant must therefore investigate whether there are other studies that contain/describe the stated deficiencies. BYLieve aimed to assess alpelisib plus endocrine therapy in this setting in three cohorts defined by immediate previous treatment (see study design Figure 15); here, we report results from cohort A. BYLieve is the first, prospective clinical study to examine the use of alpelisib plus fulvestrant for hormone receptor-positive, HER2-negative, PIK3CA-mutated advanced breast cancer solely in the post-CDK4/6 inhibitor setting. Thus, although BYLieve was excluded in the literature review, as this is a non-randomized study, BYLieve is the only study that has investigated the efficacy of alpelisib in post CDK4/6 patients with PIK3CA mutation. Hence, we included the study and the BYLieve study design is listed below. (12)

BYLieve (CBYL719X2402; NCT03056755) is a phase II, open-label, three cohort, non-comparative trial (NCT03056755), with the primary goal to assess the efficacy and safety of alpelisib + ET (fulvestrant or letrozole) in patients with PIK3CA-mutated HR+/HER2– aBC in the post-CDK4/6 setting. The trial enrolled patients in 19 countries (including Denmark in Cohort B + C) at 198 trial sites. (41)

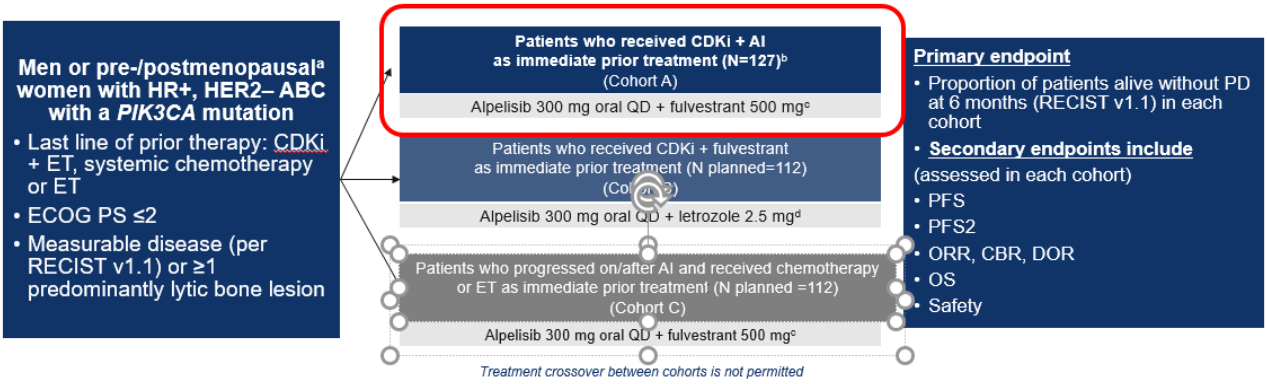


Figure 15: BYLieve study design. [a]Men in the letrozole cohort and premenopausal women also received goserelin 3.6 mg SC every 28 days or leuprolide 7.5 mg IM every 28 days for adequate gonadal suppression. [b]Enrollment in each cohort continued until at least 112 patients with a centrally confirmed PIK3CA mutation was reached. [c]IM on D1 and D15 of Cycle 1 and D1 for all other cycles thereafter. [d]Oral QD. aBC, advanced breast cancer; AI, aromatase inhibitor; CDKi, cyclin-dependent kinase inhibitor; ECOG PS, Eastern Cooperative Oncology Group performance status; ET, endocrine therapy; CBR, clinical benefit rate; D, day; DOR, duration of response; IM, intramuscularly; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PFS2, PFS on next-line treatment; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; RECIST, Response Evaluation Criteria In Solid tumors; SC, subcutaneously; QD, once daily. (12).

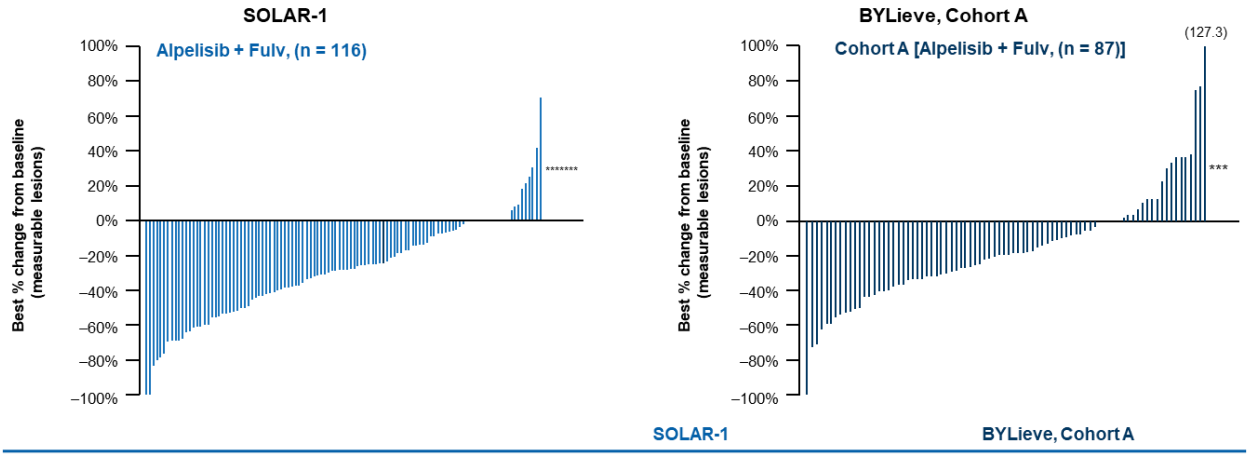
Progression free survival – cohort A: The primary endpoint for the prior CDK inhibitor + AI cohort (cohort A) was met (lower bound of 95% CI was > 30%) at the data cut-off (17-Dec-2019). A that timepoint, 50.4% of cohort A patients were still progression-free (n=61; 95% CI, 41.2-59.6) as presented at the ASCO 2020 virtual meeting (Rugo et al. 2020b). This is to be compared with 44.4% of patients in the PIK3CA-mutant cohort with prior CDK inhibitor treated patients in SOLAR-1 being alive without disease progression at 6 months following treatment with alpelisib plus fulvestrant. Median PFS (key secondary endpoint) in BYLieve cohort A was 7.3 months, [n=72 (59.5%) with event]; 95% CI, 5.6-8.3). (12).

PFS Effect of Alpelisib Over Standard Treatments in Real-World Setting (42): A post-hoc analysis compared progression-free survival from BYLieve cohort A were compared with real-world PFS of a similar group of patients (N=95) with HR+/HER2–, PIK3CA-mutated aBC in the US after CDKi-based therapy from the de-identified US Flatiron Health-Foundation Medicine (FMI) clinicogenomics (CGDB) database. Differences in prognostic factors for PFS between cohorts were mitigated by 3 different matching/weighting techniques that accounted for baseline covariates (Here, patients who met relevant inclusion criteria consistent with those of the BYLieve cohort A were included (i.e. PIK3CA mutation, ≤2 previous treatment lines for advanced breast cancer, and no more than one previous line of chemotherapy for advanced breast cancer; previous exposure to CDK4/6 inhibitor; and no fulvestrant exposure). Expanded methods can be found in the appendix (pp 1–2). Statistical analyses were done using SAS (version 9.4) (14). Evaluation and Comparison of PFS Alpelisib combined with fulvestrant demonstrated higher PFS treatment effect compared with Standard of Care. The unadjusted median PFS was 7.3 months (95% CI, 5.6– 8.3 months) in patients in the BYLieve cohort compared Alpelisib Versus Real-World Standard Treatment with a median real world PFS of 3.6 months (95% CI, 3.1– 6.1 months) among those in the real-world group (p = .005), which is comparable to the control-arm in SOLAR-1. (5).

Overall Survival data: Not reported yet.

Other clinical response – cohort A: Additional clinical efficacy parameters such as ORR, duration of response (DOR) and tumor size reductions were also assessed in BYLieve and demonstrated comparable reductions in tumor size as

observed in SOLAR-1 (Figure 16). In cohort A patients with measurable disease, the ORR was 21% and the DOR was 6.6 months (95%CI: 4.3; NE), whereas in the PIK3CA mutant cohort within the SOLAR-1 study in patients with measurable disease, the ORR in the treatment arm with the combination of alpelisib plus fulvestrant regardless of the prior treatment (n=169) was 35.7% (95%CI: 27.4, 44.7) and the DOR 12.6 months (95%CI: 8.5; 18.5).



	SOLAR-1	BYLieve, Cohort A
Decrease in best % change from baseline	75.9%	70.1%
Increase/zero change in best % change from baseline	18.1%	26.4%

Figure 16. BYLieve (cohort A) best change in tumor size, compared to SOLAR-1. Best percentage change in sum of diameters per investigator assessment, for patients with measurable disease at baseline SOLAR-1 data cut-off date: 12-Jun-2018; BYLieve data cut-off date: 17-Dec-2019. (18).

Median duration of exposure: 127 patients received at least one dose of study drug and were included in the safety set. Median duration of exposure in the safety set to either alpelisib or fulvestrant was 7·4 months (IQR 2·8–9·2), to alpelisib was 5·1 months (1·8–8·6), and to fulvestrant was 6·5 months (2·3–9·0). Median average daily dose of alpelisib was 299·1 mg (IQR 262·1–300·0; appendix p 9). Median duration of exposure to study treatment based on number of lines (0–3) of previous therapy in the metastatic setting for all patients (n=127), regardless of type of therapy, ranged from 7·1 months to 8·3 months. (14)

Safety – cohort A: In general, the overall incidence of adverse events for BYLieve was similar to that observed in SOLAR-1. Overall AE-related discontinuations were 20.5% in BYLieve (compared with 25% in SOLAR-1). There were fewer discontinuations due to hyperglycaemia in BYLieve compared to SOLAR-1 (1.6% and 6.3%) (18). See table overview section, Table 19.

The safety profile observed in BYLieve suggests that adverse event management strategies are effective, and that implementation of management strategies and education are critical for improving therapeutic efficacy. Adverse events were consistent with the reported safety profile of alpelisib. (5, 17). Overall, fewer treatment discontinuations due to adverse events were observed in BYLieve (21%) than in SOLAR-1 (25%). A notably lower number of treatment discontinuations due to hyperglycaemia were reported in BYLieve (2%) compared with SOLAR-1 (6%), along with a smaller number of any-grade hyperglycaemia events (BYLieve 58%, SOLAR-1 64%). These data suggest that hyperglycaemia was monitored and managed more effectively in BYLieve. Similar to SOLAR-1 (18), fewer rash events were observed in patients who received prophylactic antihistamines than patients who did not; small patient numbers limit further interpretation (1, 12).

Section with data overview tables

Table 14. PFS data overview.

	SOLAR-1 (5) PIK3CA mutation cohort		MONARCH-2 (14) ITT population		MONALEESA-3 (8) ITT population		PALOMA-3 (25) ITT population	
Median duration of follow-up, months	20.0		19.54		39.4		44.8	
Treatment	**Alpelisib + Fulvestrant**	**Fulvestrant + Placebo**	**Abemaciclib + Fulvestrant**	**Fulvestrant + Placebo**	**Ribociclib + Fulvestrant**	**Fulvestrant + Placebo**	**Palbociclib + Fulvestrant**	**Fulvestrant + Placebo**
Median PFS, months	11	5.7	16.4	9.3	20.5	12.8	9.5	4.6
HR (95% CI)	0.65; 95% CI: 0.50-0.85		0.55 (0.45-0.68)		0.59 (0.48-0.73)		0.46 (0.36-0.59)	
P value	p<0.001		<0.001		<0.001		<0.0001	

No cross comparison of trials is permissible as there have been no head-to-head studies conducted.

Table 15. OS data overview.

	SOLAR-1 (11) PIK3CA mutation cohort		MONARCH-2 (23) ITT population		MONALEESA-3 (29) ITT population, in table A3a data from updated analysis is presented		PALOMA-3 (26) ITT population	
Treatment	**Alpelisib + Fulvestrant**	**Fulvestrant + Placebo**	**Abemaciclib + Fulvestrant**	**Fulvestrant + Placebo**	**Ribociclib + Fulvestrant**	**Fulvestrant + Placebo**	**Palbociclib + Fulvestrant**	**Fulvestrant + Placebo**
Median OS, months	39.3	31.4	46.7	37.3	NR	40	34.9	28.0
HR (95% CI)	0.86; 95% CI: 0.64, 1.15		0.76 (0.61-0.95)		0.72 (0.57-0.92)		0.81 (0.64-1.03)	
P value	0.15		0.01		0.00455		0.09	

No cross comparison of trials is permissible as there have been no head-to-head studies conducted.

Table 16: PFS and OS in patients with visceral metastases overview

	SOLAR-1 (1, 11)		MONARCH-2 (23)		MONALEESA-3 (29, 30)		PALOMA-3 (25, 26)	
Treatment	**Alpelisib + Fulvestrant**	**Fulvestrant + Placebo**	**Abemaciclib + Fulvestrant**	**Fulvestrant + Placebo**	**Ribociclib + Placebo**	**Fulvestrant + Placebo**	**Palbociclib + Fulvestrant**	**Fulvestrant + Placebo**
Median PFS, months	9.0	3.7	14.7	6.5	16.6	10.6	9.2	3.4
HR (95% CI)	0.66; 95% CI: 0.49-0.88		0.471 (0.371-0.598)		0.616 (0.487-0.779)		0.47 (0.35-0.61)	
Median OS, months	37.2	22.8	40.3	32.2	46.9	39.4	27.6	24.7
HR (95% CI)	0.68; 95% CI: 0.46, 1.00		0.675 (0.511-0.891)		0.73 (0.55-0.98)		0.85 (0.64-1.13)	

No cross comparison of trials is permissible as there have been no head-to-head studies conducted.

Table 17: PFS differences between PIK3CA mutant and wild-type populations within each treatment arm

Study	Treatment	Median PFS (95% CI)	
		PIK3CA mutant	PIK3CA WT
SOLAR-1 (5)	Alpelisib + Fulvestrant	11.0 (7.5-14.5)	7.4 (5.4-9.3)
	Fulvestrant	5.7 (3.7-7.4)	5.6 (3.9-9.1)
MONARCH-2 (7)	Abemaciclib + Fulvestrant	15 (9.4-NA)	20 (14-NA)
	Fulvestrant	5.7 (3.8-15)	12.7 (7.9-NA)
PALOMA-3 (25)	Palbociclib + Fulvestrant	9.5 (5.7-11.2)	9.9 (9.2-13.9)
	Fulvestrant	3.6 (1.9-5.6)	4.6 (3.4-7.3)
MONALEESA-3 (31)	Ribociclib + Fulvestrant	16.36 (11.01-19.09)	22.34 (18.79-NA)
	Fulvestrant	11.1 (5.32-14.69)	16.69 (10.87-19.38)
BYLieve (12)	Alpelisib + Fulvestrant	7.3 (5.6-8.3)	NA

Exploratory analyses for all studies with the exception of SOLAR-1 and BYLieve cohort A. No cross comparison of trials is permissible as there have been no head-to-head studies conducted.

Table 18. Common AEs associated with CDK4/6 inhibitors in combination with Fulvestrant

	PALOMA-3 (25) N=345		MONALEESA-3 (8) N=483		MONARCH-2 (14) N=441	
Median duration of follow-up, months	8.9		15.8		19.5	
AE, %	**Any grade**	**Grade 3/4**	**Any grade**	**Grade 3/4**	**Any grade**	**Grade 3/4**
Neutropenia	80.8	64.6	69.6	53.4	46.0	26.5
Nausea	32.5	0.0	45.3	1.4	45.1	2.7
Fatigue	39.1	2.3	31.5	1.7	39.9	2.7
Diarrhea	21.4	0.0	29.0	0.6	86.4	13.4
Alopecia	16.8	0.0	18.6	0.0	15.6	0.0
Vomiting	16.8	0.3	26.7	1.4	25.9	0.9
Arthralgia	14.2	0.3	24.0	0.6	11.6	0.2
Leukopenia	49.6	27.5	28.4	14.1	28.3	8.8
Hot flush	15.4	0.0	13.3	0.0	10.4	0.0
Abdominal pain	7.8	0.6	-	-	35.4	2.5
Infections[a]	41.7	2.0	-	-	42.6	6.6
Discontinuation rates	Palbociclib + fulvestran	Placebo + fulvestrant	Ribociclib + fulvestrant	Placebo + fuvestrant	Abemaciclib + fulvestrant	Placebo + fulvestrant
N (%)	14 (4%)	3 (2%)	41 (8.5%)	10 (4.1%)	70 (15.9%)	7 (3%)

Table 19. Safety comparison SOLAR-1 and BYLieve cohort A: Most frequently reported adverse events in SOLAR-1 Safety population compared to BYLieve (11, 12)

	SOLAR-1 Alpelisib + fulvestrant N= 284		SOLAR-1 Placebo + fulvestrant N= 287		BYLieve Alpelisib + fulvestrant n=127	
			15.8		19.5	
AE, %	**Any grade**	**Grade 3/4**	**Any grade**	**Grade 3/4**	**Any grade**	**Grade 3/4**
Hyperglycaemia	282 (99.3)	216 (76)	264 (92.0)	102 (35.5)	76 (70%)	36 (29%)
Diarrhoea	181 (63.7)	104 (36.6)	28 (9.8)	1 (0.6)	74 (59%)	7 (6%)
Nausea	164 (57.7)	19 (6.7)	45 (15.7)	1 (0.3)	58 (46%)	0 (0%)
Decreased appetite	127 (44.7)	7 (2.5)	64 (22.3)	1 (0.3)	36 (29%)	1 (1%)
Rash	101 (35.6)	2 (0.7)	30 (10.5)	1 (0.3)	36 (29%)	12 (19%)
Vomiting	101 (35.6)	28 (9.9)	17 (5.9)	1 (0.3)	30 (27%)	2 (2%)
Weight decrease	77 (27.1)	2 (0.7)	28 (9.8)	1 (0.3)	16 (13%)	2 (2%)
Fatigue	76 (26.8)	11 (3.9)	6 (2.1)	0	37 (29%)	1 (1%)
Stomatitis	70 (24.6)	7 (2.5)	18 (6.3)	0	37 (27%)	2 (2%)
Asthenia	69 (24.3)	10 (3.5)	49 (17.1)	3 (1.0)	0 (0%)	0 (0%)
Alopecia	58 (20.4)	5 (1.8)	37 (12.9)	0	16 (13%)	0 (0%)
Discontinuation rates*	**Alpelisib + fulvestrant N= 284**		**Placebo + fulvestrant** N= 287		**Alpelisib + fulvestrant** n=127	
N (%)	71 (25%)		12 (4.2%)		26 (21%)	

AEs occurrence in each trial were reported naively. Doses and terms for AEs may vary between trials. No cross comparison of trials is permissible as there have been no head-to-head studies conducted. Infection is defined as any event having a preferred term of the system organ class infections and infestations.

6.2 Summary of clinical efficacy and safety of alpelisib in current indication

HR+/HER2- PIK3CA-mutated aBC represents a high unmet need, due to higher degree of endocrine resistance and overall shorter PFS/worse prognosis. Consequently, statistically significant improved PFS confers the greatest immediate benefit for these patients. To address this, SOLAR-1 was designed (and powered) to primarily assess the added clinical benefit of alpelisib in this patient population through evaluating PFS. (3).

SOLAR-1 demonstrated a statistically significant and clinically meaningful improvement in PFS in favor of alpelisib plus fulvestrant (HR=0.65, 95% CI: 0.50-0.85), regardless of treatment line; with a HR of 0.48 (95% CI: 0.17-1.36) in the subgroup of patients with prior CDK4/6 inhibitor use. The latter was further supported by BYLieve cohort A data, suggesting similar clinical benefit in post-CDK treated patients. In addition to PFS, OS was a key secondary endpoint in SOLAR-1. The final OS analysis demonstrated a clinically important (although not statistically significant) survival benefit in the PIK3CA-mutated, alpelisib-treated patient cohort – in particular in those patients with visceral involvement. In these patients who in general are more challenging to treat, the incremental survival was over 14 months (37.2 vs 22.8 months (HR 0.68; 95% CI: 0.46, 1.00)). Consistent with observations in SOLAR-1, BYLieve shows that alpelisib plus fulvestrant is a valid treatment option with manageable tolerability for patients with HR+/HER2-, PIK3CA mutated aBC in the post-CDK4/6 inhibitor plus AI setting. The primary endpoint for the prior CDK 4/6 inhibitor + AI treated patient cohort (cohort A) was met (lower bound of 95% CI was > 30%), with 50.4% of patients alive without disease progression at 6 months. (5, 11, 12).

In conjunction with the comparison of effect presented in section 5.3 and the review of the clinical evidence available for the treatments in the first line setting of treatment for HR+/HER2- PIK3CA mutated aBC, a simple economic comparison of expected treatment costs has been chosen. The same has been chosen in the post CDK4/6 setting, to simplify the approach and provide a more uniform and comparable setting for both lines of treatment.

7 Other considerations

7.1 PIK3CA testing

Danish clinical practice does not routinely examine patients for PIK3CA mutation. However, the PIK3CA mutation can be detected by using either real-time polymerase chain reaction (RT-PCR) or next generation sequencing (NGS) which are both laboratory techniques implemented at the hospitals in Denmark. In connection with Novartis' sponsored collaboration, 7 Danish pathology departments have implemented PIK3CA NGS mutation analysis on tumor tissue. The local NGS platform of the departments was used, and the results showed that the platforms in question were able to identify the expected mutations. The results from 'PIK3CA testing in breast cancer – a national quality implementation study', were presented as electronic records at Dansk Patologiselskabs Årsmøde 2020 (see poster attached in email to Medicines Council). In connection with the expected approval of alpelisib for metastatic ER+/HER2- breast cancer, the Danish pathology departments have updated the national pathology guideline to include PIK3CA analysis which has just been published on https://www.dmcg.dk/Kliniske-retningslinjer/kliniske-retningslinjer-opdelt-paa-dmcg/brystcancer/patologiprocedurer-og-molekylarpatologiske-analyser-ved-brystkraft/ See the section "Characterization of the invasive tumor component". The implementation of the PIK3CA test is therefore possible to introduce nationally at short notice.

Validated tests using either NGS or RT-PCR methodology can be used to identify patients harboring PIK3CA mutation, in line with recommendations from EMA (SmPC, section 4.2). According to the Danish pathology group the price for the NGS-test is approx. DKK 4 014 per patient and the DRG cost for one RT-PCR test is DKK 3 444 per patient. The method used to detect the PIK3CA mutation in the clinical study SOLAR-1 was the Qiagen Therascreen PIK3CA RGQ PCR kit (supplementary appendix to (5)) and we evaluate it to be consistent in functionality with any validated PCR test selected by the hospital. Therefore, we have calculated the total cost of testing using a PCR test (see additional information in the attached technical document section 2.8), with the estimate that 2-3 patients need to be tested to find one patient with the mutation when assuming the percent of positive patients is 36.43% (35).

7.2 Candidate patient population

According to the scientific committee under the Medicine Council, patients harboring PIK3CA mutations have poor prognosis compared to wildtype patients. This is based on clinical evidence showing that patients with PIK3CA mutations develop endocrine resistance more often and/or faster than patients without the mutation (43, 44). Data also show that the PIK3CA mutated patient population has a poorer response to chemotherapy compared to wildtype patients (5). This is consistent with studies, showing that activation of the PI3K/protein kinase pathway B (AKT) pathway could mediate resistance to chemotherapy in breast cancer (6). Data from prospective subgroup analyses in several of the CDK4/6 studies have demonstrated that median PFS consistently is decreased in the PIK3CA-mutant patients compared to the wildtype population - regardless of therapy (7-9).

Alpelisib is the first drug whose mechanism of action enables a targeted treatment strategy for PIK3CA mutated patients with ER+/HER2- breast cancer (5). This makes alpelisib an important treatment contribution to the Danish breast cancer patients. With the current data available we see alpelisib as an add-on to fulvestrant treatment after CDK4/6i + AI treatment. We also suggest using alpelisib prior to chemotherapy as clinical data suggest, that this patient population present a resistance to chemotherapy and a worse outcome (5). According to ESMO guideline, prolonging the time to chemotherapy is of great value due to the limited efficacy of chemotherapy as well as the chemotherapy-related long-term toxicity (45). Prolonging time to chemotherapy will therefore also improve quality of life (45-48). Chemotherapy is currently the only recommended in case of visceral crisis for the HR+/HER2- aBC patient population (flowchart fig 2 in (45)).

Estimated patient numbers 1. line and 2. line:
As shown in Figure 1 page 7 in the Medicines Council protocol, it is estimated that approx. 50-70 patients with inoperable locally advanced or metastatic ER+/HER2- breast cancer (and harboring a mutation in the PIK3CA gene) yearly will be offered CDK4/6 inhibitors in combination with fulvestrant (1./2.line).

As indicated in the Medicines Council protocol approx. 80% of the 210-290 patients, who are offered CDK4/6 inhibitors in combination with AI in 1.line will eventually progress and subsequently be candidates for fulvestrant treatment (if not previously given) or chemotherapy for disease progression (2.line). This is estimated to be 170-230 patients yearly. In total, it is estimated by the Medicines Council/scientific committee that approx. 220-300 patients will annually be possible candidates for alpelisib.

We foresee that the estimated patient numbers in both 1.line and 2.line could be affected by different patient characteristics i.e., high ECOG performance status, visceral crisis, fragile patients, comorbidities, monitoring needs and other variables, which is likely to reduce the numbers of patients estimated by the Medicines Council by 50% (1.line n= 25-35 and 2.line n= 85-115.)

As mentioned in the Medicines Council protocol, EMA recognizes that the indication of alpelisib does not fit into current clinical practice. EMA mentions in the EPAR, that patients who have progressed on a CDK4/6 inhibitor in combination with AI are relevant candidates for treatment with alpelisib in combination with fulvestrant (1). This is

also according to international consensus guideline committee's and the recommendation from international guidelines (49).

7.3 Supplementary health economic analysis

7.3.1 Inclusion of chemotherapy patients in the budget impact analysis.

Per request from The Medicines Council, a scenario analysis has been calculated, where 10% of post CDK4/6i aBC patients are assumed to receive chemotherapy instead of fulvestrant. This is a rather small proportion of patients and despite incurring a lower cost per cycle for treatment, the overall impact on the analysis is minimal with an incremental change of approximately DKK 2 000, when comparing to mono fulvestrant alone. The base case of 10% patients was arbitrarily chosen, but as shown, has no great impact on the final budget impact calculations. A further explanation can be found in the technical document in the budget impact section.

7.4 Patients with visceral metastasis (or others who may not be considered for treatment with fulvestrant)

7.4.1 Visceral Metastasis

In the SOLAR-1 study 341 patients with PIK3CA mutation were included, of these 193 (56.6%) had visceral metastasis. Tumor responses were improved with alpelisib vs placebo in patients with or without visceral metastasis. The majority (n=170; 88.1%) of patients with visceral metastasis had lung and/or liver metastases and median PFS was 9.0 vs 3.7 months in the alpelisib (n=84) vs PBO (n=86) arms (HR 0.62; 95% CI, 0.44-0.89). PFS HRs (95% CI) for alpelisib vs placebo in patients with presence of liver metastases (ALP, n=49; PBO, n=54) or lung involvement (alpelisib, n=57; PBO, n=68) were 0.58 (0.37-0.90) and 0.65 (0.42-1.01), respectively. PFS HRs (95% CI) for alpelisib vs placebo in patients without lung and/or liver metastases (ALP, n=85; PBO, n=86) and in patients with bone-only metastases (alpelisib, n=42; PBO, n=35) were 0.69 (0.47-1.01) and 0.62 (0.33-1.18), respectively. Median PFS for patients with bone-only metastases in the ALP vs PBO arms was 19.1 vs 13.0 months. Conclusions: Treatment benefit from alpelisib + fulvestrant was maintained across patient subgroups analysed, including patients with visceral metastasis and bone-only metastases, and was consistent with the benefit observed in the PIK3CA-mutated cohort in SOLAR-1 (5). This patient group should be taken into consideration for alpelisib treatment.

7.4.1 Endocrine Resistance

The patients with endocrine resistance in SOLAR-1 was divided into subgroups of primary resistance, secondary resistance and sensitivity. The subgroup analysis of PFS was for the primary resistance (n=45); HR=0.64 (CI: 0.31-1.32), for the secondary resistance (n= 247); HR=0.66 (CI: 0.49–0.90) and for the sensitive group (n=39); HR=0.87 (CI: 0.35–2.17) (5), demonstrating a treatment benefit for these patient groups.
Currently fulvestrant is not part of the Danish standard treatment for patients with visceral metastasis or endocrine resistance, however with the data from SOLAR-1 we suggest that The Medicines Council re-evaluate this and add alpelisib-fulvestrant as a treatment option.

8 Economic comparison – this has been moved to the technical document

9 Budget impact – this has been moved to the technical document

10 Discussion and conclusion

Discussion:
Treatment regimens consisting of endocrine therapy in combination with CDK4/6 inhibitors in the first-line setting are becoming the standard-of-care for the majority of patients with endocrine-sensitive/resistant disease as reflected in both national and international breast cancer clinical practice guidelines (49, 50). However, both de novo and acquired resistance to treatment with endocrine-based CDK4/6 inhibitor therapy has been observed, ultimately leading to treatment failure and disease relapse (51, 52). Activation of the PI3K/AKT/mTOR pathway plays an important role in acquired resistance to endocrine-based CDK4/6 inhibitor therapy. Inhibition of the activated PI3K/AKT/mTOR pathway (as achieved with alpelisib) may thus counteract this resistance, thereby restoring endocrine sensitivity and thus provide a new therapeutic approach to the treatment of metastatic breast cancer (53, 54).

In order to evaluate the **clinical question 1** regarding the value of alpelisib in combination with fulvestrant compared to CDK4/6 inhibitors in combination with fulvestrant, it is relevant and important to take into account, that SOLAR-1 is the only phase III trial powered to demonstrate a significant clinical benefit in this population. None of the CDK4/6 registrational trials (MONALEESA-3 (NCT02422615), PALOMA-3 (NCT01942135), MONARCH-2 (NCT02107703) were designed to specifically investigate nor stratify for PIK3CA mutations. This was also supported/confirmed in the SLR based on the two search strings provided by The Medicines Council (Appendix B). However, prospectively analysis of the PIK3CA mutated patient populations within these trials have been investigated due to growing evidence showing worse prognosis in the PIK3CA mutated patient population than those with wild-type disease.

Currently, alpelisib is the only treatment specifically targeting the PIK3CA mutated patient population. The ITC showed no significant differences between CDK4/6 treatment when compared to alpelisib. However, abemaciclib was numerically favored for PFS and palbociclib was numerically favored for OS. These findings are counter intuitive, as one would expect the same proportional hazards between OS and PFS within the same study. Thus, it would be expected that the study with the greatest PFS benefit would also show the greatest OS benefit. Further, the Medicines Council has previously concluded that there is comparable effect between the three CDK4/6 inhibitors, which further supports the observed differences are due to chance. The findings of the ITC shows that individual patient level data is needed in order to perform a meaningful analysis and preferably with studies powered to show significant effect within the subgroup of interest (i.e. PIK3CA mutated patients). Despite the limitations of the ITC, it does indicate the relative efficacy in PIK3CA mutated patients, when treated with either a CDK4/6 or alpelisib. In summary, the ITC provides an indication of the relative effect between CDK4/6 treatment in combination with fulvestrant compared to alpelisib in combination with fulvestrant. However, the studies examining treatment with CDK4/6 inhibitors are not powered to show significant differences in the PIK3CA mutated subgroup and therefor all results should be interpreted with caution.

It is difficult to evaluate clinical question 2 due to lack of data reporting on fulvestrant mono-therapy in second line post-CDK4/6 + AI treatment. However, there is a clear unmet medical need in the PIK3CA mutated patient population and the value of alpelisib plus fulvestrant has been investigated through two studies: SOLAR-1 and BYLieve, which

both showed statistically difference in the primary end point, PFS. This suggests that alpelisib plus fulvestrant is a valid treatment option with manageable tolerability for patients with HR+/HER2-, PIK3CA mutated aBC in the post-CDK4/6 inhibitor plus AI setting. No other studies were identified with power to answer clinical question 2.

Conclusion:
Considering the clear unmet medical need in HR+/HER2- aBC patient harboring mutations in the PI3k pathway as described above and the consistent efficacy and well described safety profile, alpelisib (Piqray®) is considered to be a valuable addition to the currently treatments available to this patient group.

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12 Appendix A

12.1 Literature search

Table A1 Inclusion and exclusion criteria

Inclusion criteria	**Population:** • Patients with locally advanced or metastatic ER+ / HER2- breast cancer and mutation in the PIK3CA gene who have received endocrine monotherapy as first-line treatment for metastatic disease • Patients with locally advanced or metastatic ER + / HER2- breast cancer and mutation in the PIK3CA gene relapse at or shortly after the end of endocrine monotherapy as adjuvant therapy. **Intervention(s):** The following therapies, either as monotherapy or as part of a combination therapy: • alpelisib, Piqray • abemaciclib, Verzenios • Ribociclib, Kisqali + fulvestrant, Faslodex • CDK4/6-inhibitor + fulvestrant, Faslodex **Comparator(s):** The following therapies, either as monotherapy or as part of a combination therapy: • Fulvestrant, Faslodex monotherapy **Outcomes:** Efficacy outcomes • Overall survival (OS) • Progression-free survival (PFS) • HRQoL • Safety outcomes o AEs, SAEs, All-cause discontinuation, discontinuation due to AE

Table A1 Inclusion and exclusion criteria	
	Settings (if applicable): N/A **Study design:** • Randomized clinical trials **Language restrictions**: English only **Other search limits or restrictions applied:** Publications on cost effectiveness are included
Exclusion criteria	**Population:** • Not HR+ HER2- subtype, or no outcomes separately for this subtype • Not advanced breast cancer, or mixed population, but no results separately for advanced breast cancer • Not PIK3CA mutant carrier • Not previous receive treatment with CDK4/6-inhibitor in combination with aromatase inhibitor (AI) or fulvestrant. **Intervention(s):** Not include the interventions of interest **Comparator(s):** Not include the drug of interest **Outcomes:** • Studies not reporting any listed outcomes of relevance • Studies reporting relevant outcomes, but in groups of a mixed population, without reporting data specifically for the patient group of interest **Settings (if applicable):** N/A **Study design:** • Single-arm trials • Case reports • Guidelines • Editorials & opinion pieces • Reviews • Study protocols **Language restrictions**: Not English **Other search limits or restrictions applied:** N/A

12.2 Main characteristics of included studies

Table A2a Main study characteristics SOLAR-1	
Trial name	SOLAR-1
NCT number	NCT02437318

Table A2a Main study characteristics SOLAR-1	
Objective	Evaluate the efficacy and safety of an α-specific PI3K inhibitor plus fulvestrant in patients with PIK3CAmutated, HR-positive, HER2-negative advanced breast cancer who had received endocrine therapy previously
Publications – title, author, journal, year	Alpelisib plus fulvestrant for PIK3CA-mutated, hormone receptor-positive, human epidermal growth factor receptor-2-negative advanced breast cancer: final overall survival results from SOLAR-1, André et al. Annals of Oncology, 2021. Patient-Reported Outcomes in Patients With PIK3CA-Mutated Hormone Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative Advanced Breast Cancer From SOLAR-1, Ciruelos et al., J Clin Oncol, 2021. Time course and management of key adverse events during the randomized phase III SOLAR-1 study of PI3K inhibitor alpelisib plus fulvestrant in patients with HR-positive advanced breast cancer, Rugo et al., Annals of Oncology, 2020. Alpelisib for PIK3CA-Mutated, Hormone Receptor-Positive Advanced Breast Cancer, André et al., NEJM, 2019.
Study type and design	A phase III randomized double-blind, multicenter, placebo-controlled study Allocation: Randomized Intervention Model: Parallel Assignment Masking: Triple (Participant, Care Provider, Investigator) Primary Purpose: Treatment No crossover was allowed. Status: Active not recruiting.
Follow-up time	In the PIK3CA-mutant cohort, the median follow-up from randomization to data cut-off (23 April 2020) was 42.4 months (range, 33.1-55.7 months). By the time of data cut-off, 21 (12.4%) patients in the alpelisib plus fulvestrant arm versus 7 patients (4.1%) in the placebo plus fulvestrant arm were still receiving study treatment (11).
Population (inclusion and exclusion criteria)	Inclusion Criteria: 1. If female, patient is postmenopausal 2. Patient has identified PIK3CA status 3. Patients may be: a) relapsed with documented evidence of progression while on (neo) adjuvant endocrine therapy or within 12 months from completion of (neo)adjuvant endocrine therapy with no treatment for metastatic disease; b) relapsed with documented evidence of progression more than 12 months from completion of (neo)adjuvant endocrine therapy and then subsequently; progressed with documented evidence of progression while on or after only one line of endocrine therapy for metastatic disease; c) newly diagnosed advanced breast cancer, then relapsed with documented evidence of progression while on or after only one line of endocrine therapy 4. Patient has recurrence or progression of disease during or after AI therapy (i.e. letrozole, anastrozole, exemestane).

Table A2a Main study characteristics SOLAR-1	
	5. Patient has a histologically and/or cytologically confirmed diagnosis of estrogen-receptor positive breast cancer by local laboratory and has HER2 negative breast cancer 6. Patient has either measurable disease per RECIST 1.1 criteria OR at least one predominantly lytic bone lesion must be present 7. Patient has adequate bone marrow function Exclusion Criteria: 8. Patient with symptomatic visceral disease or any disease burden that makes the patient ineligible for endocrine therapy per the investigator's best judgment 9. Patient has received prior treatment with chemotherapy (except for neoadjuvant/ adjuvant chemotherapy), fulvestrant, any PI3K, mTOR or AKT inhibitor (pre-treatment with CDK4/6 inhibitors is allowed) 10. Patient with inflammatory breast cancer at screening 11. Patients with Child pugh score B or C 12. Patients with an established diagnosis of diabetes mellitus type I or not controlled type II 13. Patient has Eastern Cooperative Oncology Group performance status 2 or more 14. Patient with CNS involvement unless he/she is at least 4 weeks from prior therapy completion to starting the study treatment and has stable CNS tumour at time of screening and not receiving steroids and/or enzyme inducing ant-epileptic medications for brain metastases 15. Patient has participated in a prior investigational study within 30 days prior to enrollment or within 5 half-lives of the investigational product, whichever is longer 16. Patient has a history of acute pancreatitis within 1 year of screening or a past medical history of chronic pancreatitis 17. Patient who relapsed with documented evidence of progression more than 12 months from completion of (neo)adjuvant endocrine therapy with no treatment for metastatic disease
Intervention	**Experimental: fulvestrant + alpelisib:** Alpelisib (300 mg; oral; once daily) in combination with fulvestrant (500 mg; intramuscular injection on Day 1 and Day 15 of Cycle 1, and then Day 1 of each subsequent 28-day cycle). (n= 284) **Placebo Comparator: fulvestrant + placebo:** Placebo (300 mg; oral; once daily) in combination with fulvestrant (500 mg; intramuscular injection on Day 1 and Day 15 of Cycle 1, and then Day 1 of each subsequent 28-day cycle). (n= 288)

Table A2a Main study characteristics
SOLAR-1

Baseline characteristics

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Cohort with *PIK3CA*-Mutated Cancer		Cohort without *PIK3CA*-Mutated Cancer	
	Alpelisib–Fulvestrant Group (N=169)	Placebo–Fulvestrant Group (N=172)	Alpelisib–Fulvestrant Group (N=115)	Placebo–Fulvestrant Group (N=116)
Age — yr				
Median	63	64	62	63
Range	25–87	38–92	39–82	32–88
Female sex — no. (%)	168 (99.4)	172 (100)	115 (100)	116 (100)
ECOG performance-status score — no. (%)†				
0	112 (66.3)	113 (65.7)	84 (73.0)	79 (68.1)
1	56 (33.1)	58 (33.7)	30 (26.1)	37 (31.9)
Missing data	1 (0.6)	1 (0.6)	1 (0.9)	0
Sites of metastases — no. (%)‡				
Breast	1 (0.6)	3 (1.7)	5 (4.3)	4 (3.4)
Bone only	42 (24.9)	35 (20.3)	26 (22.6)	23 (19.8)
Visceral site				
Any	93 (55.0)	100 (58.1)	66 (57.4)	74 (63.8)
Liver	49 (29.0)	54 (31.4)	41 (35.7)	36 (31.0)
Lung	57 (33.7)	68 (39.5)	37 (32.2)	55 (47.4)
Lung or liver	84 (49.7)	86 (50.0)	56 (48.7)	56 (48.3)
No. of metastatic sites — no. (%)				
0	0	1 (0.6)	0	0
1	63 (37.3)	52 (30.2)	44 (38.3)	33 (28.4)
2	58 (34.3)	60 (34.9)	35 (30.4)	38 (32.8)
≥3	48 (28.4)	59 (34.3)	36 (31.3)	45 (38.8)
Previous treatment — no. (%)§				
Any CDK4/6 inhibitor	9 (5.3)	11 (6.4)	7 (6.1)	8 (6.9)
Chemotherapy¶	101 (59.8)	107 (62.2)	78 (67.8)	72 (62.1)
Line of treatment in advanced disease — no. (%)‖				
First line	88 (52.1)	89 (51.7)	71 (61.7)	62 (53.4)
Second line	79 (46.7)	82 (47.7)	42 (36.5)	53 (45.7)
Endocrine status — no. (%)**				
Primary resistance	23 (13.6)	22 (12.8)	31 (27.0)	26 (22.4)
Secondary resistance	120 (71.0)	127 (73.8)	66 (57.4)	65 (56.0)
Sensitivity	20 (11.8)	19 (11.0)	16 (13.9)	20 (17.2)

* Any differences between the two trial groups were less than 10% in the cohort of patients with *PIK3CA*-mutated cancer. The gene *PIK3CA* encodes for the alpha isoform of phosphatidylinositol 3-kinase (PI3Kα). Percentages may not total 100 because of rounding. Further data regarding the baseline characteristics of the patients are provided in Table S10 in the Supplementary Appendix. CDK denotes cyclin-dependent kinase.

† Eastern Cooperative Oncology Group (ECOG) performance-status scores are assessed on a scale from 0 to 5, with higher numbers indicating greater disability.

‡ One patient in the placebo group in the cohort with *PIK3CA*-mutated cancer had locally advanced disease with no metastases.

§ All patients had previously received treatment with an aromatase inhibitor.

¶ Chemotherapy was for patients receiving neoadjuvant or adjuvant therapy only. One patient in the placebo group of the cohort with *PIK3CA*-mutated cancer received chemotherapy for advanced disease (which was a protocol deviation).

‖ Three patients in each trial cohort (two patients in the alpelisib–fulvestrant group and one in the placebo–fulvestrant group in each cohort) were excluded because of protocol deviations.

** Primary endocrine resistance was defined as relapse within 24 months while the patient was receiving adjuvant endocrine therapy or progression within 6 months while the patient was receiving endocrine therapy in the context of metastatic disease. Secondary endocrine resistance was defined as relapse that occurred after at least 24 months while the patient was receiving adjuvant endocrine therapy, relapse that occurred within 12 months after the end of adjuvant endocrine therapy, or progression that occurred after at least 6 months while the patient was receiving endocrine therapy in the context of metastatic disease. After enrollment began, the trial protocol was updated to exclude patients who had a relapse at least 12 months after the completion of neoadjuvant or adjuvant endocrine therapy and had not been treated for metastatic disease (endocrine sensitive).

(5)

Primary and secondary endpoints	**Primary outcomes are:** Progression-free Survival (PFS) Per Investigator Assessment in the PIK3CA Mutant Cohort (Time Frame: Once approximately 243 PFS events in this cohort had been observed, up to 32 months). PFS, defined as the time from the date of randomization to the date of the first documented progression or death due to any cause. PFS will be assessed via a local radiology assessment according to RECIST 1.1.

Secondary outcomes are:

- Overall Survival (OS) for Patients with PI3KCA Mutant Status (Time Frame: Up to approximately 59 months). OS is defined as the time from date of randomization to date of death due to any cause.
- Overall Response Rate (ORR) (Time Frame: Up to approximately 36 months). ORR is defined as the proportion of patients with best overall response of complete response (CR), or partial response (PR) based on local investigator's assessment according to RECIST 1.1.
- Time to Definitive Deterioration of Eastern Cooperative Oncology Group (ECOG) Performance Status (Time Frame: Baseline, up to approximately 36 months). Deterioration of Eastern Cooperative Oncology Group Performance Status (PS) Safety and Tolerability of alpelisib in Combination with fulvestrant (Time Frame: Up to approximately 37 months).
- Safety will be determined by type, frequency and severity of adverse events per CTCAEv4.03 and type, frequency and severity of laboratory toxicities per CTCAEv4.03. Patients will be followed up for the duration of the study.
- Time to 10% Deterioration in the Global Health Status/Quality of Life (QOL) Scale Score of the EORTC QLQ-C30 (Time Frame: Up to approximately 36 months). Composite measure of change from baseline in the domain scores, health states, overall health status, and index values at the time of each assessment will be summarized.
- Plasma concentration-time profile of alpelisib given in combination with fulvestrant and appropriate pharmacokinetics (PK) parameters (time frame: day 8 and day 15 of cycle 1, then day 1 of cycles 2,4, 6. Assessment of any potential impact of fulvestrant on the pharmacokinetics of alpelisib by collection of sparse and trough PK samples. PK parameters includes, but not limited to, Cmin, Cmax, t1/2, AUC last for alpelisib (and any relevant metabolites) and fulvestrant.
- PFS Based on Radiology Assessments and Using RECIST 1.1 criteria (Time Frame: Baseline, up to approximately 36 months). PFS in patients with PIK3CA mutant status and patients with PIK3CA non-mutant status as measured in ctDNA.
- Clinical Benefit Rate (Time Frame: up to approximately 36 months). Clinical benefit rate is defined as the proportion of patients with a best overall response of CR or PR or SD or Non-CR/Non-PD lasting more than 24 weeks based on local investigator assessment.
- Change in the Global Health Status/(QOL) Scale Score of the EORTC QLQ-C30 (Time Frame: baseline, up to approximately 36 months). Composite measure of change from baseline in the domain scores, health states, overall health status, and index values at the time of each assessment will be summarized.
- Summary Statistics of fulvestrant and alpelisib Plasma Concentrations (Time Frame: Day 8 and Day 15 of Cycle 1, then Day 1 of Cycles 2,4, 6, 8]. Assessment of any potential impact of fulvestrant on the pharmacokinetics of alpelisib by collection of sparse and trough PK samples.
- PFS for Patients with PIK3CA Non-mutant Status (Time Frame: Up to approximately 36 months). PFS based on local radiology assessments and using RECIST 1.1 criteria in the PIK3CA non-mutant cohort.

  OS for Patients with PIK3CA Non-mutant Status (Time Frame: Up to approximately 59 months). OS is defined as the time from date of randomization to date of death due to any cause.

Table A2a Main study characteristics SOLAR-1	
Method of analysis	OS was analyzed using Kaplan Meier methodology, and Cox regression, adjusted for stratification parameters, to estimate HR and 95% CIs.
Subgroup analyses	Characteristics of the cohort A (patients with PIK3CA mutation):

Subgroup		No. of patients
All subjects		341
Lung/liver metastases	Yes	170
	No	171
Bone-only disease	Yes	77
	No	264
Prior CDK4/6 inhibitor treatment	Yes	20
	No	321
ER status	Positive	339
PgR status	Positive	252
	Negative	84
ER and PgR status	Both positive	250
	Positive - negative	84
Line of advanced anticancer treatment	First line	177
	Second line	161
Endocrine status	Primary resistance	45
	Secondary resistance	246
	Sensitive	39
ECOG status	0	225
	1	114

(11)

Overall survival by subgroups in the cohort of patients with PIK3CA-mutated cancer.

Full analysis set, PIK3CA-mutant cohort. Within each randomization stratum, Cox proportional hazards model was stratified by the other randomization stratum. Subgroup analyses were also carried out and included the study stratification factors of lung/liver metastases and prior CDK4/6 inhibitors. (11)

Post hoc exploratory analysis was performed in 95 patients (56.2%) in the alpelisib plus fulvestrant arm and 109 patients (63.4%) in the placebo plus fulvestrant arm, investigating when patients went on to receive their first chemotherapy (TTC) in the metastatic setting (with censoring at the last contact date or death), following discontinuation of study treatment.

Table A2b Main study characteristics MONARCH-2	
Trial name	MONARCH-2
NCT number	NCT02107703
Objective	The primary objective of MONARCH-2 is to compare abemaciclib plus fulvestrant versus placebo plus fulvestrant with respect to progression free survival (PFS) for women with HR+, HER2- locally advanced or metastatic breast cancer. An important secondary objective of this study is to compare the 2 arms with respect to overall survival (OS).

Table A2b Main study characteristics MONARCH-2	
Publications – title, author, journal, year	MONARCH 2: Abemaciclib in Combination with Fulvestrant in Women With HR+/HER2- Advanced Breast Cancer Who Had Progressed While Receiving Endocrine Therapy, Sledge et al., J Clin Oncol, 2017 Health-Related Quality of Life in MONARCH 2: Abemaciclib plus Fulvestrant in Hormone Receptor-Positive, HER2-Negative Advanced Breast Cancer After Endocrine Therapy, Kaufman et al., Oncologist, 2020 The Effect of Abemaciclib Plus Fulvestrant on Overall Survival in Hormone Receptor-Positive, ERBB2-Negative Breast Cancer That Progressed on Endocrine Therapy-MONARCH 2: A Randomized Clinical Trial, Sledge et al., JAMA Oncol, 2020 Safety and efficacy of abemaciclib plus endocrine therapy in older patients with hormone receptor-positive/human epidermal growth factor receptor 2-negative advanced breast cancer: an age-specific subgroup analysis of MONARCH 2 and 3 trials, Goetz et al., Breast Cancer Res Treat, 2021 Management of Abemaciclib-Associated Adverse Events in Patients with Hormone Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative Advanced Breast Cancer: Safety Analysis of MONARCH 2 and MONARCH 3, Rugo et al., Oncologist, 2021 Abemaciclib in combination with endocrine therapy for East Asian patients with HR+, HER2- advanced breast cancer: MONARCH 2 & 3 trials, Toi et al., Cancer Sci, 2021
Study type and design	A phase III, multicenter study Allocation: Randomized Intervention Model: Parallel Assignment Masking: Double (Participant, Investigator) Primary Purpose: Treatment Status: Active, not recruiting
Follow-up time	Treatment period: until disease progression or other discontinuation criteria are fulfilled. Short-term follow-up (postdiscontinuation): 30 days Long-term follow-up (postdiscontinuation): until death e.g.: median follow-up of 7.3 months (range 0.5–16.5)
Population (inclusion and exclusion criteria)	**Inclusion Criteria:** 1. Have a diagnosis of HR+, HER2- breast cancer 2. Have locally advanced disease not amenable to curative treatment by surgery or metastatic disease. In addition, participants must fulfill 1 of the following criteria: a) relapsed with radiologic evidence of progression while receiving neoadjuvant or adjuvant endocrine therapy, with no subsequent endocrine therapy received following progression b) relapsed with radiologic evidence of progression within 1 year from completion of adjuvant endocrine therapy, with no subsequent endocrine therapy received following progression c) relapsed with radiologic evidence of progression more than 1 year from completion of adjuvant endocrine therapy and then subsequently relapsed with radiologic evidence of progression after receiving treatment with either an antiestrogen or an aromatase inhibitor as first-line endocrine therapy for metastatic disease. Participants may not have received more than 1 line of endocrine therapy or any prior chemotherapy for metastatic disease

d) presented de novo with metastatic disease and then relapsed with radiologic evidence of progression after receiving treatment with either an antiestrogen or an aromatase inhibitor as first line endocrine therapy for metastatic disease. Participants may not have received more than 1 line of endocrine therapy or any prior chemotherapy for metastatic disease or the endocrine naïve cohort: Must not have received prior endocrine therapy in current or prior disease setting

3. Have postmenopausal status due to either surgical/natural menopause or ovarian suppression (initiated at least 28 days prior to Day 1 of Cycle 1) with a gonadotropin-releasing hormone (GnRH) agonist such as goserelin
4. Have a negative serum pregnancy test at baseline (within 14 days prior to randomization) and agree to use medically approved precautions to prevent pregnancy during the study and for 12 weeks following the last dose of abemaciclib if postmenopausal status is due to ovarian suppression with a GnRH agonist
5. Have either measurable disease or nonmeasurable bone only disease
6. Have a performance status ≤1 on the ECOG scale
7. Have discontinued previous therapies for cancer (including specifically, aromatase inhibitors, anti-estrogens, chemotherapy, radiotherapy, and immunotherapy) for at least 21 days for myelosuppressive agents or 14 days for nonmyelosuppressive agents prior to receiving study drug, and recovered from the acute effects of therapy (until the toxicity resolves to either baseline or at least Grade 1) except for residual alopecia or peripheral neuropathy

Exclusion Criteria:

1. Are currently receiving an investigational drug in a clinical trial or participating in any other type of medical research judged not to be scientifically or medically compatible with this study
2. Have visceral crisis, lymphangitic spread, or leptomeningeal carcinomatosis visceral crisis is not the mere presence of visceral metastases but implies severe organ dysfunction as assessed by symptoms and signs, laboratory studies, and rapid progression of the disease
3. Have clinical evidence or history of central nervous system metastasis
4. Have received prior treatment with chemotherapy (except for neoadjuvant/ adjuvant chemotherapy), fulvestrant, everolimus, or any CDK4/6 inhibitor. For the endocrine naïve cohort: In addition, have received treatment with any prior endocrine therapy
5. Have received treatment with a drug that has not received regulatory approval for any indication within 14 or 21 days prior to randomization of study drug for a nonmyelosuppressive or myelosuppressive agent, respectively
6. Have received recent (within 28 days prior to randomization) yellow fever vaccination
7. Have had major surgery within 14 days prior to randomization of study drug to allow for post-operative healing of the surgical wound and site(s)
8. Have a personal history within the last 12 months of any of the following conditions: syncope of cardiovascular etiology, ventricular tachycardia, ventricular fibrillation, or sudden cardiac arrest
9. Have inflammatory breast cancer or a history of any other cancer (except nonmelanoma skin cancer or carcinoma in-situ of the cervix), unless in complete remission with no therapy for a minimum of 3 years
10. Have received an autologous or allogeneic stem-cell transplant

	11. Have active bacterial or fungal infection, or detectable viral infection Have initiated bisphosphonates or approved Receptor activator of nuclear factor kappa-B (RANK) ligand targeted agents <7 days prior to randomization
Intervention	**Experimental: Abemaciclib + Fulvestrant**: 150 milligrams (mg) abemaciclib given orally once every 12 hours in 28 day cycles. 500 mg fulvestrant administered as two 250-mg injections intramuscularly (IM) on Days 1 and 15 of Cycle 1, then on Day 1 of Cycle 2 and beyond. Participants may continue to receive treatment until discontinuation criteria are met. (n= 446) **Placebo Comparator: Placebo + Fulvestrant**: Placebo will be supplied as capsules administered orally every 12 hours in 28 day cycles. 500 mg fulvestrant administered as two 250-mg injections IM on Days 1 and 15 of Cycle 1, then on Day 1 of Cycle 2 and beyond. Participants may continue to receive treatment until discontinuation criteria are met. (n= 223)
Baseline characteristics	**Table 1.** Patient and Disease Baseline Characteristics Characteristic — Abemaciclib + Fulvestrant (n = 446) — Placebo + Fulvestrant (n = 223) Age, years, median (range) — 59 (32-91) — 62 (32-87) ET resistance* Primary — 111 (24.9) — 58 (26.0) Secondary — 326 (73.1) — 163 (73.1) Most recent ET† Neoadjuvant or adjuvant — 263 (59.0) — 133 (59.6) Metastatic — 171 (38.3) — 85 (38.1) Prior AI Yes — 316 (70.9) — 149 (66.8) No — 130 (29.1) — 74 (33.2) PgR status‡ Positive — 339 (76.0) — 171 (76.7) Negative — 96 (21.5) — 44 (19.7) Metastatic site§ Visceral — 245 (54.9) — 128 (57.4) Bone only — 123 (27.6) — 57 (25.6) Other — 75 (16.8) — 38 (17.0) Measurable disease Yes — 318 (71.3) — 164 (73.5) No — 128 (28.7) — 59 (26.5) Race‖ Asian — 149 (33.4) — 65 (29.1) Caucasian — 237 (53.1) — 136 (61.0) Other — 29 (6.5) — 13 (5.8) ECOG performance status¶ 0 — 264 (59.2) — 136 (61.0) 1 — 176 (39.5) — 87 (39.0) Prior chemotherapy for neoadjuvant or adjuvant treatment Yes — 267 (59.9) — 134 (60.1) No — 179 (40.1) — 89 (39.9) Menopausal status# Pre- or perimenopause — 72 (16.1) — 42 (18.8) Postmenopause — 371 (83.2) — 180 (80.7) Note. Data given as No. (%) unless otherwise indicated. Abbreviations: AI, aromatase inhibitor; ECOG, Eastern Cooperative Oncology Group; ET, endocrine therapy; PgR, progesterone receptor. *Six patients in the abemaciclib arm and two patients in the placebo arm had not received prior ETs. †ET history was not available for 12 patients in the abemaciclib arm and five patients in the placebo arm. ‡Eight patients in each arm had unknown PgR status. §Metastatic site was not available for three patients in the abemaciclib arm. ‖A total of 31 patients in the abemaciclib arm and nine in the placebo arm had missing race information. ¶One patient had ECOG performance status of 2 in the abemaciclib arm. #Menopausal status was not available for three patients in the abemaciclib arm and one in the placebo arm. (14)
Primary and secondary endpoints	**Primary endpoint:** 1. Progression-Free Survival (PFS) (Time Frame: From Date of Randomization until Disease Progression or Death Due to Any Cause (Up To 31 Months)). PFS defined as the time from the date of randomization to the first evidence of disease progression as defined by response evaluation criteria in solid tumours (RECIST) v1.1 or death from any cause. Progressive Disease (PD) was at least a 20% increase in the sum of the diameters of target lesions, with reference being the smallest sum on

	study and an absolute increase of at least 5 mm, or unequivocal progression of non-target lesions, or 1 or more new lesions. If a participant does not have a complete baseline disease assessment, then the PFS time was censored at the date of randomization, regardless of whether or not objectively determined disease progression or death has been observed for the participant. If a participant was not known to have died or have objective progression as of the data inclusion cut-off date for the analysis, the PFS time was censored at the last adequate tumour assessment date. **Secondary endpoint:** 1. Overall Survival (OS) [(Time Frame: From Date of Randomization until Death Due to Any Cause (Up To 80 Months). OS defined as the time from the date of randomization to the date of death due to any cause. For each participant who is not known to have died as of the data-inclusion cut-off date for overall survival analysis, OS time was censored on the last date the participant is known to be alive. 2. Percentage of Participants Achieving Complete Response (CR) or Partial Response (PR) (Objective Response Rate [ORR]) (Time Frame: From Date of First Dose until Disease Progression or Death Due to Any Cause (Up To 31 Months)). 3. Duration of Response (DOR) (Time Frame: From Date of CR, PR until Disease Progression or Death Due to Any Cause (Up To 31 Months)). 4. Percentage of Participants Achieving CR, PR or Stable Disease (SD) (Disease Control Rate [DCR]) [Time Frame: From Date of First Dose until Disease Progression or Death Due to Any Cause (Up To 31 Months). 5. Percentage of Participants With CR, PR or SD with a Duration of At Least 6 Months (Clinical Benefit Rate [CBR]) (Time Frame: From Date of First Dose until Disease Progression or Death Due to Any Cause (Up To 31 Months). 6. Change from Baseline in Pain and Symptom Burden Assessment Using the Modified Brief Pain Inventory-Short Form (mBPI-sf) (Time Frame: Baseline, End of Study (Up To 31 Months)) 7. Pharmacokinetics (PK): Area Under the Concentration Curve (AUC) of Abemaciclib, Its Metabolites M2 and M20 (Time Frame: Cycle 1 Day 1 2-4 hours (h) post dose, Cycle 1 Day 15 4 and 7h post dose, Cycle 2 Day 1 pre dose and 3h post dose, Cycle 3 Day1 pre dose). 8. Change from Baseline in Health Status Using the EuroQol 5-Dimension 5 Level (EQ-5D 5L) (Time Frame: Baseline, End of Study (Up To 31 Months). Change From Baseline to Short Term Follow up in Quality of Life Using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) (Time Frame: Baseline, Short Term Follow Up (Up To 31 Months)). Change from Baseline to Short Term Follow up in Quality of Life Using the EORTC QLQ-BR23 (Breast) Questionnaire (Time Frame: Baseline, Short Term Follow Up (Up To 31 Months)).
Method of analysis	The primary end point, investigator-assessed PFS, was evaluated using a log-rank test stratified by metastatic site and ET resistance. The final analysis was planned at 378 PFS events, which would provide approximately 90% power assuming a hazard ratio (HR) of 0.703 at a one-sided a of 0.025, which corresponds to a 2.75-month improvement over the true median PFS for the control arm of 6.5 months. A control for the secondary end point of OS was maintained using a hierarchical testing approach. The odds ratio estimator and the stratified Cochran-Mantel-Haenszel test were used to compare the rates of binary end points. Two-sided P values were used to compare efficacy between treatment groups and for interaction tests associated with the subgroup factors. An exploratory mixed-model analysis was used to compare change in tumor size over time. Unless otherwise noted, all hypothesis tests were performed at the

twosided .05 level, and all confidence intervals used a 95% confidence level. SAS (version 9.2 or later; SAS Institute, Cary, NC) was used for statistical analyses.

Subgroup analyses

Subgroups Analyzed	No.
Overall	669
ET resistance	
Primary	169
Secondary	489
PgR status	
Negative	140
Positive	510
Metastatic site	
Visceral	373
Bone only	180
Other	113
Measurable disease	
Yes	482
No	184
Age group, years	
< 65	424
≥ 65	245
Geographic region	
North America	178
Europe	279
Asia	212
Race	
Caucasian	373
Asian	214
Other	42
ECOG PS	
0	400
1	263
Menopausal status	
Pre- or perimenopause	114
Postmenopause	551
Organs involved, No.	
≥ 3	200
2	202
1	264

(14)

Progression-free survival (PFS) of patient subgroups. HRs are unstratified and estimated with the adjustment of arm 3 subgroup interaction, except the overall PFS. The overall PFS estimates were stratified by metastatic site and ET resistance. The factor levels that consisted of < 5% of randomly assigned patients were omitted from the analysis.

Table A2c Main study characteristics PALOMA-3	
Trial name	PALOMA-3
NCT number	NCT01942135
Objective	The primary objective of the study is to demonstrate the superiority of palbociclib in combination with fulvestrant or fulvestrant alone in prolonging PFS in women with HR+, HER2- metastatic breast cancer whose disease has progressed after prior ET. The safety between the two treatment arms will also be compared.
Publications – title, author, journal, year	Fulvestrant plus palbociclib versus fulvestrant plus placebo for treatment of hormone-receptor-positive, HER2-negative metastatic breast cancer that progressed on previous endocrine therapy (PALOMA-3): final analysis of the multicentre, double-blind, phase 3 randomised controlled trial. Cristofanilli et al., The lancet. Oncology, 2016. Overall Survival with Palbociclib and Fulvestrant in Advanced Breast Cancer. Turner et al., NEJM, 2018. Predictors of prolonged benefit from palbociclib plus fulvestrant in women with endocrine-resistant hormone receptor-positive/human epidermal growth factor receptor 2-negative metastatic breast cancer in PALOMA-3. Cristofanilli et al., European journal of cancer, 2018. The Genetic Landscape and Clonal Evolution of Breast Cancer Resistance to Palbociclib plus Fulvestrant in the PALOMA-3 Trial. O'Leary et al., Cancer Discovery, 2018. Early circulating tumor DNA dynamics and clonal selection with palbociclib and fulvestrant for breast cancer, O'Leary et al., Nature Communications, 2018. Cyclin E1 Expression and Palbociclib Efficacy in Previously Treated Hormone Receptor-Positive Metastatic Breast Cancer, Turner et al., Journal of clinical oncology, 2019. Circulating Tumor DNA Markers for Early Progression on Fulvestrant With or Without Palbociclib in ER+ Advanced Breast Cancer. O'Leary et al., Journal of the National Cancer Institute, 2020. Inactivating NF1 mutations are enriched in advanced breast cancer and contribute to endocrine therapy resistance. Pearson et al., Clinical cancer research, 2020.
Study type and design	Phase III, placebo-controlled, mulitcenter Allocation: Randomized Intervention Model: Parallel Assignment Masking: Triple (Participant, Care Provider, Investigator) Primary Purpose: Treatment Status: Active, not recruiting.
Follow-up time	Updated data cut-off April 13, 2018. Median follow-up 44.8 months.

Table A2c Main study characteristics PALOMA-3	
Population (inclusion and exclusion criteria)	**Inclusion Criteria:** 1. Women 18 years or older with metastatic or locally advanced disease, not amenable to curative therapy 2. Confirmed diagnosis of HR+/HER2- breast cancer 3. Any menopausal status 4. Progressed within 12 months from prior adjuvant or progressed within 1 month from prior advanced/metastatic endocrine breast cancer therapy 5. On an LHRH agonist for at least 28 days, if pre-/peri-menopausal, and willing to switch to goserelin (Zoladex ®) at time of randomization. 6. Measurable disease defined by RECIST version 1.1, or bone-only disease 7. Eastern Cooperative Oncology Group (ECOG) PS 0-1 8. Adequate organ and marrow function, resolution of all toxic effects of prior therapy or surgical procedures 9. Patient must agree to provide tumor tissue from metastatic tissue at baseline **Exclusion Criteria:** 1. Prior treatment with any CDK inhibitor, fulvestrant, everolimus, or agent that inhibits the PI3K-mTOR pathway 2. Patients with extensive advanced/metastatic, symptomatic visceral disease, or known uncontrolled or symptomatic CNS metastases 3. Major surgery or any anti-cancer therapy within 2 weeks of randomization 4. Prior stem cell or bone marrow transplantation 5. Use of potent CYP3A4 inhibitors or inducers
Intervention	**Experimental: Palbociclib + fulvestrant:** Palbociclib 125 mg/day orally continuously dosed for 3 weeks followed by 1 week off; repeated at each subsequent cycle. Fulvestrant 500 mg intramuscularly on Days 1 and 15 of Cycle 1, and then on Day 1 of each subsequent 28 day cycle. (n= 345) **Active Comparator: Placebo + fulvestrant:** Placebo orally continuously dosed for 3 weeks followed by 1 week off; repeated at each subsequent cycle. Fulvestrant 500 mg intramuscularly on Days 1 and 15 of Cycle 1, and then on Day 1 of each subsequent 28 day cycle. (n= 172)

Table A2c Main study characteristics
PALOMA-3

Baseline characteristics

Subgroup	No. of Patients (%)
All patients	
Stratified analysis	521 (100)
Unstratified analysis	521 (100)
Sensitivity to previous hormonal therapy	
Yes	410 (79)
No	111 (21)
Site of metastatic disease	
Visceral	311 (60)
Nonvisceral	210 (40)
Menopausal status at study entry	
Postmenopausal	413 (79)
Premenopausal or perimenopausal	108 (21)
Age	
<65 yr	392 (75)
≥65 yr	129 (25)
Race or ethnic group	
White	385 (74)
Asian	105 (20)
Black or other	29 (6)
Hormone-receptor status	
ER-positive and PR-positive	351 (67)
ER-positive and PR-negative	142 (27)
Disease-free interval	
≤24 mo	62 (12)
>24 mo	292 (56)
Previous chemotherapy	
Neoadjuvant or adjuvant treatment only	214 (41)
Treatment for metastatic disease	177 (34)
None	130 (25)
Previous lines of therapy for metastatic disease	
0	114 (22)
1	225 (43)
2	131 (25)
≥3	51 (10)
ESR1 mutation status	
Positive	106 (20)
Negative	289 (55)
PIK3CA mutation status	
Positive	133 (26)
Negative	262 (50)

Baseline values from the intent to treat population (all patients was randomized into the study). (26).

Primary and secondary endpoints

Primary outcomes:

PFS as Assessed by the Investigator (Time Frame: From randomization date to date of first documentation of progression or death (assessed up to 12 months)). PFS is the time from the date of randomization to the date of the first documentation of objective progression of disease (PD) or death due to any cause in absence of documented PD. Participants lacking an evaluation of tumor response after randomization had their PFS time censored on the date of randomization with the duration of a day. Participants with documentation of PD or death after a long interval (2 or more incomplete or non-evaluable assessments) since the last tumor assessment were censored at the time of last objective assessment that did not show PD. The length of PFS was calculated as PFS time (months) = [progression/death date (censor date) – randomization date + 1]/30.4. Progression is defined using Response Evaluation Criteria in Solid Tumors (RECIST v1.1) a 20% increase in the sum of

diameters of target lesions and the sum must also demonstrate an absolute increase of at least 5mm or unequivocal progression of existing non-target lesions or the appearance of new lesions.

Secondary Outcomes:

1. Overall Survival (OS) - Number of Participants Who Died (Time Frame: From randomization until death (up to approximately 36 months)). OS is defined as the time from date of randomization to date of death due to any cause. In the absence of confirmation of death, survival time was censored to last date the participant was known to be alive. For participants lacking survival data beyond the date of their last follow-up, the OS time was censored on the last date they were known to be alive. Participants lacking survival data beyond randomization were to have their OS times be censored at randomization.
2. Objective Response (OR) (Time Frame: From randomization until end of treatment (assessed up to 12 months)). OR is defined as the overall complete response (CR) or partial response (PR) according to the RECIST version 1.1 Objective Response Rate (ORR) is defined as the proportion of participants with CR or PR relative to all randomized participants and randomized participants with measurable disease at baseline. Participants who do not have on-study radiographic tumor re-evaluation, who received anti-tumor treatment other than the study medication prior to reaching a CR or PR, or who died, progressed, or dropped out for any reason prior to reaching a CR or PR were counted as non-responders in the assessment of ORR. Per response evaluation criteria in solid tumors criteria (RECIST v1.1) for target lesions and assessed by MRI: Complete Response (CR), Disappearance of all target lesions; Partial Response (PR), ≥30% decrease in the sum of the longest diameter of target lesions (longest for non-nodal and short axis for nodal target lesions); Overall Response (OR) = CR + PR.
3. Duration of Response (DR) (Time Frame: From randomization until end of treatment (assessed up to 12 months)). DR is defined as the time from the first documentation of objective tumor response (CR or PR) to the first documentation of disease progression or to death due to any cause, whichever occurs first. If tumor progression data included more than 1 date, the first date was used. DR was calculated as [the date response ended (ie, date of PD or death) - first CR or PR date + 1)]/30.4. Kaplan-Meier estimate of median of the DR is provided below. No inferential statistical analysis were done for DR. The DR was only calculated for the participants with a CR or PR.
4. Clinical Benefit Response (CBR) (Time Frame: From randomization until end of treatment (assessed up to 12 months)). CBR is defined as the overall complete response (CR), partial response (PR) , or stable disease (SD) ≥24 weeks according to the RECIST version 1.1. Clinical Benefit Response Rate (CBRR) is defined as the proportion of participants with CR, PR, or SD ≥24 weeks relative to all randomized participants and randomized participants with measurable disease at baseline. Participants who do not have on-study radiographic tumor re-evaluation, who received antitumor treatment other than the study medication prior to reaching a CR or PR, a best response of SD ≥24 weeks, or who died, progressed, or dropped out for any

reason prior to reaching a CR or PR and a best response of SD ≥24 weeks was counted as non-responders in the assessment of CBR. Per RECIST v1.1 for target lesions and assessed by MRI: CR, disappearance of all target lesions; PR, ≥30% decrease in the sum of the longest diameter of target lesions; OR = CR + PR.

5. Survival Probabilities at Months 12, 24 and 36 (Time Frame: From randomization until death (assessed up to 36 months)). One-, Two- or Three-year Survival Probability is defined as the probability of survival 1 year, 2 or 3 years after the date of randomization based on the Kaplan-Meier estimate. Survival time was censored to last date the participant is known to be alive.

6. Observed Plasma Trough Concentration (Ctrough) for Palbociclib (Time Frame: Cycle 1/Day 15 and Cycle 2/Day 15) Ctrough for palbociclib (if applicable). The method of dispersion applied here is "percent coefficient of variation" (%CV).

7. Ctrough for Fulvestrant (Time Frame: Cycles 2/Day 1 and Cycle 3/Day 1). Ctrough for Fulvestrant (if applicable). The method of dispersion applied here is "percent coefficient of variation" (%CV).

8. Ctrough for Goserelin (Time Frame: Cycles 2/ Day 1 and Cycle 3/ Day 1). Cmin for goserelin (if applicable). The method of dispersion applied here is "percent coefficient of variation" (%CV).

9. Change From Baseline Between Treatment Comparison in European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) Functional Scale Scores (Time Frame: From Cycle 1 to 14, as of 05 December 2014.). The EORTC-QLQ-C30 is a 30-item questionnaire composed of five multi-item functional subscales (physical, role, emotional, cognitive , and social functioning), three multi-item symptom scales (fatigue, nausea/vomiting, and pain), a global quality of life (QOL) subscale, and six single item symptom scales assessing other cancer-related symptoms (dyspnea, sleep disturbance, appetite loss, constipation, diarrhea, and the financial impact of cancer). The questionnaire employs 28 4-point Likert scales with responses from "not at all" to "very much" and two 7-point Likert scales for global health and overall QOL. Responses to all items are then converted to a 0 to 100 scale. For functional and global QOL scales, higher scores represent a better level of functioning/QOL. For symptom-oriented scales, a higher score represents more severe symptoms. A 10-point or higher change in scores from baseline is considered clinically significant.

10. Change From Baseline Between Treatment Comparison in EORTC QLQ-C30 Symptom Scale Scores (Time Frame: From Cycle 1 to 14, as of 05 December 2014.). The EORTC-QLQ-C30 is a 30-item questionnaire composed of five multi-item functional subscales (physical, role, emotional, cognitive , and social functioning), three multi-item symptom scales (fatigue, nausea/vomiting, and pain), a global quality of life (QOL) subscale, and six single item symptom scales assessing other cancer-related symptoms (dyspnea, sleep disturbance, appetite loss, constipation, diarrhea, and the financial impact of cancer). The questionnaire employs 28 4-point Likert

scales with responses from "not at all" to "very much" and two 7-point Likert scales for global health and overall QOL. Responses to all items are then converted to a 0 to 100 scale. For functional and global QOL scales, higher scores represent a better level of functioning/QOL. For symptom-oriented scales, a higher score represents more severe symptoms. A 10-point or higher change in scores from baseline is considered clinically significant.

11. Change From Baseline Between Treatment Comparison in European Organization for Research and Treatment of Cancer Breast Cancer Module (EORTC QLQ BR23) Functional Scale Scores (Time Frame: From Cycle 1 to 14, as of 05 December 2014.). The EORTC-QLQ-BR23 is a 23-item breast cancer-specific companion module to the EORTC-QLQ-C30 and consists of four functional scales (body image, sexual functioning, sexual enjoyment, future perspective) and four symptom scales (systemic side effects, breast symptoms, arm symptoms, upset by hair loss). QLQ-BR23 questionnaire employs 4-point scales with responses from 'not at all' to 'very much'. All scores are converted to a 0 to 100 scale. For functional scales, higher scores represent a better level of functioning.

12. Change From Baseline Between Treatment Comparison in EORTC QLQ BR23 Symptom Scale Scores (Time Frame: From Cycle 1 to 14, as of 05 December 2014.) The EORTC-QLQ-BR23 is a 23-item breast cancer-specific companion module to the EORTC-QLQ-C30 and consists of four functional scales (body image, sexual functioning, sexual enjoyment, future perspective) and four symptom scales (systemic side effects, breast symptoms, arm symptoms, upset by hair loss). QLQ-BR23 questionnaire employs 4-point scales with responses from 'not at all' to 'very much'. All scores are converted to a 0 to 100 scale. For symptom-oriented scales, a higher score represent more severe symptoms.

13. Change From Baseline Between Treatment Comparison in EuroQoL 5D (EQ-5D)- Health Index Scores (Time Frame: From Cycle 1 to 14, as of 05 December 2014.). The EuroQol-5D (version 3L) is a brief self-administered, validated instrument consisting of 2 parts. The first part consists of 5 descriptors of current health state (mobility, self-care, usual activities, pain/discomfort, and anxiety/ depression); a participant is asked to rate each state on a three level scale (1=no problem, 2=some problem, and 3=extreme problem) with higher levels indicating greater severity/ impairment Published weights are available that allow for the creation of a single summary score called the EQ-5D index, which basically ranges from 0 to 1 with low scores representing a higher level of dysfunction and 1 as perfect health. The second part consists of the EQ-5D general health status as measured by a visual analog scale (EQ-5D VAS). EQ-5D VAS measures the participant's self-rated health status on a scale from 0 (worst imaginable health state) to 100 (best imaginable health state).

14. Change From Baseline Between Treatment Comparison in EQ-5D Visual Analog Scale (VAS) Scores Scale (Time Frame: From Cycle 1 to 14, as of 05 December 2014.) The EuroQol-5D (version 3L) is a brief self-administered, validated instrument consisting of 2 parts. The second part consists of the EQ-5D general health status as measured by a visual analog scale (EQ-5D

	VAS). EQ-5D VAS measures the participant's self-rated health status on a scale from 0 (worst imaginable health state) to 100 (best imaginable health state). 15. Time to Deterioration (TTD) (Time Frame: Baseline, Day 1 of Cycles 2 to 4, Day 1 of every alternate cycle after that until the end of treatment). A time to event analysis was pre-specified for pain. An analysis of TTD in pain defined as time between baseline and first occurrence of increase of ≥10 points in pain. Deterioration will be defined increase in score of 10 points or greater from baseline. The Kaplan-Meier estimates of quartiles (time to deterioration) with 95% CI is mentioned below. 16. Percentage of Participants With Treatment-Emergent Adverse Events (TEAEs; All Causalities) (Time Frame: From the signing of the informed consent until 28 days after the last dose of study medication up to 14 months). An AE is any untoward medical occurrence in a clinical investigation patient administered a product or medical device; the event need not necessarily have a causal relationship with the treatment or usage. An SAE is any untoward medical occurrence at any dose that results in death; is life-threatening; requires hospitalization; results in persistent or significant disability or in congenital anomaly/birth defect. Severity will be graded by the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 4.0.
Method of analysis	PFS: Exploratory analyses of PFS were conducted for different subgroups among the patients who received palbociclib plus fulvestrant. The Kaplan-Meier method was used to estimate the median PFS, and the two-sided log-rank test was performed for the PFS comparisons. Hazard ratios and two-sided 95% confidence intervals were estimated using Cox proportional hazards model. (15). OS: The median overall survival was estimated with the use of the Kaplan–Meier method, and the significance was determined with the use of a one-sided log-rank test with stratification according to presence or absence of sensitivity to previous endocrine therapy and the presence or absence of visceral metastases at randomization in the intention-to-treat population. All the P values reported herein are two-sided. The prespecified significance threshold was a two-sided P value of 0.047, which was adjusted for the planned interim analyses. (26)
Subgroup analyses	Subgroup analyses of overall survival were performed in prespecified subgroups (all subgroups defined in Baseline characteristics above). An exploratory subgroup analysis evaluated overall survival according to ESR1 and PIK3CA mutation status, as assessed in baseline circulating tumor DNA. (26)

Table A2d Main study characteristics MONALEESA-3	
Trial name	MONALEESA-3
NCT number	NCT02422615
Objective	This phase III study evaluated ribociclib plus fulvestrant in patients with hormone receptor positive/human epidermal growth factor receptor 2–negative advanced breast cancer who were treatment naîve or had received up to one line of prior endocrine therapy in the advanced setting.
Publications – title, author, journal, year	Ribociclib plus fulvestrant for advanced breast cancer: Health-related quality-of-life analyses from the MONALEESA-3 study, Fasching et al., Breast, 2020. Overall Survival with Ribociclib plus Fulvestrant in Advanced Breast Cancer, Slamon et al., NEJM, 2020 Phase III Randomized Study of Ribociclib and Fulvestrant in Hormone Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative Advanced Breast Cancer: MONALEESA-3, Slamon et al., J Clin Oncol, 2018
Study type and design	Phase III, double-blind, placebo-controlled study Allocation: Randomized Intervention Model: Crossover Assignment Intervention Model Description: After the overall survival results, the protocol has been amended in January 2020 to ensure access to ribociclib medication to all ongoing patients in the control arm. These patients will be allowed to cross-over to the ribociclib arm, based on the investigator's best judgement and an individualized benefit-risk assessment. Hereafter: Masking: None (Open Label) Masking Description: After the overall survival results, the protocol has been amended in January 2020 to allow for unblinding of all patients and of the principal investigators (as to the initial treatment allocation). Primary Purpose: Treatment Status: Active, not recruiting
Follow-up time	The median duration of follow-up for all patients was 39.4 months (minimum, 35.8 months)
Population (inclusion and exclusion criteria)	**Inclusion Criteria:** 1. Patient is an adult male/female ≥ 18 years old at the time of informed consent and has signed informed consent before any trial related activities and according to local guidelines. Female patients must be postmenopausal. 2. Patient has a histologically and/or cytologically confirmed diagnosis of estrogen-receptor positive and/or progesterone receptor positive breast cancer by local laboratory and has HER2-negative breast cancer.

3. Patient must have either measurable disease by RECIST 1.1 or at least one predominantly lytic bone lesion.
4. Patient has advanced (loco regionally recurrent not amenable to curative therapy, e.g. surgery and/or radiotherapy, or metastatic) breast cancer.
5. Patients may be:
    a. newly diagnosed advanced/metastatic breast cancer, treatment naïve
    b. relapsed with documented evidence of relapse more than 12 months from completion of (neo)adjuvant endocrine therapy with no treatment for advanced/metastatic disease
    c. relapsed with documented evidence of relapse on or within 12 months from completion of (neo)adjuvant endocrine therapy with no treatment for advanced/metastatic disease
    d. relapsed with documented evidence of relapse more than 12 months from completion of adjuvant endocrine therapy and then subsequently progressed with documented evidence of progression after one line of endocrine therapy (with either an antiestrogen or an aromatase inhibitor) for advanced/metastatic disease
    e. newly diagnosed advanced/metastatic breast cancer at diagnosis that progressed with documented evidence of progression after one line of endocrine therapy (with either an antiestrogen or an aromatase inhibitor)
6. Patient has an Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1
7. Patient has adequate bone marrow and organ function

Exclusion Criteria:

1. Patient with symptomatic visceral disease or any disease burden that makes the patient ineligible for endocrine therapy per the investigator's best judgment.
2. Patient has received prior treatment with chemotherapy (except for neoadjuvant/ adjuvant chemotherapy), fulvestrant or any CDK4/6 inhibitor.
3. Patient with inflammatory breast cancer at screening.
4. Patient with CNS involvement unless they are at least 4 weeks from prior therapy completion to starting the study treatment and have stable CNS tumour at the time of screening and not receiving steroids and/or enzyme inducing anti-epileptic medications for brain metastases
5. Clinically significant, uncontrolled heart disease and/or cardiac repolarization abnormality
6. Patient is currently receiving any of the following substances and cannot be discontinued 7 days prior to start the treatment:
    a. Known strong inducers or inhibitors of CYP3A4/5
    b. That have a known risk to prolong the QT interval or induce Torsades de Pointes.

Table A2d Main study characteristics MONALEESA-3	
	c. Those have a narrow therapeutic window and are predominantly metabolized through CYP3A4/5. d. Herbal preparations/medications, dietary supplements.
Intervention	**Experimental: Ribociclib + fulvestrant:** Ribociclib 600mg daily oral (days 1 to 21 in a 28-day Cycle) in combination with fulvestrant 500mg i.m. injections every 28 days (Cycle n Day 1) with 1 additional dose on Day 15 of Cycle 1. (n= 484) **Placebo Comparator: Ribociclib placebo + fulvestrant**: Ribociclib placebo 600mg daily oral (days 1 to 21 in a 28-day Cycle) in combination with fulvestrant 500mg i.m. injections every 28 days (Cycle n Day 1) with 1 additional dose on Day 15 of Cycle 1. (n= 242)

Table A2d Main study characteristics
MONALEESA-3

Baseline characteristics

Table 1. Demographics and Baseline Characteristics

Characteristic	Ribociclib + Fulvestrant (n = 484), No. (%)	Placebo + Fulvestrant (n = 242), No. (%)
Gender		
Female	484 (100)	242 (100)
Age, year		
Median	63.0	63.0
Range	31–89	34–86
Race		
White	406 (83.9)	213 (88.0)
Asian	45 (9.3)	18 (7.4)
Native American	5 (1.0)	1 (0.4)
Black	3 (0.6)	2 (0.8)
Unknown	15 (3.1)	5 (2.1)
Other	10 (2.1)	3 (1.2)
ECOG PS		
0	310 (64.0)	158 (65.3)
1	173 (35.7)	83 (34.3)
Missing	1 (0.2)	1 (0.4)
Disease stage at study entry		
II	2 (0.4)	0 (0.0)
III	4 (0.8)	2 (0.8)
IV	478 (98.8)	239 (98.8)
Missing	0 (0.0)	1 (0.4)
Hormone receptor status		
ER positive	481 (99.4)	241 (99.6)
PR positive	353 (72.9)	167 (69.0)
Disease-free interval, months*		
De novo	97 (20.0)	42 (17.4)
Non-de novo	387 (80.0)	199 (82.2)
≤12	22 (4.5)	9 (3.7)
>12	365 (75.4)	190 (78.5)
Missing	0 (0.0)	1 (0.4)
Prior endocrine therapy status†		
Treatment naïve	238 (49.2)	129 (53.3)
Up to one line of endocrine therapy	236 (48.8)	109 (45.0)
Prior endocrine therapy setting		
(Neo)adjuvant	289 (59.7)	142 (58.7)
Advanced	110 (22.7)	40 (16.5)
Prior chemotherapy		
Adjuvant	209 (43.2)	101 (41.7)
Neoadjuvant	65 (13.4)	30 (12.4)
Metastatic sites		
0	2 (0.4)	0 (0.0)
1	151 (31.2)	73 (30.2)
2	156 (32.2)	76 (31.4)
3	114 (23.6)	48 (19.8)
4	38 (7.9)	34 (14.0)
≥5	23 (4.8)	10 (4.1)
Missing	0 (0.0)	1 (0.4)
Sites of metastases		
Bone	367 (75.8)	180 (74.4)
Bone only	103 (21.3)	51 (21.1)
Visceral	293 (60.5)	146 (60.3)
Lung	146 (30.2)	72 (29.8)
Liver	134 (27.7)	63 (26.0)
Lung or liver	242 (50.0)	121 (50.0)
Central nervous system	6 (1.2)	2 (0.8)
Other‡	102 (21.1)	51 (21.1)
Lymph nodes	199 (41.1)	115 (47.5)
Soft tissue	23 (4.8)	14 (5.8)
Skin	20 (4.1)	8 (3.3)
Breast	4 (0.8)	1 (0.4)
None	2 (0.4)	0 (0.0)
Missing	0 (0.0)	1 (0.4)

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; ER, estrogen receptor; PR, progesterone receptor.
*De novo includes patients with no first recurrence/progression or with a first recurrence/progression within 90 days of diagnosis with no prior medication. For non-de novo disease, disease-free interval is defined as the time from initial diagnosis to first recurrence/progression.
†Fourteen patients not included because of missing data or criteria not being met.
‡Other visceral sites include metastatic site other than soft tissue, breast, bone, lung, liver, central nervous system, skin, and lymph nodes.

(8)

Table A2d Main study characteristics MONALEESA-3	
Primary and secondary endpoints	**Primary outcomes are:** Progression Free Survival (PFS) Per Investigator Assessment (Time Frame: Up to approximately 26 months). The primary endpoint of the study is PFS, defined as the time from the date of randomization to the date of the first documented progression or death due to any cause. PFS will be assessed via a local radiology assessment according to RECIST 1.1 **Secondary outcomes are:** • Overall Survival (OS). Time Frame: Up to approximately 58 months. Time from date of randomization to the date of death from any cause. • Progression Free Survival (PFS) Per Blinded Independant Review Committee (BICR) (Time Frame: Up to approximately 26 months) • Overall Response Rate (ORR) (Time Frame: Up to approximately 26 months). Overall response rate (ORR) is defined as the proportion of patients with the best overall response of complete response (CR) or partial response (PR) according to RECIST 1.1. • Time to Definitive Deterioration of ECOG Performance Status in One Category of the Score (Time Frame: Up to approximately 26 months). Time to definitive deterioration of ECOG performance status in one category of score is defined as the time from the date of randomization to the date of event, which is defined as at least one score lower than the baseline. • Safety and Tolerability of LEE011 [(Time Frame: Up to approximately 26 months). Safety will be determined by type, frequency and severity of adverse events per CTCAE version 4.03 and type, frequency and severity of laboratory toxicities per CTCAE version 4.03. • Time to Definitive 10% Deterioration in the Global Health Status/Quality of Life (QOL) Scale Score of the EORTC QLQ-C30 (Time Frame: Up to approximately 26 months). The time to definitive 10% deterioration is defined as the time from the date of randomization to the date of event, which is defined as at least 10% relative to baseline worsening of the corresponding scale score (without further improvement above the threshold) or death due to any cause. • Change from Baseline in the Global Health Status/QoL Scale Score of the EORTC QLQ-C30 (Time Frame: Up to approximately 26 months). Change from baseline in the domain scores, health states, overall health status, and index values at the time of each assessment will be summarized. • Clinical Benefit Rate (CBR) (Time Frame: Up to approximately 26 months). Clinical benefit rate (CBR), defined as the proportion of patients with a best overall response of complete response (CR) or partial response (PR) or stable disease (SD) lasting 24 weeks or longer as defined in RECIST 1.1 • Time to Response (TTR) (Time Frame: Up to approximately 26 months). Time from randomization to the first documented and confirmed response (complete response or partial response) as defined by RECIST 1.1 Duration of Response (DOR) (Time Frame: Up to approximately 26 months). Time from the first documented response (CR or PR) to the first documented progression or death due to underlying cancer as defined in RECIST 1.1
Method of analysis	For the primary analysis, PFS, the treatment effect was estimated using a Cox proportional hazards model overall and in relevant subgroups. The central PFS assessment used in support of the primary efficacy end point was analyzed using a Cox proportional hazards model. The primary PFS analysis was to be performed after observing approximately 364 local PFS events to detect a hazard ratio of 0.67 with 95% power and a one-sided 2.5% level of significance. OS was compared between the treatment groups using a stratified logrank test at a one-sided 2.5% level if the

primary PFS end point was significant. A three-look design was used, with up to two OS interim analyses (the first was performed at the time of the PFS analysis) and a final OS analysis planned. The Lan-DeMets a-spending function with O'Brien-Fleming boundary was used to control for multiplicity. ORR and clinical benefit rate were compared between treatment arms using the Cochran-Mantel-Haenszel x2 test at a one-sided 2.5% level. All efficacy analyses were performed in the full analysis set, comprising all randomly assigned patients. Safety analyses were performed in patients who received at least one dose of any study treatment and had at least one postbaseline safety assessment.

Subgroup analyses

Subgroup	Ribociclib+Fulvestrant	Placebo+Fulvestrant
	no. of deaths/total no. (%)	
All patients	167/484 (34.5)	108/242 (44.6)
Treatment line of endocrine-based therapy for advanced disease		
First line	63/237 (26.6)	47/128 (36.7)
Early relapse or second line	102/237 (43.0)	60/109 (55.0)
Liver or lung involvement		
Yes	97/242 (40.1)	57/122 (46.7)
No	70/242 (28.9)	51/119 (42.9)
Bone lesion only		
Yes	27/102 (26.5)	22/51 (43.1)
No	140/382 (36.6)	86/190 (45.3)
No. of sites of metastasis		
<3	93/308 (30.2)	60/147 (40.8)
≥3	74/176 (42.0)	48/94 (51.1)
Most recent therapy		
Adjuvant or neoadjuvant therapy	99/264 (37.5)	72/151 (47.7)
Therapy for metastatic disease	45/112 (40.2)	19/42 (45.2)
Age		
<65 yr	85/258 (32.9)	54/129 (41.9)
≥65 yr	82/226 (36.3)	54/113 (47.8)
ECOG score		
0	92/311 (29.6)	64/158 (40.5)
1	74/172 (43.0)	44/83 (53.0)
Race		
Asian	15/45 (33.3)	4/18 (22.2)
White	137/407 (33.7)	99/214 (46.3)
Other	9/17 (52.9)	2/5 (40.0)
Geographic region		
Asia	13/40 (32.5)	4/16 (25.0)
Europe and Australia	123/347 (35.4)	79/173 (45.7)
Latin America	4/6 (66.7)	1/3 (33.3)
North America	22/69 (31.9)	23/43 (53.5)
Other	5/22 (22.7)	1/7 (14.3)
PgR status		
Positive	118/353 (33.4)	72/167 (43.1)
Negative	40/113 (35.4)	32/69 (46.4)
Hormone-receptor status		
ER-positive and PgR-positive	115/350 (32.9)	72/167 (43.1)
Other	52/134 (38.8)	36/74 (48.6)

Analyses were performed in the following subgroups:

- patients receiving first-line therapy
- patients receiving second-line therapy plus those with early relapse (within 12 months after completion of adjuvant or neoadjuvant endocrine therapy).

Table A2d Main study characteristics MONALEESA-3	
	Hazard ratios were estimated on the basis of a stratified Cox proportional-hazards model, except in subgroups related to stratification factors (presence or absence of lung or liver metastases and previous endocrine therapy), for which an unstratified analysis was used. Although not prespecified an additional exploratory analysis was carried out to assess the consistency of survival benefit in subgroups based on previous response to endocrine therapy. (8)

Table A2e Main study characteristics BYLieve	
Trial name	BYLieve
NCT number	NCT03056755
Objective	Study assessing the efficacy and safety of alpelisib plus fulvestrant or letrozole, based on prior endocrine therapy, in patients with PIK3CA mutation with advanced breast cancer who have progressed on or after prior treatments.
Publications – title, author, journal, year	Alpelisib plus fulvestrant in PIK3CA-mutated, hormone receptor-positive advanced breast cancer after a CDK4/6 inhibitor (BYLieve): one cohort of a phase 2, multicentre, open-label, non-comparative study, Rugo et al., Lancet Oncol, 2021. Effectiveness of Alpelisib + Fulvestrant Compared with Real-World Standard Treatment Among Patients with HR+, HER2-, PIK3CA-Mutated Breast Cancer, Turner et al., Oncologists, 2021
Study type and design	This is a phase II, multicenter, open-label, three-cohort, non-comparative study Allocation: Non-Randomized Intervention Model: Parallel Assignment Masking: None (Open Label) Primary Purpose: Treatment Status: Active, recruiting.
Follow-up time	Median follow-up (from enrolment to data cutoff) was 11.7 months (range 8.5–15.9).
Population (inclusion and exclusion criteria)	**Inclusion Criteria:** • Patient is male or female 18 years or older • Males or females with advanced (locoregionally recurrent or metatstatic) breast cancer not amenable to curative therapy • In case of women, both premenopausal and postmenopausal patients are allowed to be included in study; menopausal status is relevant for the requirement of LHRH agonist (examples for use in this study include but not limited to goserelin, leuprolide or locally available treatment) to be used concomitantly with alpelisib and letrozole/fulvestrant.

a) Patient is postmenopausal woman defined as either:

- Prior bilateral oophorectomy or
- Age ≥60 or
- Age <60 and amenorrhea for 12 or more months (in the absence of chemotherapy, tamoxifen, toremifene, or ovarian suppression) and FSH and/or estradiol in the postmenopausal range per local normal range.

  If patient is taking tamoxifen or toremifene and age <60, then FSH and plasma estradiol levels should be in post-menopausal range per local normal range. Note: For women using therapy-induced amenorrhea other than ovarian radiation, goserelin or leuprolide, etc., serial measurements of FSH and/or estradiol are needed to ensure menopausal status

b) Patient is premenopausal defined as either:

- Patient had last menstrual period within the last 12 months or
- If on tamoxifen or toremifene with in the past 14 days, plasma estradiol and FSH must be in the premenopausal range per local normal range, or
- In case of therapy induced amenorrhea, plasma estradiol and/or FSH must be in the premenopausal range per local normal range

- Patient has histological and/or cytological confirmed ER+ and/or PgR+ aBC
- Patient has confirmed HER2-negative advanced breast cancer (aBC)
- Patient has a PIK3CA mutation confirmed by Novartis designated central lab or patient has a pathology report confirming PIK3CA mutant status by certified laboratory (using validated PI3KCA mutation assay) either from tissue or blood and must (mandatory) send tumor tissue to Novartis designated central lab for confirmation of mutational status.
- Patient must have:

  a) Documented evidence of tumor progression on or after CDK 4/ 6 inhibitor combination treatment; CDK 4/6 inhibitor must be the last treatment regimen prior to study entry,

  b) AI treatment (either in adjuvant or metastatic setting) and received systemic chemotherapy or ET (as monotherapy or in combination except CDK 4/6i + AI) as last treatment regimen in cohort C

  c) Maintenance therapies, where applicable, must be regarded as part of the main treatment.

  d) No more than two (2) prior anti-cancer therapies for aBC

  e) Received no more than one prior regimen of chemotherapy in the metastatic setting

- Patient has either measurable disease per RECIST v1.1 or at least one predominantly lytic bone lesion must be present
- ECOG performance status ≤ 2
- Patient has fasting plasma glucose (FPG) ≤140 mg/dL (7.7 mmol/L) and glycosylated hemoglobin (HbA1c) ≤ 6.4% (both criteria have to be met)
- Patient has adequate bone marrow, coagulation, liver and renal function

Exclusion Criteria:

1. Patient has known hypersensitivity to alpelisib, fulvestrant or letrozole
2. Patient has received prior treatment with any PI3K inhibitors
3. Patient with an established diagnosis of diabetes mellitus type I or uncontrolled type II
4. Patient has a concurrent malignancy or malignancy within 3 years of study screening period, with the exception of adequately treated, basal or squamous cell carcinoma, non-melanoma skin cancer or curatively resected cervical cancer
5. Patient has received radiotherapy ≤ 4 weeks or limited field radiation for palliation ≤ 2 weeks prior to enrollment, and who has not recovered to grade 1 or better from related side effects of such therapy
6. History of acute pancreatitis within 1 year of screening or past medical history of pancreatitis
7. Patients with central nervous system (CNS) involvement unless they meet all of the following criteria:
    a. At least 4 weeks from prior therapy completion (including radiation and/or surgery) to starting the study treatment
    b. Clinically stable CNS tumor at the time of screening untreated or without evidence of progressions for at least 4 weeks after treatment as determined by clinical examination and brain imaging (MRI or CT) during screening period and stable low dose of steroids for 2 weeks prior to initiating study treatment
8. Patient with severe liver impairment (Child Pugh score B/C)
9. Patient has impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of the study drugs
10. Patient has documented pneumonitis/interstitial lung disease which is active and requiring treatment
11. Patient has a history of severe cutaneous reactions like Stevens-Johnson-Syndrome (SJS), Erythema Multiforme (EM), Toxic Epidermal Necroloysis (TEN) or Drug Reaction with Eosinphilia and Systemic Symptoms (DRESS).
12. Patient is concurrently using other anti-cancer therapy. All anti-cancer therapy must be discontinued prior to day one of study treatment.
13. Subjects with unresolved osteonecrosis of the jaw.

Intervention	**Experimental, Prior CDK 4/6 + aromatase**: Patients who received any Cyclin-Dependent Kinases 4 and 6 (CDK 4/6) inhibitor plus aromatase inhibitor as treatment (immediately prior) will receive alpelisib 500 mg oral + fulvestrant 500 mg intramuscular (i.m). (n=127, n=121 with centrally confirmed PIK3CA mutation and n=6 with PIK3CA mutations per local assessment). **Experimental, Prior CDK 4/6 + fulvestrant:** Patients who received any CDK 4/6 inhibitor plus fulvestrant as treatment (immediately prior) will receive alpelisib 300 mg oral + letrozole 2.5 mg oral. (n=81, n=73 with centrally confirmed PIK3CA mutation and n=8 with PIK3CA mutation per local assessment and participated in trial as per protocol). **Experimental, Prior systemic chemo or ET:** Patients who received systemic chemotherapy or endrocrine therapy (ET) , (including monotherapy or in combination with targeted therapy except CDK 4/6i + AI) as immediate prior treatment will receive alpelisib 300 mg oral + fulvestrant 500 mg i.m. (n=1, with centrally confirmed PIK3CA mutation). Still recruiting.

Table A2e Main study characteristics
BYLieve

Baseline characteristics

	Cohort A (n=127)
Age, years	
Mean (SD)	56·7 (10·7)
Median (IQR)	58 (48–65)
Range	33–83
<50	39 (31%)
≥50 to <65	56 (44%)
≥65	32 (25%)
Sex	
Female	127 (100%)
Race	
Asian	12 (9%)
Black	6 (5%)
White	81 (64%)
Missing	1 (1%)
Other	3 (2%)
Pacific Islander	1 (1%)
Unknown	23 (18%)
Ethnicity	
East Asian	7 (6%)
Hispanic or Latino	20 (16%)
Mixed ethnicity	1 (1%)
Not reported	32 (25%)
Other	42 (33%)
Russian	0
South Asian	3 (2%)
Southeast Asian	3 (2%)
Unknown	19 (15%)
Body mass index, kg/m²*	
Mean (SD)	26·1 (5·5)
Median (range)	25·3 (16·1–46·6)
Diabetic diagnosis status†	
Normal	68 (54%)
Prediabetic	48 (38%)
Diabetic	3 (2%)
Missing	8 (6%)
Menopausal status	
Premenopausal	28 (22%)
Postmenopausal	99 (78%)
ECOG performance status	
0	79 (62%)
1	41 (32%)
2	2 (2%)
Missing	5 (4%)

(Table 1 continues in next column)

	Cohort A (n=127)
(Continued from previous column)	
Stage at study entry	
III	3 (2%)
IV	124 (98%)
Lines of previous medical therapy in the metastatic setting‡	
0	15 (12%)§
1	89 (70%)
2	21 (17%)
3	2 (2%)
Lines of previous endocrine therapy in the metastatic setting	
0	15 (12%)§
1	98 (77%)
2	14 (11%)
Endocrine status at study entry¶	
Primary endocrine resistance	26 (21%)
Secondary endocrine resistance	76 (60%)
Endocrine sensitivity	1 (1%)
Previous exposure to fulvestrant or chemotherapy as first-line treatment in the metastatic setting	
Fulvestrant	0
Chemotherapy	8 (6%)
Current extent of disease, metastatic sites	
Bone	108 (85%)
Bone only	24 (19%)
Visceral	85 (67%)
Lung	43 (34%)
Liver	59 (46%)
Other	8 (6%)
Lymph nodes	37 (29%)
Skin	4 (3%)
Breast	5 (4%)
CNS	2 (2%)
Other	12 (9%)

Data are n (%), unless stated otherwise. Metastatic sites and number of organs involved were derived from case report form page of diagnosis and extent of cancer, if available. ECOG=Eastern Cooperative Oncology Group. *n=117. †Diabetic diagnosis status at baseline is defined per American Diabetes Association 2017.[34] ‡Two patients received three lines of therapy for advanced disease and were not eligible for the study. §Ten patients received a CDK4/6 inhibitor in the adjuvant setting, three patients in the neoadjuvant setting, and one patient in the palliative setting. One patient received medication in the metastatic setting, but was classified as having received zero lines of previous medical therapy in the metastatic setting due to inappropriate regimen coding. ¶If sufficient data were not available to determine endocrine status, patients were not coded.

Table 1: **Patient characteristics at baseline**

(12)

Primary and secondary endpoints

Primary outcomes are:

- The percentage of patients who are alive without disease progression (Time Frame: Date of first dose to approximately 6 months in last enrolling cohort). Assess the percentage of patients without disease progression based on local investigator assessment per RECIST in cohort A, cohort B and cohort C. Each cohort will be assessed when last patient in each cohort has reached 6 months, but final primary assessment will occur upon completion of 6 months of last enrolling cohort.

Secondary outcomes are:

	• Progression free survival (PFS) for each cohort (Time Frame: date of first dose to up to approximately 25 months). PFS is defined as the time from the date of first dose of study medication to the date of the first documented progression or death due to any cause occurring in the study. PFS will be assessed based on local investigator's assessment according to RECIST v1.1 • Progression free survival (PFS) on next line treatment PFS2) for each cohort (Time Frame: Date of first dose to date of first documented progression up to approximately 25 months). Progression free survival (PFS) on next line treatment (PFS2) is defined as time from the date of first dose of study medication to the date of first documented progression on next-line therapy or death from any cause. • Percentage of participants Overall response rate (ORR) for each cohort (Time Frame: Date of first dose and up to approximately 25 months). ORR based on local investigator's assessment according to RECIST v1.1 in each cohort. • Percentage of participants with clinical benefit rate (CBR) for each cohort (Time Frame: Date of first dose and up to approximately 25 months). Clinical Benefit Rate (CBR) based on local investigator's assessment according to RECIST v1.1 in each cohort. • Duration of response (DOR) (Time Frame: Date of first documented response to first documented progression or death up to approximately 25 months). Duration of Response is the time from the date of first documented response (confirmed CR or PR) to the date of first documented progression or death due to underlying cancer. Percentable of overall suvivial (OS) for each cohort (Time Frame: Date of first dose and up to approximately 25 months). Overall Survival is defined as the time of start of treatment to date of death or lost to follow-up.
Method of analysis	The primary endpoint was calculated with a one-sided 2.5% level of significance (two-sided 95% CIs) using the Clopper and Pearson exact method for each cohort separately to reject the null hypothesis. Thus, the primary endpoint was considered clinically meaningful if the lower bound of the 95% CI was more than 30%. Patients who progressed, died, or discontinued the study before 6 months were counted as event in the analysis. To have a power of more than 90% when the true proportion of patients alive and without progression at 6 months was at least 45%, the required sample size in each cohort was 112 patients (increased from 80 on approval of a protocol amendment, dated Jan 30, 2019). The overall response rate and clinical benefit rate were calculated based on the modified full analysis set and are summarised using descriptive statistics, along with two-sided exact binomial 95% CIs. Progression-free survival, overall survival, and time to response were estimated using the Kaplan-Meier method with 95% CI, with time to response calculated as part of the prespecified analysis of duration of response. Duration of response was calculated using Kaplan-Meier estimation. 95% CIs were calculated from PROC LIFETEST output using method of Brookmeyer and Crowley. For analysis of change from baseline, patients with measurable disease at baseline were included. (12)
Subgroup analyses	Overall response in the subset of patients with measurable disease at baseline was a prespecified analysis (n=100) (12). A post-hoc analysis compared progression-free survival with alpelisib plus fulvestrant in cohort A with a similar group of patients with PIK3CA-mutated advanced breast cancer treated with standard post-CDK4/6 inhibitor treatments in the real-world setting. This study used the de-identified, electronic health record-derived, nationwide US-based Flatiron Health-Foundation Medicine advanced breast cancer Clinico-genomic Database (CGDB) for patients who met relevant inclusion criteria consistent with those of the BYLieve cohort A (PIK3CA mutation, ≤2 previous treatment lines for advanced breast cancer, and no more than one previous line of

	chemotherapy for advanced breast cancer; previous exposure to CDK4/6 inhibitor; and no fulvestrant exposure) (42).

12.3 Results per study

Table A3a Results of study SOLAR-1											
Trial name:	SOLAR-1 (PIK3CA mutated population except for safety data)										
NCT number:	NCT02437318										
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
mOS for PIK3CA mutated cohort	Alpelisib + Fulvestrant	169	39.3 months (34 .1-44.9)	7.9 months	-	-	HR=0.86	0.64-1.15	P=0.15	OS was analysed using Kaplan Meier methodology, and Cox regression, adjusted for stratification parameters, to estimate HR and 95% CIs. OS is defined as the time from date of randomization to date of death due to any cause, and evaluated using a one-sided stratified log-rank test and was carried out with an O'BrieneFleming efficacyboundary of P≤0.0161	(11)
	Placebo + Fulvestrant	172	31.4 months (26.8-41.3)								

Table A3a Results of study SOLAR-1										
mPFS for PIK3CA mutated cohort	Alpelisib + Fulvestrant	169	11.0 months (7.5-14.5)	5.3 months	-	-	HR=0.65	0.50-0.85	<0.001	Primary outcomes are Progression-free Survival (PFS) Per Investigator Assessment in the PIK3CA Mutant Cohort. PFS was be assessed via a local radiology assessment according to RECIST 1.1.	(5)
	Placebo + Fulvestrant	172	5.7 months (3.7-7.4)								
mPFS for PIK3CA mutated cohort	Alpelisib + Fulvestrant	115	7.4 months (5.4-9.3)	1.8 months	-	-	HR=0.85	0.58-1.25	Posterior probability of hazard ratio <1.00, 79.4%	Primary outcomes are Progression-free Survival (PFS) Per Investigator Assessment in the PIK3CA Mutant Cohort. PFS was be assessed via a local radiology assessment according to RECIST 1.1.	(5)
	Placebo + Fulvestrant	116	5.6 months (3.9-9.1)								
HRQoL-QC30	Alpelisib + Fulvestrant	169	mTTD 14.8 moths		-	-	HR=1.03	0.72-1.48	-	Time to deterioration in Global Health Status/QoL and Physical, Emotional, and Social functioning was defined as a	(21)

Table A3a Results of study SOLAR-1						
for PIK3CA mutated cohort	Placebo + Fulvestrant	172	mTTD 14.8 months			worsening in score by >10% compared with baseline with no later improvement above this threshold during the treatment period or death because of any cause, as supported by EORTC QLQ-C30 interpretation guidelines

Table A3a Results of study SOLAR-1											
Global Health Status/QoL for PIK3CA mutated cohort	Alpelisib + Fulvestrant LS Mean Change From Baseline (95% CI)	169	Change from baseline over time -3.5 (-8.02-1.02)	3.77	-	-	Overall treatment difference -3.77	-8.35-0.80	Overall treatment status P=0.101	Over time, there was a numeric decrease in Global Health Status/QoL scores relative to baseline in both treatment arms. There was no overall change from baseline over time in the alpelisib treatment arm (-3.50; 95% CI, -8.02 to 1.02) or the placebo treatment arm (0.27; 95% CI, 24.48 to 5.02). No statistically significant between-group differences were observed in patterns of change over time (Fig 1A in publication) (21). Similarly, overall treatment effect in Global Health Status/QoL was not statistically significant between both treatment arms (-3.77; 95% CI, -8.35 to 0.80; P 5 .101; Fig 1A in publication) (21)	(21)
	Placebo + Fulvestrant LS Mean Change From Baseline (95% CI)	172	0.27 (-4.48-5.02)								
mOS in patients with lung	Alpelisib + Fulvestrant	84	37.2 months (28.7-43.6)	14.4 months	-	-	HR=0.68	0.46-1.00	-	data cut-off April 23, 2020 Kaplan Meier methodology, and Cox regression, adjusted	(11)

Table A3a Results of study SOLAR-1											
and/or liver metastases (sub-group) for PIK3CA mutated cohort	Placebo + Fulvestrant	86	22.8 months (19.0-26.8)							for stratification parameters, to estimate HR and 95% CIs	
mOS in patients with a PIK3CA mutation in ctDNA PIK3CA mutated (explorative endpoint)	Alpelisib + Fulvestrant	92	34.4 months (28.7-44.9)	9.2 months	-	-	HR:0.74	0.51-1.08	-	Kaplan Meier methodology, and Cox regression, adjusted for stratification parameters, to estimate HR and 95% CIs	(11)
	Placebo + Fulvestrant	94	25.2 months (20.7-29.6)								
mPFS in endocrine	Alpelisib + Fulvestrant	143	9.4 months (7.0-12.9)	5.2 months	-	-	HR=0.64	0.48-0.84	-	Using a data cut-off date of 12 Jun 2018	(55)

Table A3a Results of study SOLAR-1										
resistant population (sub-group) for PIK3CA mutated cohort	Placebo + Fulvestrant	149	4.2 months (3.6-7.3)						Note that between abstract and publication there were minor corrections in number of patients defined as endocrine resistant and endocrine sensitive.	
Safety for PIK3CA mutated cohort	Alpelisib + Fulvestrant	284	Any AE Grade 3-4 76%	- 40.5%	CI: 33.1%-47.9%	-	-	-	Safety was assessed continuously, per the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.03, in the safety population (mutant and non-mutant cohorts) until 30 days after the last dose of study treatment, as previously reported.	(18)
	Placebo + Fulvestrant	287	Any AE Grade 3-4 35.5%							

Table A3a Results of study MONARCH-2	
Trial name:	MONARCH-2

Table A3a Results of study MONARCH-2											
NCT number:	NCT02107703										
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
mOS ITT population	Abemaciclib +fulvestrant	446	46.7 months (CI Not Reported)	9.4 months	-	-	HR=0.757	0.606–0.945	0.01	The median survival is based on the Kaplan–Meier estimator. The HR is based on a Cox proportional hazards model with adjustment for stratification, and study arm.	(23)
	Placebo + fulvestrant	223	37.3 months (CI Not Reported)								
mPFS ITT population	Abemaciclib +fulvestrant	446	16.4 months (14.4 - 19.3)	7.1 months	-	-	HR=0.553	0.449–0.681	<0.001	The survival rates are based on the Kaplan–Meier estimator. The HR is based on a Cox proportional hazards model with	(14)

Table A3a Results of study MONARCH-2

	Placebo + fulvestrant	223	9.3 months (7.4 - 11.4)						adjustment for stratification, and study arm.	
		PIK3CA mutant	PIK3CA WT	PIK3CA mutant	PIK3CA WT					(7)
mPFS differences between PIK3CA mutant and wild-type populations within each treatment arm	Abemaciclib + Fulvestrant (Mut: n= 58) (WT: n=91)	15 (9.4-NA)	20 (14-NA)	9.3	7.3		Mut HR: 0.46 WT HR=0.68	Mut (0.24-0.78) WT (0.42-1.09)	-	
	Fulvestrant (Mut: n=38) (WT: n=51)	5.7 (3.8-15)	12.7 (7.9-NA)							
Safety ITT population	Abemaciclib +fulvestrant	441	Any AE Grade 3+4 60.5%	37.7%	CI: 30.5%-44.9%	-	-	-	-	(14)

Table A3a Results of study MONARCH-2										
	Placebo + fulvestrant	223	Any AE Grade 3+4 22.8%							
	Abemaciclib +fulvestrant	446	16.8 months						Time to deterioration of modified Brief Pain Inventory, Short Form "worst pain" and increased analgesic use.	(24)
HRQoL mTTD ITT population	Placebo + fulvestrant	223	11.9 months	4.9 months	-	-	HR= 0.9	0.707-1.145	0.4	TTSD was defined as a ≥ 10-point deterioration compared with a patient's baseline score, followed by all subsequent scores meeting the MID criteria compared with baseline. The ≥10-point criteria was based on established thresholds for EORTC QLQ-C30 MID.	

Table A3a Results of study MONARCH-2										
mOS in patients with lung and/or liver metastases (sub-group from ITT population)	Abemaciclib + fulvestrant	245	40.3 months (CI: Not reported)	8.1 months	-	-	0.675	0.511-0.891	-	(23)
	Placebo + fulvestrant	128	32.2 months (CI: Not reported)							

Table A3a Results of study PALOMA-3											
Trial name:	PALOMA-3										
NCT number:	NCT01942135										
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
mOS ITT population	Palbociclib + fulvestrant	347	34.9 months (28.8 - 40.0)	6.1 months	Not reported		HR=0.81	0.64-1.03	0.09	*The median survival is based on the Kaplan–Meier estimator. The HR is based on a Cox proportional hazards model with adjustment for stratification, and study arm.*	(26)
	Placebo + fulvestrant	174	28.0 months (23.6 - 34.6)								
mPFS ITT population	Palbociclib + fulvestrant	347	9.5 months (9.2-11.0)	4.9 months	Not Reported		HR=0.46	0.36-0.59	<0·0001	*The survival rates are based on the Kaplan–Meier estimator. The HR is based on a Cox proportional hazards model with adjustment for stratification, and study arm.*	(25)
	Placebo + fulvestrant	174	4.6 months (3.5-5.6)								

Table A3a Results of study PALOMA-3

		PIK3CA mutant	PIK3CA WT	PIK3CA mutant	PIK3CA WT		(25)
mPFS differences between PIK3CA mutant and wild-type populations within each treatment arm	Palbociclib + Fulvestrant (Mut: n=85) (WT: n=180)	9.5 months (5.7-11.2)	9.9 months (9.2-13.9)	5.9 months	5.3 months		
	Fulvestrant (Mut: n=44) (WT: n=86)	3.6 (1.9-5.6)	4.6 (3.4-7.3)				
EORTC QLQ-C30	Palbociclib + fulvestrant	334	66.1 (64.5–67.7)	-		The PRO -evaluable population is defined as a	(28)

Table A3a Results of study PALOMA-3									
Global QoL ITT population				3.1 months	Not Reported		HR=0.641	0.45-0.91	0.0065	subset of ITT participants, who have completed a baseline and at least one post -baseline PRO assessment prior to end of study treatment. Analysis based on repeated measures mixed-effects model with an intercept term, treatment, time, treatment-by-time, and baseline as covariate. EORTC QLQ-C30 for patients with events	
	Placebo + fulvestrant	166	63.0 (60.6–65.3)								
mOS in patients with lung and/or liver metastases (sub-group)	Palbociclib + Fulvestrant (n=206)	27.6 months (24.4-31.2)		2.9 months	-	-	HR=0.85	0.64-1-13	-		(25)
	Fulvestrant (n=105)	24.7 months (20.8-31.8)									

Table A3a Results of study PALOMA-3

Safety ITT population	Palbociclib + fulvestrant	345	Grade 3-4 reported in 251 (73%)	51%	CI: 42.9%-58.4%	-	-	-	-	(25)
	Placebo + fulvestrant	172	Grade 3-4 reported in 38 (22%)							

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Table A3a Results of study MONALEESA-3											
Trial name:	MONALEESA-3										
NCT number:	NCT01942135										
				Estimated absolute difference in effect			**Estimated relative difference in effect**			**Description of methods used for estimation**	**References**
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
mOS updated analysis ITT population	**Ribociclib + Fulvestrant**	484	53.7 months (46.9-NR)	12.2 months	-	-	HR=0.726	0.588–0.897		Kaplan–Meier method was applied to estimate rates of overall survival. The treatment effect (hazard ratio (HR) with two-sided 95% confidence interval) was analyzed using a Cox proportional hazards model overall and in predefined subgroups.	(30)
	Placebo + Fulvestrant	242	41.5 months (37.4-49.0)								
mPFS ITT population	Ribociclib + Fulvestrant	265	20.5 months (18.5-23.5)	7.7 months	-	-	HR=0.593	0.48-0.732	<0.001	Kaplan–Meier method was applied to estimate rates of progression free survival. The treatment effect (hazard ratio	(8)

Table A3a Results of study MONALEESA-3

	Placebo + Fulvestrant	163	12.8 months (10.9-16.3)						(HR) with two-sided 95% confidence interval) was analyzed using a Cox proportional hazards model overall and in predefined subgroups.	
mPFS differences between PIK3CA mutant and wild-type populations within each treatment arm	Ribociclib + Fulvestrant (Mut: n=75/135) WT n=108/265) Fulvestrant (Mut: n=49/76) WT n=70/124)	PIK3CA mutant 16.36 months (11.01-19.09) 11.1 months (5.32-14.69)	PIK3CA WT 22.34 months (18.79-NA) 16.49 months (10.87-19.38)	PIK3CA mutant 5.26 months	PIK3CA WT 5.65 months	-	Mut HR=0.75 WT HR=0.67	0.52-1.08 0.49-0.91	-	(31)

Table A3a Results of study MONALEESA-3										
EORTC QLQ-C30 global health/QOL scores at baseline	Ribociclib + Fulvestrant Fulvestrant	447 224	65.5 (±19.1 68.4 (±18.5)	2.9			--			(32)
TTD ≥10% in global HRQoL ITT population	Ribociclib + Fulvestrant Placebo + Fulvestrant	159/484 83/242		76	-	-	HR=0.81	0.60-1.1	-	Kaplan–Meier method was applied to estimate rates of overall survival. The treatment effect (hazard ratio (HR) with two-sided 95% confidence interval) was analyzed using a Cox proportional hazards model overall and in predefined subgroups.	(32)
mOS in patients with lung and/or liver metastases (sub-group)	Ribociclib + Fulvestrant Fulvestrant	46.9 months (38.1-NR) 39.4 months (29.9-44.9)		7.5 months	-		0.73	0.55-0.98	-		(30)

Table A3a Results of study MONALEESA-3											
Safety ITT population	Ribociclib + Fulvestrant	483	Grade 3-4 reported in 78.3%	48.8%	CI: 42.0%-55.6%	-	-	-	-	-	(56)
	Placebo + Fulvestrant	241	Grade 3-4 reported in 29.5%								

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Table A3a Results of study BYLieve											
Trial name:	BYLlieve (CBYL719X2402) Cohort A a non-comparative study										
NCT number:	NCT03056755										
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
>30% alive and without progression at 6 months PIK3CA mutated population (Cohort A)	Alpelisib + fulvestrant	127	50.4% (41.2-59.6)	-	-	-	-	-	-	The primary endpoint was calculated with a one-sided 2·5% level of significance (two-sided 95% CIs) using the Clopper and Pearson exact method for each cohort separately to reject the null hypothesis of no treatment effect, or proportion of patients alive and without progression at 6 months was 30% or less. Thus, the primary endpoint was considered clinically meaningful if the lower bound of the 95% CI was more than 30%.	(12)

Table A3a Results of study BYLieve											
mPFS PIK3CA mutated population (Cohort A)	Alpelisib + fulvestrant	127	7.3 months (59%) CI: 5.6-8.3)	-	-	-	-	-	-	Progression-free survival were estimated using the Kaplan-Meier method with 95% CI, with time to response calculated as part of the prespecified analysis of duration of response.	(12)
mPFS differences between PIK3CA mutant and wild-type populations within each treatment arm	Alpelisib + Fulvestrant (Mut: n=127)	PIK3CA mutant 7.3 (5.6-8.3)	PIK3CA WT N/A	PIK3CA mutant Months N/A	PIK3CA WT Months N/A						(12)
Safety PIK3CA mutated population (Cohort A)	Alpelisib + fulvestrant	127	Grade 3-4 85 (67%) CI: 58.7-75.1%*	-	-	-	-	-	-	* For BYLieve it is calculated as CI to the mean for the single-arm (Fulvestrant + alpelisib)	(12)

13 Appendix B - Systematic Literature Review

See attached file: Alpelisib SLR Report_Medicinrådet_Final_20072021

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14 Appendix C - Plots of Schoenfeld Residuals

Smoothed curves were fit to Schoenfeld residuals for PFS for subgroups of the PIK3CA cohort in SOLAR-1 trial, as shown in Figure 17.The smoothed curve fit to Schoenfeld residuals for the ET-resistant subgroup is downward sloping during the first 8 months but is approximately linear after month 9. The p-value on the test of non-proportionality for this group is not statistically significant at a significance level of 0.05.

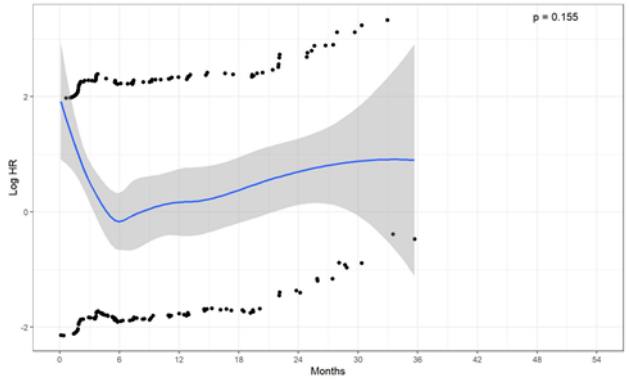

Figure 17. Plot of Smoothed Curve fit to Schoenfeld Residuals for PFS, SOLAR-1

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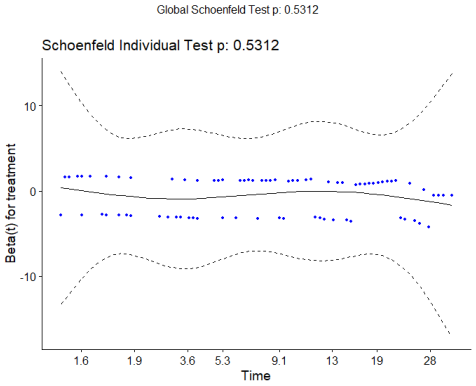

Plots of smoothed curves fit to Schoenfeld residuals for PFS for subgroups in the MONALEESA-3 trials are shown in Figure 18. The smoothed curve fit to Schoenfeld residuals oscillates up and down during follow-up, but the p-value is not statistically significant.

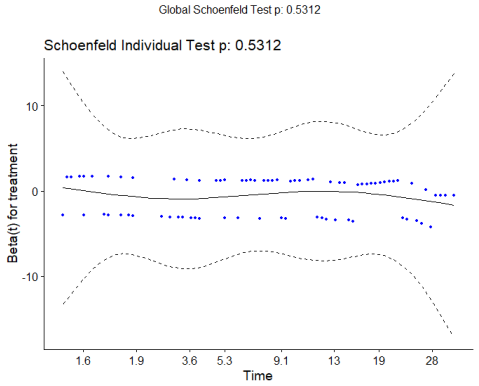

Figure 18. Plot of Smoothed Curve fit to Schoenfeld Residuals for PFS, MONALEESA-3

In Figure 19, a smoothed curve was fit to Schoenfeld residuals for PFS for patients enrolled in MONARCH-2. The smoothed curve has a relatively constant slope throughout much of the follow-up period and the p-value is not statistically significant, which suggests the PH assumption may be reasonable.

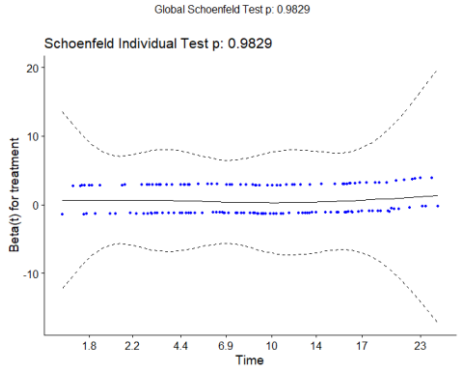

Figure 19 of Smoothed Curve fit to Schoenfeld Residuals for PFS, MONARCH-2

In Figure 20, a smoothed curve was fit to Schoenfeld residuals for PFS for the PIK3CA mutant subgroup of PALOMA-3. The slope of the curve is increasing slightly after approximately month 3 but the p-value on the test of non-proportionality is not significant, suggesting the PH assumption may be reasonable.

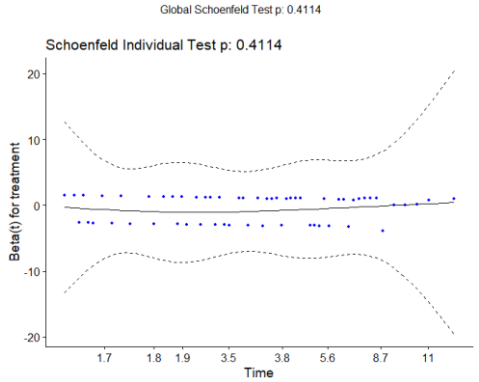

Figure 20. Plot of Smoothed Curve fit to Schoenfeld Residuals for PFS, PALOMA-3

Smoothed curves were fit to Schoenfeld residuals for OS of the PIK3CA cohort in SOLAR-1 trial, as shown in Figure 21. The p-values for the tests of non-proportionality are not significant.

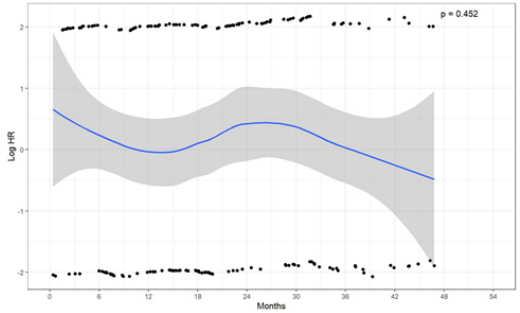

Figure 21. Plot of Smoothed Curve fit to Schoenfeld Residuals for OS, SOLAR-1

Figure 22 displays smoothed curves fit to Schoenfeld residuals for OS in MONALEESA-3. The p-values for the PIK3CA mutated subgroup is not statistically significant, suggesting the PH assumption may be reasonable for OS.

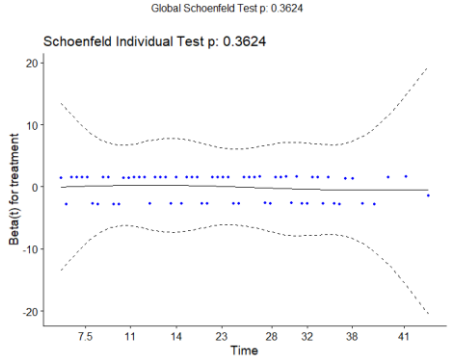

Figure 22. Plot of Smoothed Curve fit to Schoenfeld Residuals for OS, MONALEESA-3

In Figure 23, we present smoothed curves fit to Schoenfeld residuals for OS in MONARCH-2. The curve appears to be slightly upward sloping, but the p-value is not statistically significant at a significance level of 0.05, suggesting the PH assumption is not violated.

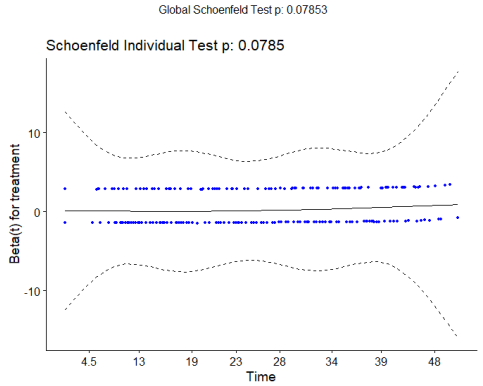

Figure 23. Plot of Smoothed Curve fit to Schoenfeld Residuals for OS, MONARCH-2

K-M plots of OS were not available for the PIK3CA mutant subgroup of PALOMA-3. In Figure 24, smoothed curves fit to Schoenfeld residuals for OS among the ITT population of PALOMA-3. The smoothed curve fit to Schoenfeld residuals is approximately linear throughout follow-up and the p-value is not statistically significant, suggesting the PH assumption would be valid.

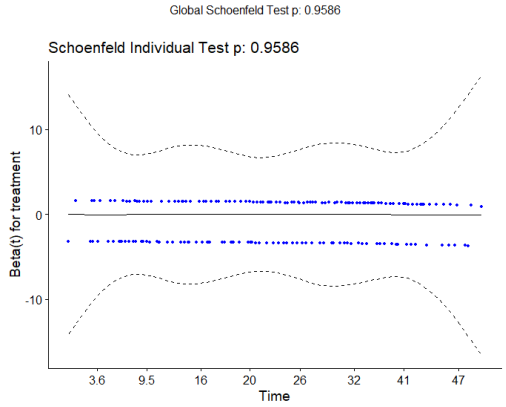

Figure 24. Plot of Smoothed Curve fit to Schoenfeld Residuals for OS, PALOMA-3

Application for the assessment of Piqray(R) for postmenopausal women, and men, with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer with a PIK3CA mutation

Economic section

1 Abbreviations 2
2 Economic comparison 3
2.1 Medication costs 3
2.1.1 Dosing 3
2.1.2 Drug costs 4
2.2 Relative dose intensity 4
2.3 Treatment duration 5
2.4 Patient costs 5
2.5 Health care costs 5
2.6 Adverse events 6
2.7 Cost of testing 8
2.8 Table of key assumptions 8
2.9 Results 8
2.9.1 Economic analysis on first line – Clinical question 1 8
2.9.2 Economic analysis on second line (post-CDK4/6 population) – Clinical question 2 9
2.10 Sensitivity analyses 11
2.10.1 Drug wastage 11
2.10.2 Cost of testing 12
2.10.3 Treatment duration 13
3 Budget impact 14
3.1 Sensitivity analysis 17
3.2 Conclusions of budget impact analysis 18
4 References 19

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1 Abbreviations

Abbreviation	Full form
aBC	Advanced breast cancer
ADL	Activities of daily living
AE	Adverse event
CDK4/6i	cyclin-dependent kinase 4 and 6 inhibitor
CTCAE	Common Terminology Criteria for Adverse Events
DRG	Diagnose related grouping
EPAR	European Public Assessment Report
HCP	Health care professional
HR+	Hormone receptor positive
HER2-	human epidermal growth factor receptor 2 negative positive
ITC	Indirect treatment comparison
IV	Intravenous
PCR	Polymerase chain reaction
PIK3CA	Phosphatidylinositol-4,5-Bisphosphate 3-Kinase Catalytic Subunit Alpha
PPP	Pharmacy purchase price
RDI	Relative dose intensity

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1.1 Economic comparison

As shown in the indirect treatment comparison (ITC) of the three CDK4/6 inhibitors (see medical section), the differences in effect are minimal and within margins of error. Based on the ITC a comparable effect can be assumed, and a cost comparison has been provided to represent the financial impact of choosing between CDK4/6 inhibitors (represented by Verzenios® as it is the current 1st choice of the three CDK4/6 inhibitors) and alpelisib (Piqray®) in the first line treatment of PIK3CA mutated HR+/HER2- advanced breast cancer (aBC) (clinical question 1). An overview of the patient population is not described in this report. For further information on the clinical characteristics of the patient population see the medical part of the application.

A cost comparison against mono fulvestrant and chemotherapy is also provided, as it represents treatment in the post-CDK4/6 population (clinical question 2). For this analysis it was assumed that 90% of patients would receive fulvestrant and 10% would receive chemotherapy. It should be noted that there is a difference of effect in the post CDK4/6 setting. Due to a small sample size, this difference has not been possible to implement into a full health economic model. However, a simplified analysis is presented.

All costs within the analysis are assumed to occur within the first year of treatment, as the median time on treatment is less than 6 months, and those patients with prolonged treatment would not have a significant impact on the overall results. As such, survival times and the required extrapolations of effects are not included.

The timeframe of the economic models is the mean treatment length from BYLieve and SOLAR-1. These are both less than a year and as a result, the timeframe of the model is less than a year. Due to the model, only evaluating costs which occur within a year, a simple one-off cost for the different variables has been used and no state transitions are included in the model. The cycle length used for the cost calculations was chosen to match the cycle length of each drug of choice, being 28 days for alpelisib + fulvestrant, abemaciclib + fulvestrant and mono fulvestrant therapy. For chemotherapy, a cycle of 21 days was used since capecitabin was chosen as the relevant chemotherapy.

For a more complete overview of the incremental costs for each cost group, please see the attached Excel® model "Cost comparison and Budget impact analysis, Alpelisib – chemo included".

1.2 Medication costs

1.2.1 Dosing

Fulvestrant is administered subcutaneously and requires a visit to the hospital. It is injected to the buttocks (1-2 minutes) as two 5 mL injections and can be administered during an outpatient visit. The dosing schedule for fulvestrant is the same whether given alone [1] or in combination with alpelisib [2] or abemaciclib [3]. In the first cycle 500 mg of fulvestrant is administered on day 1 and 15. For the subsequent cycles 500 mg of fulvestrant is administered once on day 1 of every cycle.

Piqray® is taken orally once every day as two simultaneous 150 mg tablets [3] and therefore incurs no further administration costs. The same is true for Verzenios®, which is taken orally twice daily as 150 mg tablets [3].

For chemotherapy, capecitabin was chosen based on health care professional (HCP) opinion. In earlier lines, paclitaxel may be a treatment option, however chemotherapy would not be cycled and consequently paclitaxel is not an option this late in the treatment algorithm. According to the EPAR of Xeloda [4], capecitabin should be administered at 1250 mg per m^2 body surface area for 14 days followed by a 7-day rest period. Additionally,

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docetaxel should be administered at 75 mg per m^2 body surface area for 1 hour intravenously once every 21 days [4].

Drug holiday

Due to either the physician's or the patient's decision, e.g., in case of a serious adverse event, the patient could stop the treatment temporarily. At re-initiation of treatment, patients would most often have their dose adjusted. Thus, for a subset of patients included in SOLAR-1, some patients had a temporarily stop from alpelisib+fulvestrant or mono-fulvestrant, which was noted as a drug holiday [2]. This is also in line with the SmPC of abemaciclib [3]. Drug holiday was taken into consideration and included in the calculation of mean RDI, which is further described in section 1.3.

Table 1. Dosing schedule and cost of administration for fulvestrant, Verzenios®, Piqray®, capecitabin and docetaxel

Brand name	Dosing	Administration	Cost /DKK	DRG
Fulvestrant «TEVA»	Cycle 1: day 1 and 15 Cycle 2+: Day 1	Subcutaneous	1735	09MA98
Verzenios®	Twice daily	Oral	0	NA
Piqray®	Once daily	Oral	0	NA
Capecitabin	Every day for 14 days, 7 days rest	Oral	0	NA
Docetaxel	Once every 3 weeks	Intravenous	1735	09MA98

1.2.2 Drug costs

Drug costs were sourced from medicinpriser.dk and no discounts are applied to the PPP [5]. A mean body surface area of 1.74 was used when calculating the costs for chemotherapy [6].

Table 2. Drug costs used for the economic comparison and the budget impact analysis [7].

Brand name	Cycle	Strength	Amount in package	Generic name	Price per pack (PPP) /DKK	Price per cycle
Fulvestrant «TEVA»	1	250 mg	2 inj. solutions	Fulvestrant	4 310.00	8 620.00
	2+	250 mg	2 inj. solutions	Fulvestrant	4 310.00	4 310.00
Verzenios®	1+	150 mg	56 tablets	Abemaciclib	19 443.37	19 443.37
Piqray®	1+	150 mg	56 tablets	Alpelisib	24 730.14	24 730.14
Capecitabin «accord»	1+	500 mg	120 tablets	Capecitabin	250.00	419.07
Capecitabin «stada»	1+	150 mg	60 tablets	Capecitabin	199.00	
Docetaxel «accord»	1+	160 mg	8 ml	Docetaxel	309.00	252.03

1.3 Relative dose intensity

A regular relative dose intensity (RDI) calculation is not relevant for the economic comparison, as both products have flat pricing (same cost per pack independent of strength). A reduction in dose will therefore not surmount to a reduction in costs and should be excluded from the calculation.

In order to calculate the dose reductions from drug holidays only, $RDI_{drug\ holiday}$ is calculated. $RDI_{drug\ holiday}$ is derived by subtracting "dose intensity" from "average dose" to find the impact on RDI exclusively from drug holidays.

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For alpelisib, the mean dose intensity was 240.1 mg/day, and the average daily dose was 272.0 [8].

Through this we get:

$$RDI_{drug\ holiday,alpelsib} = \frac{300 - (272.0 - 240.1)}{300} = 89.37\%$$

The RDI for abemaciclib in MONRACH-2 was 91.03 % [9]. The publication does not specify whether this was median or mean, but as median is most often reported, it is assumed to be the case. In comparison, the median RDIs for ribociclib and palbociclib in MONALEESA-3 and PALOMA-3 were 92.1 % and 93.0 % respectively [10] [11]. In order to include the mean RDI of abemaciclib excluding down dosing, a similar calculation was performed. Data is not publicly available for abemaciclib, so data on palbociclib is used instead, as both have a flat price per pack.

The mean RDI, excluding drug holidays, for palbociclib [12] in PALOMA-3 was:

$$RDI_{drug\ holiday,palbociclib} \frac{125-(116,8-0,868*125)}{125} = 93.4\%$$

The median RDI for palbociclib is 93.0 %. Since the median and the mean values are so close to one another, it was decided to use the median RDI for abemaciclib as a proxy for the mean RDI excluding dose adjustment.

For fulvestrant and chemotherapy, RDI was assumed to be 1.

1.4 Treatment duration

The length of treatment used in the economic comparison was taken from SOLAR-1 to represent the average time on treatment, when treating HR+/HER2- PIK3CA mutated aBC with either alpelisib or abemaciclib + fulvestrant in the first line setting. For treatment in the post-CDK4/6 setting, average time of treatment data was taken from BYLieve for alpelisib + fulvestrant, fulvestrant monotherapy and chemotherapy.

For Clinical question 1, in SOLAR-1, the median drug exposure was 5.5 months, which was chosen for both abemaciclib and alpelisib. For the same patients, the median time on fulvestrant was 8.2 months. [8]

For Clinical question 2, in BYLieve the median drug exposure was 5.1 months for alpelisib and 6.5 months for fulvestrant. As mono fulvestrant was not included in BYLieve, we applied 5.1 months for both fulvestrant, chemotherapy and alpelisib + fulvestrant in the economical comparison. [13]

Lastly, all data on treatment duration was changed from months to 21 days or 28 days cycles depending on regiment, when used for the calculations in the model.

1.5 Patient costs

No costs of travel for patients are included in the analysis, as the time consumption related to each treatment is fairly similar, with each option taking an hour or less.

1.6 Health care costs

To represent the overall costs associated with the treatment of PIK3CA mutated HR+/HER2- advanced breast cancer, a simple cost model was created. In this model the costs of treatment initiation, follow-up care, adverse events and testing are included.

For fulvestrant, alpelisib and abemaciclib, the cost of treatment initiation and follow-up care was set to 3470 DKK and 1735 DKK, respectively, representing an outpatient visit in the MDC09 category [14]. General check-ups were

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assumed to occur during treatment administration days. Therefore, the cost of follow-up for docetaxel was set to DKK 1735 once per cycle (21 days). Per the same logic, the cost of follow-up for alpelisib, abemaciclib and fulvestrant alone was set to DKK 1735. For completeness, the cost of blood-glucose testing was included for alpelisib. In the initial cycle, the cost of a blood-glucose measuring device was included at DKK 269 [15]. In the follow-up setting, the cost of monitoring blood-glucose was set to equal the strips needed to perform the tests (DKK 131.40 for 200 strips) [16]. No costs related to training in blood-glucose measurement were included, as training was assumed to be handled during the initial consultations. It should be noted that the cost of blood-glucose testing is sourced from an online dispensary and the actual costs may differ. However, the effect of these costs on the results are minute. Testing costs are likely captured in the DRG of an outpatient visit and are therefore estimated to be 0 in terms of DRG coding for the individual patient.

According to guidelines on methodology [17], no discounting was applied to any costs as they were all expected to occur within the first year of treatment.

Table 3. Health care costs related to treatments included in the economic model.

	Cost /DKK	Source
Initiation of therapy, fulvestrant, alpelisib and abemaciclib	2 x 1735 = 3470	[14]
Follow-up care, fulvestrant, alpelisib and abemaciclib, chemotherapy	1735	[14]
Initiation of therapy, chemotherapy	1735	[14]
Blood-glucose measuring device	269	[15].
Blood-glucose test strips	131.40 / 200 pcs.	[16].

1.7 Adverse events

The cost of treating adverse events are based on DRG rates. Where the CTCAE criteria for adverse events advised hospitalization or intervention, a more costly DRG was chosen. E.g., Stomatitis: "IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated" versus Fatigue "Fatigue not relieved by rest, limiting self-care ADL" [18]. Otherwise, these costs were assumed equal to those of an outpatient contact. The rates of treatment related adverse events were sourced from the respective studies and EPARs. Chemotherapy related grade 3 and 4 AEs were not obtainable through the EPAR of Xeloda [4] and have been conservatively assumed to be equal to the AE rates of mono fulvestrant therapy. As with healthcare costs, all costs are assumed to occur within the first year of treatment, and consequently no discounting has been applied [1] [4] [3] [2] [9] [19].

Table 4. Rate and costs of grade 3 and 4 adverse events used in economic comparison [14] applied [1] [4] [3] [2] [9] [19]. [18].

Adverse Event	Alpelisib + Fulvestrant	Abemaciclib + Fulvestrant	Fulvestrant	Cost	DRG code	DRG text
Abdominal pain	0.00 %	2.50 %	0.00 %	1 735	09MA98	MDC09, Sammedagspakke
Anemia	4.90 %	7.20 %	1.68 %	4 732	16PR02	Transfusion af blod, øvrig
Decreased leukocyte count	0.00 %	8.80 %	0.32 %	1 735	09MA98	MDC09, Sammedagspakke
Diarrhea	7.00 %	11.70 %	0.47 %	1 735	09MA98	MDC09, Sammedagspakke
Dyspnea	0.00 %	2.70 %	0.00 %	1 735	09MA98	MDC09, Sammedagspakke
Fatigue	5.60 %	2.30 %	0.00 %	1 735	09MA98	MDC09, Sammedagspakke
Hyperglycemia	36.60 %	0.00 %	0.60 %	1 735	09MA98	MDC09, Sammedagspakke
Hypertension	4.60 %	0.00 %	0.00 %	1 735	09MA98	MDC09, Sammedagspakke
Hypokalaemia	6.30 %	0.00 %	0.00 %	31 983	23MA05	Anden kontaktårsag til sundhedsvæsenet
Hypocalcaemia	2.10 %	0.00 %	0.00 %	31 983	23MA05	Anden kontaktårsag til sundhedsvæsenet
Increased ALT	4.20 %	5.10 %	1.80 %	1 735	07MA14	MDC09, Sammedagspakke
Increased AST	0.00 %	2.90 %	0.00 %	1 735	09MA98	MDC09, Sammedagspakke
Infection	0.00 %	6.20 %	0.00 %	52 345	04MA05	Infektioner og betændelse i luftveje, pat. mindst 65 år
Leukopenia	0.00 %	8.80 %	0.00 %	0	NA	Lab value
Lymfopenia	0.00 %	3.10 %	0.00 %	0	NA	Lab value
Nausea	2.80 %	2.10 %	0.00 %	5 297	06MA11	Malabsorption og betændelse i spiserør, mave og tarm, pat. mindst 18 år, u. kompl. bidiag.
Neutropenia, asymptomatic	0.00 %	25.40 %	0.00 %	1 735	09MA98	MDC09, Sammedagspakke
Rash	19.40 %	0.00 %	0.00 %	1 735	09MA98	MDC09, Sammedagspakke
Stomatitis	2.50 %	0.50 %	0.00 %	52 345	04MA05	Infektioner og betændelse i luftveje, pat. mindst 65 år
Thrombocytopenia	0.00 %	3.20 %	0.00 %	0	NA	Lab value
Venous thromboembolism	0.00 %	2.00 %	0.00 %	1 735	09MA98	MDC09, Sammedagspakke.
Total costs	**DKK 5 718**	**DKK 5 059**	**DKK 135**			

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1.8 Cost of testing

The cost of testing was sourced from the DRG list and DRG 31PR03: "Genetisk risikovurdering og rådgivning" [14] was chosen as the most appropriate cost. The total cost of this DRG is 3 444 DKK. The proportion of positive tested patients is assumed at 36.43 % [20] resulting in a total cost per identified patient of $\frac{1}{36.40\%} xDKK\ 3\ 444 = DKK\ 9\ 461.54$.

1.9 Table of key assumptions

Table 5. Table of key assumptions in the economic analysis.

Basic Assumptions	Base-case
Model type	Economic comparison
Time horizon	Less than 1 year
Discount rate	NA
Included costs	Medication costs Health care costs Cost of adverse events
Dosing	Not relevant
Additional lines of treatment	No

1.10 Results

The results of the economic analysis regarding clinical question 1 and 2 are presented below.

1.10.1 Economic analysis on first line – Clinical question 1

With the above assumptions, using pharmacy purchase prices, the cost difference of treating patients with PIK3CA mutated HR+/HER2- aBC with Piqray® compared to Verzenios® is approximately DKK 35 000.

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Table 6. Cost difference, when treating HR+/HER2- PIK3CA mutated advanced breast cancer between abemaciclib in combination with fulvestrant and alpelisib in combination with fulvestrant, in the first line setting.

	Piqray® + Fulvestrant /DKK	Verzenios® + Fulvestrant /DKK	Difference /DKK
Initial costs	3 739	3 470	269
Follow-up costs	13 721	13 630	91
AE costs	5 718	5 059	659
Test costs	9 462	0	9 462
Drug costs	173 756	147 617	26 139
Total treatment costs	206 396	169 776	**36 620**

When comparing alpelisib to a CDK4/6 inhibitor the effect size, adverse event profile and HRQoL seem to be comparable between abemaciclib + fulvestrant and alpelisib + fulvestrant. As such, the economic comparison does not include measures of effect and is solely based on the expected costs of treatment with either combination. The analysis shows that alpelisib + fulvestrant is more costly than abemaciclib + fulvestrant. However, this cost difference must be seen in the context of expanding treatment choice for physicians. As such, only a few patients with HR+/HER2- PIK3CA mutated aBC are expected to be treated with alpelisib + fulvestrant in this setting. Piqray® is a targeted medicine with a very limited patient population. Novartis believes that the slightly higher drug cost is within reason for a novel precision medicine specifically targeted towards patients expressing the PIK3CA mutation.

1.10.2 Economic analysis on second line (post-CDK4/6 population) – Clinical question 2

Novartis has explored the possibility of developing a health economic model that could capture differences in efficacy observed between alpelisib+fulvestrant vs. mono-fulvestrant. This should be based on post-CDK4/6 patients only, and therefore focus on "Clinical question 2". Traditionally a partitioned survival model would be a suitable structure, which would include the health states: progression free survival, post progression and death.

As described in the Clinical dossier, the BYLieve trial included patients previously treated with CDK4/6 inhibitors. This study was however one-armed and only data on alpelisib+fulvestrant was collected.

CDK4/6 inhibitors have only recently become a choice in the first line treatment of HR+/HER2- advanced breast cancer, whereas fulvestrant is a more established treatment that has been in use for years. The systematic literature review, conducted for this submission (section 4 of the medical section), did not identify any literature exploring the efficacy of mono-fulvestrant in the post-CDK4/6 setting. This means that an indirect treatment comparison between alpelisib+fulvestrant and mono-fulvestrant could not be performed. To our knowledge, SOLAR-1 is the only RCT that captures the efficacy of mono-fulvestrant in post CDK4/6 patients. As presented in the figure below [21], only 9 patients treated with mono-fulvestrant and 11 patients treated with alpelisib+fulvestrant were included in SOALR-1. The relative efficacy data fits with what was observed for the full population in SOLAR-1 with a separation of the curves in favor of alpelisib+fulvestrant. As is evident by the stepwise development in the curves, the small sample size would introduce a great deal of uncertainty in a health economic model. As such, this data is not sufficient to populate a partitioned survival model.

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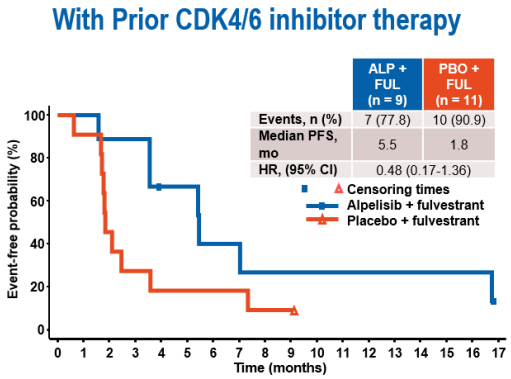

Figure 1 Progression free survival in patients treated in SOLAR-1, previously treated with CDK4/6 inhibitors.

Considering the limited data available, Novartis has provided a simple analysis on the incremental cost of additional time in a progression free state. Among the 20 patients with prior CDK4/6 inhibitor treatment included in SOLAR-1, the HR was 0.48 (95% CI: 0.17-1.36); median PFS was prolonged by 3.7 months in favor of patients treated with alpelisib, with 1.8 months PFS (95% CI: 1.7- 3.6) in the comparator arm and 5.5 months PFS (95% CI: 1.6, 16.8) in the alpelisib plus fulvestrant arm. A crude estimation of the cost of prolonging median PFS between the available treatments is presented in Table 7.

In the post CDK4/6 inhibitor setting, the difference in the cost of treating patients with PIK3CA mutated HR+/HER2- aBC with alpelisib + fulvestrant compared to monotherapy fulvestrant is approximately DKK 145 000.

Table 7 Cost and progression free survival difference between alpelisib+fulvestrant and mono-fulvestrant for the treatment of HR+/HER2- PIK3CA mutated advanced breast cancer after progression on CDK4/6.

Treatment	Alpelisib+fulvestrant	Fulvestrant	Difference
Median PFS (months)	5.5	1.8	3.7
Average treatment cost (DKK)	185 742	39 476	**146 266**

This analysis comes with great limitations and the results should be interpreted with caution. In the post-CDK4/6 treatment setting of patients with HR+/HER2- PIK3CA mutated aBC, alpelisib+fulvestrant incurs, on average, an additional cost of approximately DKK 145 000 when compared to mono-fulvestrant treatment. Along with the higher treatment costs, alpelisib+fulvestrant treated patients also retain three times the median duration of progression free disease ($\frac{5.5}{1.8} = 3.1$).

As per request from the Medicines Council, chemotherapy was included in the economic analysis. However, as with mono-fulvestrant therapy, the literature search described in section 4 of the medical section did not find any studies examining the effect of chemotherapy for patients in the post CDK4/6 inhibitors setting, for the treatment of HR+/HER2- PIK3CA mutated aBC. As such chemotherapy was not possible to include in the comparison and hence a purely economic comparison was made. In this comparison, the proportion of patients treated with chemotherapy was set to 10 % of the total patient population. The results of this comparison are presented in Table 8 and show a very small increment of approximately DKK 2 000 compared to treatment with 100% fulvestrant.

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Table 8. Cost difference, when treating HR+/HER2- PIK3CA mutated advanced breast cancer after progression on CDK4/6, between alpelisib in combination with fulvestrant and fulvestrant monotherapy or chemotherapy.

	Piqray® + Fulvest. / DKK	Chemo / DKK	Diff. / DKK	Fulvest. / DKK	Diff. / DKK	Weighted / DKK	Diff. / DKK
Initial costs	3 739	1 735	2 004	3 470	269	3 297	443
Follow-up costs	10 528	11 007	- 429	7 821	2 706	8 140	2 388
AE costs	5 718	135	5 583	135	5 583	135	5 583
Test costs	9 462	0	9 462	0	9 462	0	9 462
Drug costs	156 296	4 929	151 367	28 049	128 246	25 737	130 558
Total treatment costs	185 742	17 805	**167 937**	39 476	**146 266**	37 309	**148 434**

1.11 Sensitivity analyses

1.11.1 Drug wastage

Drug wastage was included in a sensitivity analysis. For alpelisib and abemaciclib, it was assumed that all treatment stops, be it due to death, progression or permanent termination of treatment would occur, on average, mid-way through the cycle. It is possible to adjust for drug waste by adding half of a pack to the drug costs. Fulvestrant is injected once per cycle and no corrections are necessary. For capecitabine, the pack sizes of 150 mg and 500 mg, equate to 30 days of treatment. This was adjusted to 1 cycle for simplicity. For capecitabine, half of a pack for both the large and small pack was added to the costs in the sensitivity analysis. For docetaxel, a full pack injection fluid was added in the sensitivity analysis. The results are presented in the table 9 and 10 which demonstrate an incremental difference increase of approximately DKK 3 000 in the first line setting and DKK 12 000 in the post CDK4/6 setting when compared to the results presented in Table 6 and 8, respectively.

Table 9. Cost difference, when treating HR+/HER2- PIK3CA mutated advanced breast cancer between abemaciclib in combination with fulvestrant and alpelisib in combination with fulvestrant and including drug wastage.

	Piqray® + Fulvestrant / DKK	Verzenios® + Fulvestrant / DKK	Difference / DKK
Initial costs	3 739	3 470	269
Follow-up costs	13 721	13 630	91
AE costs	5 718	5 059	659
Test costs	9 462	0	9 462
Drug costs	186 121	157 339	228 783
Total treatment costs	218 761	179 498	**39 263**

Table 10. Cost difference, when treating HR+/HER2- PIK3CA mutated advanced breast cancer after progression on CDK4/6i, between alpelisib in combination with fulvestrant and fulvestrant monotherapy or chemotherapy, including drug wastage.

	Piqray® + Fulvest. / DKK	Chemo / DKK	Diff. / DKK	Fulvest. / DKK	Diff. / DKK	Weighted / DKK	Diff. / DKK
Initial costs	3 739	1 735	2 004	3 470	269	3 297	443
Follow-up costs	10 528	11 007	- 429	7 821	2 706	8 140	2 388
AE costs	5 718	135	5 583	135	5 583	135	5 583
Test costs	9 462	0	9 462	0	9 462	0	9 462
Drug costs	168 661	5 571	163 089	28 049	140 611	25 802	142 859
Total treatment costs	198 107	18 448	**179 659**	39 476	**158 632**	37 373	**160 734**

1.11.2 Cost of testing

It can be argued that genetic testing may become a standard of care regardless of the reimbursement status of Piqray®. If the cost of testing is removed from the analysis, the cost difference is offset by DKK 9 462 in favor of Piqray® and is approximately DKK 25 000 and 140 000 in the first line and post CDK4/6 settings respectively. For more information, please see medical part section 7.1 PIK3CA testing. The detailed results are presented in the tables below:

Table 11. Cost difference, when treating HR+/HER2- PIK3CA mutated advanced breast cancer between abemaciclib in combination with fulvestrant and alpelisib in combination with fulvestrant and excluding test costs.

	Piqray® + Fulvestrant / DKK	Verzenios® + Fulvestrant / DKK	Difference / DKK
Initial costs	3 739	3 470	269
Follow-up costs	13 721	13 630	91
AE costs	5 718	5 059	659
Test costs	0	0	0
Drug costs	173 756	147 617	26 139
Total treatment costs	196 935	169 776	**27 158**

Table 12. Cost difference, when treating HR+/HER2- PIK3CA mutated advanced breast cancer after progression on CDK4/6i, between alpelisib in combination with fulvestrant and fulvestrant monotherapy or chemotherapy, excluding test costs.

	Piqray® + Fulvest. / DKK	Chemo / DKK	Diff. / DKK	Fulvest. / DKK	Diff. / DKK	Weighted / DKK	Diff. / DKK
Initial costs	3 739	1 735	2 004	3 470	269	3 297	443
Follow-up costs	10 528	11 007	- 429	7 821	2 706	8 140	2 388
AE costs	5 718	135	5 583	135	5 583	135	5 583
Test costs	0	0	0	0	0	0	0
Drug costs	156 296	4 929	151 367	28 049	128 246	25 737	130 558
Total treatment costs	176 281	17 805	**158 475**	39 476	**136 805**	37 309	**138 972**

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1.11.3 Treatment duration

In the base case, we have applied the median treatment duration to be consistent with the outcomes reported in the medical section, e.g., median PFS and OS. However, the mean treatment duration was applied in a sensitivity analysis. In SOLAR-1 [8], the mean drug exposure was 8.0 months for alpelisib and 10.0 month for fulvestrant in the alpelisib + fulvestrant arm, which was chosen for both comparators in the first line setting. In BYLieve the mean drug exposure was 5.8 months for alpelisib and 6.7 month for fulvestrant (for the alpelisib treated patients) [22]. The time on treatment for fulvestrant and chemotherapy was chosen to be 5.8 months, as this the lowest reported treatment length. The impact of the results is approximately DKK 12 000 in the first line setting and DKK 14 000 in the post CDK4/6 setting, when changing duration of treatment from median to mean. A complete overview of the results is presented in the tables below:

Table 13. Cost difference, when treating HR+/HER2- PIK3CA mutated advanced breast cancer between abemaciclib in combination with fulvestrant and alpelisib in combination with fulvestrant in the first line setting, when mean time on treatment is used

	Piqray® + Fulvestrant /DKK	Verzenios® + Fulvestrant /DKK	Difference /DKK
Initial costs	3 739	3 470	269
Follow-up costs	17 144	17 003	141
AE costs	5 718	5 059	659
Test costs	9 462	0	9 462
Drug costs	241 806	203 786	38 021
Total treatment costs	277 869	229 318	**48 551**

Table 14. Cost difference, when treating HR+/HER2- PIK3CA mutated advanced breast cancer after progression on CDK4/6, between alpelisib in combination with fulvestrant and fulvestrant monotherapy or chemotherapy.

	Piqray® + Fulvest. / DKK	Chemo / DKK	Diff. / DKK	Fulvest. / DKK	Diff. / DKK	Weighted / DKK	Diff. / DKK
Initial costs	3 739	1 735	2 004	3 470	269	3 297	443
Follow-up costs	10 916	12 756	1839	9 133	1783	9 495	1 421
AE costs	5 718	135	5 583	135	5 583	135	5 583
Test costs	9 462	0	9 462	0	9 462	0	9 462
Drug costs	173 935	5 605	168 330	31 308	142 627	28 738	145 197
Total treatment costs	203 770	20 231	**183 539**	44 046	**159 724**	41 664	**162 106**

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2 Budget impact

Since the economic comparison is bound purely to costs in year 1, the budget impact will be equivalent to the incremental cost differences, with the only differences being the number of expected patients treated multiplied by the results. Costs are not detailed further in this section, as they are presented above in section 2. An overview is however presented in the table below.

Table 15. Summary of key costs in the budget impact model.

Input	Value
Mean body surface area	1.74
Treatment cycles, first line, Piqray® and Verzenios®	5.94
Treatment cycles, first line, fulvestrant	8.86
Treatment cycles, post CDK4/6, Piqray® and mono-fulvestrant	5.51
Treatment cycles, post CDK4/6, fulvestrant in Piqray® arm	7.02
Treatment cycles, post CDK4/6, chemotherapy	7.34
Relative dose intensity, Piqray®	89.37 %
Relative dose intensity, Verzenios®	91.03 %
Relative dose intensity, fulvestrant and chemotherapy	100.00 %
# positive PCR tests	36.40 %
PCR test costs	DKK 3 444
Drug cost per cycle, Piqray®	DKK 24 730
Drug cost per cycle, Verzenios®	DKK 19 443
Drug cost per cycle, Fulvestrant	DKK 4 310
Drug costs per cycle, chemotherapy	DKK 671.09*
Adverse events, Piqray®	DKK 5 718
Adverse events, Verzenios®	DKK 5 059
Adverse events, fulvestrant and chemotherapy	DKK 135
Initial costs, Piqray®	DKK 3 739
Initial costs, Verzenios® and fulvestrant	DKK 3 470
Initial costs, chemotherapy	DKK 1 735
Follow-up costs, Piqray®	DKK 1 876
Follow-up costs, Verzenios®, fulvestrant and chemotherapy	DKK 1 735
Percent patients receiving chemotherapy post CDK4/6i	10%

*21 days cycle

The Medicines Council has estimated approximately 210-290 patients to be eligible for treatment with a CDK4/6 inhibitor and aromatase inhibitor yearly. Of these, the medicines council expects 80% will progress and be eligible for treatment with Piqray®+fulvestrant. We believe this number to be closer to 50 %. As such we have estimated 85-115 patients to be eligible for treatment in this setting. If Piqray® is approved for reimbursement, we expect a market share of approximately 20% in year one, which we expect to increase by approximately 10% each year until year five.

In the first line setting, the Medicines Council estimates there to be approximately 50-70 patients yearly. We also view this estimation to be high and have therefore adjusted patient numbers to 25-35 patients. Of these patients, we expect a market share of 20% in year one, which we expect to increase by approximately 10% each year until year five. Please see section 7.2 of the medical section for further explanation.

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In the budget impact calculations whole numbers were used for the patient populations of each treatment choice. First the proportion of patients receiving Piqray® was multiplied by the total eligible population in each treatment setting, and the result was rounded to the closest whole number. The expected number of patients treated with Piqray® was then subtracted from the total eligible population. The remaining patients were distributed to other treatments (i.e., Verzenios® in the first line; and fulvestrant monotherapy and chemotherapy in the post CDK4/6i setting). In the post CDK4/6i setting the number of patients on mono fulvestrant treatment was rounded up to the nearest whole number. Patients on chemotherapy were rounded down to the nearest whole number. This approach ensures that the total calculated population does not exceed the total original population, whilst also lowering the estimated number of patients on chemotherapy. The smaller chemotherapy population is in line with the original estimate of 5-10 % made by the Medicines Council.

We estimate the number of patients treated with Piqray® to be approximately 6 in the first line setting and approximately 20 in the post CDK4/6 setting in year one, increasing to 18 and 60 respectively in year five. A complete overview of estimated patients on each treatment, in both a scenario with reimbursement and without reimbursement of Piqray® is presented in tables 16 and 17 below.

Table 16. Expected treated patients with CDK4/6 if Piqray® is approved or the treatment of HR+/HER2- PIK3CA mutated advanced breast cancer.

	Year 1	Year 2	Year 3	Year 4	Year 5
First line					
Full eligible population	25-35	25-35	25-35	25-35	25-35
Full population used in budget impact model	30	30	30	30	30
Market share, Piqray®	20 %	30 %	40 %	50 %	60 %
Piqray®	6	9	12	26	18
Verzenios®	24	21	18	15	12
Post CDK4/6					
Full potential population	85-115	85-115	85-115	85-115	85-115
Full population used in budget impact model	100	100	100	100	100
Market share, Piqray®	20 %	30 %	40 %	50 %	60 %
Piqray®	20	30	40	50	60
Fulvestrant	72	63	54	45	36
Chemotherapy	8	7	6	5	4

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Table 17. Expected treated patients with CDK4/6i if Piqray® is not approved or the treatment of HR+/HER2- PIK3CA mutated advanced breast cancer.

	Year 1	Year 2	Year 3	Year 4	Year 5
First line					
Full eligible population	25-35	25-35	25-35	25-35	25-35
Full population used in budget impact model	30	30	30	30	30
Market share Piqray®	0%	0%	0%	0%	0%
Piqray®	0	0	0	0	0
Verzenios®	30	30	30	30	30
Post CDK4/6					
Full potential population	85-115	85-115	85-115	85-115	85-115
Full population used in budget impact model	100	100	100	100	100
Market share Piqray®	0 %	0 %	0 %	0 %	0 %
Piqray®	0	0	0	0	0
Fulvestrant	90	90	90	90	90
Chemotherapy	10	10	10	10	10

The budget impact of Piqray® reimbursement in the first line treatment of HR+/HER2- PIK3CA mutated aBC, is calculated to be approximately DKK 220 000 in year one, increasing to approximately DKK 660 000 in year five. If Piqray® is reimbursed in the post CDK4/6 treatment setting of HR+/HER2- PIK3CA mutated aBC the expected budget impact is approximately DKK 2 970 000 in year one, increasing to approximately DKK 8 905 000 in year five. The reason for the higher budget impact in the "post CDK4/6" setting is due to the higher difference in cost per patient, if alpelisib was to replace fulvestrant monotherapy versus replacing fulvestrant + Verzenios® in the first line setting.

If Piqray® is reimbursed in both settings, the approximate budget impact is estimated at DKK 3 190 000 for year one and DKK 9 565 000 for year five. For a complete overview of the incremental costs for each cost group, please see the attached Excel® model "Cost comparison and Budget impact analysis, Alpelisib – chemo included".

Table 18. Expected budget impact if Piqray® is or is not reimbursed for the treatment of HR+/HER2- PIK3CA mutated advanced breast cancer in the first line setting.

Budget impact 1. line	Year 1	Year 2	Year 3	Year 4	Year 5
If Piqray® IS approved					
Costs, Piqray®	1 238 377	1 857 566	2 476 754	3 095 943	3 715 131
Costs, Verzenios®	4 074 630	3 565 301	3 055 973	2 546 644	2 037 315
Total treatment costs	**5 313 007**	**5 422 867**	**5 532 727**	**5 642 587**	**5 752 446**
If Piqray® IS NOT approved					
Costs, Piqray®	0	0	0	0	0
Costs, Verzenios®	5 093 288	5 093 288	5 093 288	5 093 288	5 093 288
Total treatment costs	**5 093 288**	**5 093 288**	**5 093 288**	**5 093 288**	**5 093 288**
Budget impact	**219 720**	**329 579**	**439 439**	**549 299**	**659 159**

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Table 19. Expected budget impact if Piqray® is or is not reimbursed for the treatment of HR+/HER2- PIK3CA mutated advanced breast cancer in the post CDK4/6 setting.

Budget impact post CDK4/6	Year 1	Year 2	Year 3	Year 4	Year 5
If Piqray® IS approved					
Costs, Piqray®	3 714 844	5 572 266	7 429 688	9 287 110	11 144 532
Costs, fulvestrant	2 842 251	2 486 969	2 131 688	1 776 407	1 421 125
Costs, chemotherapy	142 442	124 636	106 831	89 026	71 221
Total treatment costs	**6 699 536**	**8 183 872**	**9 668 207**	**11 152 543**	**12 636 878**
If Piqray® IS NOT approved					
Costs, Piqray®	0	0	0	0	0
Costs, fulvestrant	3 552 813	3 552 813	3 552 813	3 552 813	3 552 813
Costs, chemotherapy	178 052	178 052	178 052	178 052	178 052
Total treatment costs	**3 730 865**	**3 730 865**	**3 730 865**	**3 730 865**	**3 730 865**
Budget impact	**2 968 671**	**4 453 006**	**5 937 342**	**7 421 677**	**8 906 013**

2.1 Sensitivity analysis

To test the results of the budget impact analysis, the expected patient numbers were varied by 25%. No other sensitivity analysis was performed as these would not produce significant changes on the overall budget impact. The results of the two sensitivity analyses are presented in table 20 for the first line setting and in table 21 for the post CDK4/6 setting.

Table 20. Expected budget impact if Piqray® is or is not reimbursed for the treatment of HR+/HER2- PIK3CA mutated advanced breast cancer in the first line setting, with a reduction and increase of 25% market share for Piqray®.

Budget impact 1. line	Year 1		Year 2		Year 3		Year 4		Year 5	
If Piqray® IS approved	-25%	25%	-25%	25%	-25%	25%	-25%	25%	-25%	25%
Costs, Piqray®	928 783	1 547 971	1 393 174	2 321 957	1 857 566	3 095 943	2 321 957	3 869 928	2 786 349	4 643 914
Costs, Verzenios®	4 329 295	3 819 966	3 947 298	3 183 305	3 565 301	2 546 644	3 183 305	1 909 983	2 801 308	1 273 322
Total treatment costs	**5 258 077**	**5 367 937**	**5 340 472**	**5 505 262**	**5 422 867**	**5 642 587**	**5 505 262**	**5 779 911**	**5 587 657**	**5 917 236**
If Piqray® IS NOT approved	-25%	25%	-25%	25%	-25%	25%	-25%	25%	-25%	25%
Costs, Piqray®	0	0	0	0	0	0	0	0	0	0
Costs, Verzenios®	5 093 288	5 093 288	5 093 288	5 093 288	5 093 288	5 093 288	5 093 288	5 093 288	5 093 288	5 093 288
Total treatment costs	**5 093 288**	**5 093 288**	**5 093 288**	**5 093 288**	**5 093 288**	**5 093 288**	**5 093 288**	**5 093 288**	**5 093 288**	**5 093 288**
Budget impact	**164 790**	**274 649**	**247 185**	**411 974**	**329 579**	**549 299**	**411 974**	**686 624**	**494 369**	**823 948**

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Table 21. Expected budget impact if Piqray® is or is not reimbursed for the treatment of HR+/HER2- PIK3CA mutated advanced breast cancer in the post CDK4/6i line setting, with a reduction and increase of 25% market share for Piqray®.

Budget impact post CDK4/6	Year 1		Year 2		Year 3		Year 4		Year 5	
If Piqray® IS approved	-25%	25%	-25%	25%	-25%	25%	-25%	25%	-25%	25%
Costs, Piqray®	2 786 133	4 643 555	4 272 071	7 058 204	5 572 266	9 287 110	7 058 204	11 701 759	8 358 399	13 930 665
Costs, fulvestrant	3 039 629	2 684 348	2 763 299	2 210 639	2 486 969	1 776 407	2 210 639	1 342 174	1 973 785	907 941
Cost, chemotherapy	142 442	124 636	124 636	106 831	124 636	89 026	106 831	53 416	89 026	35 610
Total treatment costs	**5 968 204**	**7 452 539**	**7 160 006**	**9 375 674**	**8 183 872**	**11 152 543**	**9 375 674**	**13 097 348**	**10 421 210**	**14 874 217**
If Piqray® IS NOT approved	-25%	25%	-25%	25%	-25%	25%	-25%	25%	-25%	25%
Costs, Piqray®	0	0	0	0	0	0	0	0	0	0
Costs, fulvestrant	3 552 813	3 552 813	3 552 813	3 552 813	3 552 813	3 552 813	3 552 813	3 552 813	3 552 813	3 552 813
Cost, chemotherapy	178 052	178 052	178 052	178 052	178 052	178 052	178 052	178 052	178 052	178 052
Total treatment costs	**3 730 865**	**3 730 865**	**3 730 865**	**3 730 865**	**3 730 865**	**3 730 865**	**3 730 865**	**3 730 865**	**3 730 865**	**3 730 865**
Budget impact	**2 237 338**	**3 721 674**	**3 429 141**	**5 644 809**	**4 453 006**	**7 421 677**	**5 644 809**	**9 366 483**	**6 690 345**	**11 143 351**

2.2 Conclusions of budget impact analysis

The total budget impact of introducing alpelisib for the treatment of first line patients with HR+/HER2- PIK3CA mutated aBC is an increased cost of approximately DKK220 000 in year one, rising to approximately DKK 1 660 000 in year five. As alpelisib provides a treatment option with a novel precision therapy, the increased cost can be viewed as a relatively small budgetary increment. In the post CDK4/6 setting the budget impact rises from just over DKK 2 970 000 in year one to approximately DKK 8 905 000 in year five.

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Medicinrådet

Medicinrådets protokol for vurdering vedrørende alpelisib til behandling af ER+/HER2- lokalt fremskreden eller metastatisk brystkræft med PIK3CA-mutation

Version 1.0

Om Medicinrådet

Medicinrådet er et uafhængigt råd etableret af Danske Regioner.

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

Om protokollen

Protokollen beskriver, hvordan Medicinrådet vil foretage vurderingen af lægemidlets værdi for patienterne. Den indeholder et eller flere kliniske spørgsmål, som den ansøgende virksomhed skal besvare i sin endelige ansøgning. Til hvert spørgsmål knytter sig en definition af patientgruppen, det lægemiddel, Medicinrådet undersøger, den behandling, Medicinrådet sammenligner med, og effektmålene. Udover de(t) kliniske spørgsmål indeholder protokollen også en beskrivelse af, hvordan litteratursøgning, -selektion og databehandling skal foregå.

Protokollen er udarbejdet med udgangspunkt i *Håndbog for Medicinrådets proces og metode vedr. nye lægemidler og indikationsudvidelser*, som du kan finde på Medicinrådets hjemmeside under siden Metoder, og den ansøgende virksomheds foreløbige ansøgning, der fortæller, hvilke data der findes for lægemidlet.

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

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Indholdsfortegnelse

1. Begreber og forkortelser ... 3

2. Introduktion ... 4

2.1 ER+/HER2- brystkræft ... 4

2.2 Alpelisib ... 5

2.3 Nuværende behandling ... 5

3. Kliniske spørgsmål ... 8

3.1 Klinisk spørgsmål 1 ... 8

3.2 Klinisk spørgsmål 2 ... 9

3.3 Effektmål ... 10

3.3.1 Kritiske effektmål ... 10

3.3.2 Vigtige effektmål ... 11

4. Litteratursøgning ... 13

5. Den endelige ansøgning ... 14

6. Evidensens kvalitet ... 17

7. Andre overvejelser ... 17

8. Relation til behandlingsvejledning ... 18

9. Referencer ... 19

10. Sammensætning af fagudvalg og kontaktinformation til Medicinrådet ... 21

11. Versionslog ... 23

12. Bilag ... 24

Bilag 1: Søgestrenge ... 24

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1. Begreber og forkortelser

AKT	Protein kinase B
CDK	*Cyclin-dependent kinase*
DBCG	*Danish Breast Cancer Group*
EMA:	Det Europæiske Lægemiddelagentur (*European Medicines Agency*)
EORTC-QLQ-BR23	*European Organisation for Research and Treatment of Cancer Quality-of-life Questionnaire-Breast 23 module*
EORTC-QLQ-C30	*European Organisation for Research and Treatment of Cancer Quality-of-life Questionnaire-Core 30*
EPAR:	*European Public Assessment Report*
EQ-5D	*EuroQol-5D*
ER	Østrogen receptor (*Estrogen receptor)*
EUnetHTA:	*European Network for Health Technology Assessment*
FDA:	*The Food and Drug Administration*
FINOSE:	Finland, Norge og Sveriges samarbejde om medicinske teknologivurderinger
GRADE:	System til at vurdere evidens (*Grading of Recommendations, Assessment, Development and Evaluation*)
HER	Human epidermal vækstfaktorreceptor 2 (*human epidermal growth factor receptor 2*)
HTA:	Medicinsk teknologivurdering (*Health Technology Assessment)*
IQWIG:	*The Institute for Quality and Efficiency in Healthcare*
ITT:	*Intention-to-treat*
MKRF:	Mindste klinisk relevante forskel
NICE:	*The National Institute for Health and Care Excellence*
PI3K	Phosphoinositide 3-kinase
PICO:	Population, intervention, komparator og effektmål (*Population, Intervention, Comparison and Outcome)*
PIK3CA	*Phosphatidylinositol-4,5-Bisphosphate 3-Kinase Catalytic Subunit Alpha*
PP:	*Per Protocol*
RR:	Relativ risiko
SMD:	*Standardized Mean Difference*

2. Introduktion

Protokollen er udarbejdet, fordi Medicinrådet har modtaget en foreløbig ansøgning fra Novartis, som ønsker, at Medicinrådet vurderer alpelisib (Piqray®) til østrogen receptor-positiv (ER+) og human epidermal vækstfaktorreceptor 2-negativ (HER-), lokalt fremskreden eller metastatisk brystkræft med mutation i *PIK3CA*. Medicinrådet modtog den foreløbige ansøgning den 22. december 2020. Novartis fik forhåndsgodkendelse (positive opinion) i EMA den 29. maj 2020 og EC-godkendelse den 27. juli 2020.

2.1 ER+/HER2- brystkræft

Brystkræft er den hyppigste kræftform hos kvinder i Danmark og forekommer oftest hos kvinder over 50 år. I Danmark bliver omkring 4.900 patienter årligt diagnosticeret med brystkræft, og ca. 66.000 patienter lever med diagnosen brystkræft [1,2]. Sygdommen kan opdeles i fire undertyper, afhængig af om kræftcellerne er hormonfølsomme, dvs. om de udtrykker østrogenreceptor (ER) og/eller human epidermal vækstfaktorreceptor 2 (HER2) eller ej. I Danmark bliver omkring 3.300 patienter årligt diagnosticeret med ER+/HER2- brystkræft, dvs. at kræftcellerne udtrykker østrogenreceptorer, men ikke vækstfaktorreceptorer [3].

Ved diagnosetidspunktet har ca. 7 % primært dissemineret sygdom, der ikke kan gøres operabelt. Dertil vil ca. 20 % af de patienter, som er diagnosticeret med tidlig brystkræft, senere få lokalt inoperabel fremskredent eller metastatisk tilbagefald. Dermed får ca. 890 patienter i Danmark årligt konstateret lokalt fremskreden inoperabel eller metastatisk ER+/HER2- brystkræft, der ikke behandles med kurativt sigte. Ved lokalt fremskreden sygdom har patienterne inoperabel brystkræft og/eller spredning til samsidige, fikserede lymfeknuder i armhulen eller langs kravebenet. Ved metastatisk sygdom har patienterne spredning til andre organer (fjernmetastaser) eller til lymfeknuder uden for samsidige loko-regionale område.

En del af patienterne vil have en mutation i *PIK3CA* (*Phosphatidylinositol-4,5-Bisphosphate 3-Kinase Catalytic Subunit Alpha)*-genet. I dansk klinisk praksis undersøger man ikke rutinemæssigt for denne mutation, men Dansk Patologisk Selskab har foretaget kvalitetssikringsprocedurer, så analysen kan blive indført nationalt med kort varsel. Internationale studier har vist, at 30-40 % af patienter med lokalt fremskreden eller metastatisk ER+/HER2- brystkræft har mutation i *PIK3CA*-genet [4,5]. Det er således forventeligt, at ca. 270-360 af de 890 patienter med lokalt fremskreden inoperabel eller metastatisk ER+/HER2- brystkræft har en mutation i *PIK3CA*-genet.

Fagudvalget understreger, at prognosen for patienter med *PIK3CA*-mutation generelt må forventes at være væsentligt lavere end for patienter uden. Dette skyldes, at patienter med *PIK3CA*-mutationen oftere og/eller hurtigere udvikler endokrin resistens end patienter uden mutationen [6,12]. Se afsnit 2.3 for yderligere information om patienternes prognose.

2.2 Alpelisib

Alpelisib (Piqray®) har følgende indikation: *Piqray er indiceret i kombination med fulvestrant til behandling af postmenopausale kvinder, og mænd, med hormonreceptor (HR) positiv, human epidermal vækstfaktorreceptor 2 (HER2) negativ, lokalt fremskreden eller metastatisk brystkræft med en PIK3CA-mutation med sygdomsprogression, efter tidligere endokrin behandling som monoterapi.*

Alpelisib gives i kombination med fulvestrant.

Alpelisib gives som tablet, 300 mg doseret én gang om dagen. Fulvestrant gives som intramuskulær injektion på dag 1, 15 og 29 i den første cyklus og derefter én gang om måneden.

Alpelisib hæmmer PI3K/AKT-signaleringskaskaden. Disse signaleringskaskader er overaktive hos patienter med en mutation i *PIK3CA*-genet, hvilket medfører øget celledeling og dermed øget tumorvækst. AKT-signaleringsvejen er desuden impliceret i udvikling af resistens over for anti-hormonel behandling [6]. Dermed bidrager behandling med alpelisib til, at anti-hormonel behandling bibeholder sin virkning.

Alpelisib er ikke godkendt til andre indikationer.

2.3 Nuværende behandling

Alpelisib er det første lægemiddel, hvis virkningsmekanisme muliggør en målrettet behandlingsstrategi til patienter med ER+/HER2- brystkræft og en *PIK3CA*-mutation. Derfor fokuserer dette afsnit på den nuværende behandling for patienter med ER+/HER2- brystkræft generelt.
Af figur 1 fremgår et overblik over behandlingen.

CDK4/6-hæmmere i kombination med aromatasehæmmer (AI) eller fulvestrant
Patienter med inoperabel lokalt fremskreden eller metastatisk ER+/HER2- brystkræft, enten på diagnosetidspunktet eller ved tilbagefald, får tilbudt CDK4/6-hæmmere i tillæg til endokrin behandling med enten AI eller fulvestrant, afhængigt af tidligere behandlinger [7]. CDK4/6-hæmmere forhindrer celledeling ved at stoppe cellecyklus [7].

Behandling efter endokrin monoterapi
Tidligere blev endokrin behandling som monoterapi benyttet som førstelinjebehandling for metastatisk sygdom, men dette er nu erstattet af CDK4/6-hæmmere i kombination med endokrin behandling [7]. Endokrin behandling som monoterapi bliver i nuværende klinisk praksis givet til patientgrupper som adjuverende behandling og i senere linjer som metastatisk behandling. Dertil kommer skrøbelige patienter, som på baggrund af forskellige medicinske og/eller compliance-mæssige årsager vurderes ikke at kunne gennemføre eller tåle CDK4/6-hæmmere. Disse patienter vil ikke kunne tages i betragtning til alpelisib.

Alpelisib har indikation til patienter, som har modtaget endokrin monoterapi for ER+/HER2- brystkræft. Der findes i nuværende dansk klinisk praksis to patientgrupper, som opfylder indikationen for alpelisib:

- Patienter, som har modtaget behandling med AI som førstelinjebehandling af metastatisk sygdom, vil ved progression blive tilbudt behandling med CDK4/6-hæmmer i kombination med fulvestrant. Denne patientgruppe opstartede endokrin monoterapi før CDK4/6-hæmmerne blev taget i brug i Danmark, og der er derfor ikke mange patienter tilbage, som har modtaget denne behandlingssekvens.
- Patienter, som får tilbagefald på eller kort tid efter adjuverende endokrin monoterapi. Disse patienter vil ligeledes blive tilbudt behandling med CDK4/6-hæmmer i kombination med fulvestrant.

Fagudvalget vurderer baseret på ovenstående, at CDK4/6-hæmmer i kombination med fulvestrant er standardbehandling efter endokrin monoterapi og dermed er komparator i klinisk spørgsmål 1.

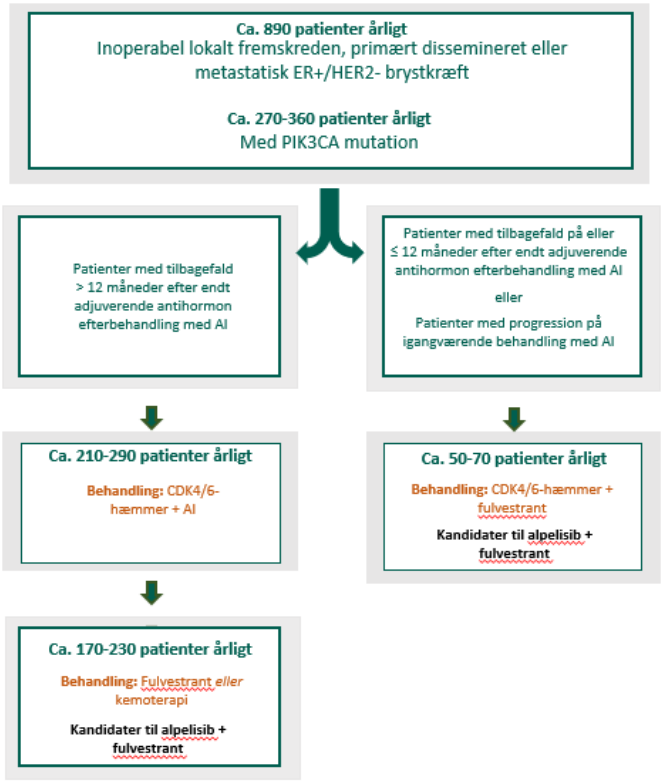
Behandling efter CDK4/6-hæmmer i kombination med AI

EMA anerkender, at alpelisibs indikation ikke passer ind i nuværende klinisk praksis, og nævner i EPAR'en, at det er patienter, der har progredieret på en CDK4/6-hæmmer i kombination med AI, der er relevante kandidater til behandling med alpelisib i kombination med fulvestrant [8]. Dette er ligeledes fagudvalgets vurdering og anbefalingen fra internationale guidelines [9].

Ved progression på en CDK4/6-hæmmer i kombination med AI er der flere mulige behandlingsalternativer, og der er på nuværende tidspunkt en vis forskel i praksis på tværs af regioner. Fælles for tilgangen er, at behandlingen vælges på baggrund af en individuel vurdering af den enkelte patient. Behandlingsvalget afhænger af, hvornår patienterne progredierer på CDK4/6-behandlingen. Patienter, som oplever tidlig progression (dvs. under 6 mdr. efter opstart af behandling), anses som at have udviklet primær endokrin resistens og forventes derfor ikke at have gavn af yderligere endokrin behandling. Disse patienter tilbydes i stedet kemoterapi. Størstedelen af patienterne oplever progression senere end 6 måneder efter opstart og formodes dermed at kunne have gavn af yderligere behandling med endokrin terapi. Disse patienter får derfor oftest tilbudt fulvestrant, men afhængig af sygdomsudbredelse, symptomer og almen tilstand vil en mindre del af patienterne blive tilbudt kemoterapi[1]. Samlet set vurderer fagudvalget, at fulvestrant er den hyppigst benyttede behandling efter behandling med en CDK4/6-hæmmer i kombination med AI, hvorfor fulvestrant vil indgå som komparator i klinisk spørgsmål 2.

[1] Fagudvalget gør opmærksom på, at patienter, der jf. nuværende praksis tilbydes kemoterapi, formentlig vil kunne tages i betragtning til behandling med alpelisib i kombination med fulvestrant, hvis denne anbefales.

Figur 1. Overblik over behandling af patienter med ER+/HER2- brystkræft



Som det fremgår af figur 1, får ca. 50-70 patienter med inoperabelt lokalt fremskreden eller metastatisk ER+/HER2- brystkræft (og mutation i *PIK3CA*-genet) tilbudt CDK4/6-hæmmere i kombination med fulvestrant. Dertil kommer ca. 210-290 patienter, som får tilbudt CDK4/6-hæmmere i kombination med AI. Af disse vil ca. 80 %, dvs. ca. 170-230 patienter, efterfølgende være kandidater til behandling med fulvestrant (hvis ikke tidligere givet) eller kemoterapi ved progression af sygdommen. Samlet vil ca. 220-300 patienter således årligt være mulige kandidater til alpelisib.

Behandlingsmål for patienter, der kan blive kandidater til alpelisib
Det er meget sjældent muligt at helbrede patienter med inoperabel lokalt fremskreden eller metastatisk brystkræft. Formålet med behandlingen med hhv. CDK4/6-hæmmere i kombination med AI/fulvestrant eller fulvestrant monoterapi er derfor at forlænge tiden til sygdomsprogression uden at påføre patienten markant flere bivirkninger, at forlænge patientens liv og om muligt at forbedre patientens livskvalitet.

Prognose for patienter, som modtager CDK4/6-hæmmere i kombination med fulvestrant (klinisk spørgsmål 1)
Overlevelsesdata for patienter, som modtager palbociclib i kombination med fulvestrant, viste en median overlevelse på ca. 35 mdr. [10]. En subgruppeanalyse fra samme studie viste, at patienter med en mutation i *PIK3CA*-genet, som modtog palbociclib i kombination med fulvestrant, havde en median overlevelse på ca. 28 måneder [10].

Prognose for patienter, som modtager fulvestrant (klinisk spørgsmål 2)
Fagudvalget har ikke kendskab til direkte opgørelser over samlet overlevelse for patienter i behandling med fulvestrant monoterapi efter behandling med en CDK4/6-hæmmer i kombination med AI. Der foreligger en metaanalyse for effekten af CDK4/6-hæmmere på samlet overlevelse for patienter med ER+/HER2-, men denne giver kun information vedr. den relative overlevelse [11].

Med forbehold for ovenstående overvejelser vurderer fagudvalget, at prognosen for patienter i klinisk spørgsmål 1 og 2 er nogenlunde sammenlignelig. Selvom de to patientpopulationer er forskellige steder i behandlingskaskaden, er det fælles for begge populationer, at det næste behandlingstrin er kemoterapi, hvorfra prognosen typisk forværres.

3. Kliniske spørgsmål

Medicinrådet bruger kliniske spørgsmål til vurderinger af lægemidlers værdi for patienterne. Til hvert spørgsmål knytter sig en definition af patientgruppen (population), af det lægemiddel, Medicinrådet undersøger (interventionen), af den behandling, Medicinrådet sammenligner med (komparator(er)), og af effektmålene.

Jf. afsnit 2.3 er der international konsensus om indplacering af alpelisib i kombination med fulvestrant efter CDK4/6-hæmmere i kombination med AI, selvom EMAs indikation indplacerer alpelisib i kombination med fulvestrant efter endokrin monoterapi. På den baggrund har fagudvalget udarbejdet to kliniske spørgsmål.

3.1 Klinisk spørgsmål 1

Hvilken værdi har alpelisib i kombination med fulvestrant sammenlignet med CDK4/6-hæmmere i kombination med fulvestrant for patienter med lokalt fremskreden eller metastatisk ER+/HER2- brystkræft og mutation i *PIK3CA*-genet?

Population
Patienter, som på nuværende tidspunkt kan tages i betragtning til behandling med CDK4/6-hæmmere i kombination med fulvestrant, dvs.:

- Patienter med lokalt fremskreden eller metastatisk ER+/HER2- brystkræft og mutation i *PIK3CA*-genet, der har modtaget endokrin monoterapi som førstelinjebehandling for metastatisk sygdom.
- Patienter med lokalt fremskreden eller metastatisk ER+/HER2- brystkræft og mutation i *PIK3CA*-genet, der får tilbagefald på eller kort tid efter endt endokrin monoterapi som adjuverende behandling.

Intervention
Alpelisib (300 mg som tablet, doseret én gang om dagen) i kombination med fulvestrant (500 mg som intramuskulær injektion på dag 1, 15 og 29 i den første cyklus og derefter én gang om måneden).

Komparator
Abemaciclib[2] (150 mg to gange dagligt) i kombination med fulvestrant (500 mg som intramuskulær injektion på dag 1, 15 og 29 i den første cyklus og derefter én gang om måneden).

Effektmål
De valgte effektmål fremgår af tabel 1.

3.2 Klinisk spørgsmål 2

Hvilken værdi har alpelisib i kombination med fulvestrant sammenlignet med fulvestrant alene for patienter med lokalt fremskreden eller metastatisk ER+/HER2- brystkræft og mutation i *PIK3CA*-genet?

Population
Patienter med lokalt fremskreden eller metastatisk ER+/HER2- brystkræft og mutation i *PIK3CA*-genet, der får tilbagefald på behandling med en CDK4/6-hæmmer i kombination med AI.

Intervention
Alpelisib (300 mg som tablet, doseret én gang om dagen) i kombination med fulvestrant (500 mg som intramuskulær injektion på dag 1, 15 og 29 i den første cyklus og derefter én gang om måneden).

Komparator
Fulvestrant (500 mg som intramuskulær injektion på dag 1, 15 og 29 i den første cyklus og derefter én gang om måneden)[3].

Effektmål
De valgte effektmål fremgår af tabel 1.

[2] Abemaciclib er det nuværende førstevalg i Medicinrådets lægemiddelrekommandation for CDK4/6-hæmmere til behandling af ER+/HER2- brystkræft. I *Baggrund for Medicinrådets behandlingsvejledning vedr. CDK4/6-hæmmere til behandling af ER+/HER2- brystkræft* blev de tre CDK4/6-hæmmere abemaciclib, palbociclib og ribociclib ligestillet for patienter med ER+/HER2- brystkræft, uanset *PIK3CA*-mutationsstatus.

[3] Som nævnt i afsnit 2.3 vil en mindre gruppe af patienter i dansk klinisk praksis modtage kemoterapi. Fagudvalget vurderer, at denne gruppe patienter er for heterogene til, at det er meningsfuldt at foretage en formel sammenligning med alpelisib i kombination med fulvestrant.

3.3 Effektmål

Medicinrådet mener, at vurderingen af lægemidlets værdi bliver bedst understøttet af de effektmål, der er nævnt i tabel 1. For hvert effektmål har Medicinrådet fastsat en mindste klinisk relevant forskel (MKRF). I det følgende afsnit argumenterer Medicinrådet for valget af effektmål og MKRF.

Tabel 1. Oversigt over valgte effektmål

Effektmål*	Vigtighed	Effektmålsgruppe**	Måleenhed	Mindste klinisk relevante forskel
Samlet overlevelse (OS)	Kritisk	Dødelighed/ overlevelse	Median overlevelse i antal måneder	5 måneder
Livskvalitet	Kritisk	Livskvalitet, alvorlige symptomer og bivirkninger	Gennemsnitlig ændring over tid	Forskel i ændring, svarende til de validerede mindste klinisk relevante forskelle for de involverede livskvalitets-spørgeskemaer
Stabilisering eller forbedring af symptomer	Vigtig	Livskvalitet, alvorlige symptomer og bivirkninger	Median PFS i antal måneder	3 måneder
Bivirkninger	Vigtig	Livskvalitet, alvorlige symptomer og bivirkninger	Andel patienter, der oplever en eller flere grad 3-4 bivirkninger	5 %-point
			Gennemgang af bivirkningsprofil	Narrativ vurdering

*For alle effektmål ønsker Medicinrådet data med længst mulig opfølgningstid, medmindre andet er angivet.
**Effektmålsgruppe refererer til de væsentlighedskriterier, som Medicinrådet lægger til grund for kategoriseringen af de relative forskelle i effekt, bivirkninger eller livskvalitet.

3.3.1 Kritiske effektmål

Samlet overlevelse (OS)
Samlet overlevelse er defineret som tiden fra randomisering til død, uafhængigt af årsag. Det er afgørende for patienterne, om behandlingen forlænger deres liv, og fagudvalget vurderer derfor, at OS er et kritisk effektmål. Fagudvalget ønsker effektmålet opgjort som median overlevelse.

Den mindste klinisk relevante forskel er valgt med udgangspunkt i ESMO-guidelinen *Magnitude of Clinical Benefit Scale* (MCBS). Denne indeholder skemaer, der indikerer, hvordan man kan fastsætte mindste klinisk relevante forskelle afhængigt af patienternes prognose [13]. Jf. afsnit 2.3 estimerer fagudvalget, at median OS ved standardbehandling

er over 12 måneder. Fagudvalget tager derfor udgangspunkt i ESMOs MCBS-skemaer, som omhandler behandlinger, der ikke forventes at være kurative, hvor OS er det primære endepunkt, og hvor prognosen for median OS er > 12 måneder.

Fagudvalget vurderer, at en forskel ift. median OS på 5 måneder er klinisk relevant.

Livskvalitet
Livskvalitet er et patientrelevant effektmål, som udover at give indblik i sygdomsbyrden kan indikere, om bivirkningerne ved lægemidlet påvirker patienternes livskvalitet. På baggrund af dette betragter fagudvalget livskvalitet som et kritisk effektmål.
Livskvalitet kan for brystkræftpatienter måles med flere forskellige instrumenter (spørgeskemaer). Fagudvalget vurderer, at nedenstående validerede spørgeskemaer, der er nævnt i prioriteret rækkefølge, er relevante. Fagudvalget lægger i prioriteringen af rækkefølgen vægt på, at man benytter de to førstnævnte i dansk klinisk praksis.
EORTC-QLQ-C30: Dette instrument måler livskvaliteten blandt kræftpatienter [16]. Det består af fem funktionsskalaer, tre symptomskalaer og en "global" livskvalitetsskala. Der anvendes en scoringsskala fra 0-100. En høj score på de fem funktionsskalaer repræsenterer et højt/positivt funktionsniveau. En høj score for global helbredsstatus repræsenterer høj livskvalitet, mens en høj score på de tre symptomskalaer repræsenterer høj forekomst af symptomer/problemer. En lille ændring i livskvalitet er defineret som en ændring på 5-10 point i en publikation, hvor størstedelen af patienterne havde brystkræft [17]. Fagudvalget læner sig op ad denne definition og betragter en forskel på ≥ 10 point mellem alpelisib i kombination med fulvestrant og de to komparatorer som klinisk relevant.
EORTC-QLQ-BR23: Dette er et sygdomsspecifikt instrument, der vurderer livskvaliteten blandt patienter med brystkræft [18]. Det er et tillæg til EORTC-QLQ-C30 og består af fire funktionsskalaer og fire symptomskalaer. Scoringen foregår på samme måde som ved EORTC-QLQ-C30. Da der tilsyneladende ikke er defineret en mindste klinisk relevant forskel for instrumentet, benytter fagudvalget sig af definitionen fra EORTC-QLQ-C30. Dette er konsistent med tilgangen i flere studier [19]. Dermed betragter fagudvalget en forskel på ≥ 10 point mellem alpelisib i kombination med fulvestrant og de to komparatorer som klinisk relevant.

EQ-5D: Dette er et velvalideret generisk spørgeskema, som anvendes til at vurdere helbredsrelateret livskvalitet [20]. Spørgeskemaet består af fem dimensioner og indeholder desuden en visuel analog skala (VAS), der går fra 0 (værst tænkelige helbred) til 100 (bedst tænkelige helbred). Fagudvalget læner sig op ad definitionerne af mindste klinisk relevante forskelle baseret på britiske kræftpatienter [21]. Dermed finder fagudvalget, at en forskel på ≥ 0,08 i EQ-5D index score og ≥ 7 point i EQ-5D VAS mellem alpelisib i kombination med fulvestrant og de to komparatorer er klinisk relevant.

3.3.2 Vigtige effektmål

Stabilisering og forbedring af symptomer
Fagudvalget ønsker at belyse andel patienter, som opnår stabilisering og forbedring af symptomer ved progressionsfri overlevelse (PFS). PFS bliver anvendt til at vurdere, hvor lang tid der går, inden patienternes sygdom udvikler sig, og er defineret som tiden fra

studierandomisering til første dokumentation af progression i henhold til RECIST v1.1 [14] eller dødsfald. 2. linje endokrin behandling er den sidste mulige standardbehandling, der ikke er kemoterapi, for patienter med metastatisk ER+/HER2- brystkræft. Fagudvalget vurderer derfor, at det er af stor værdi for patienterne at modtage en behandling, som stabiliserer deres sygdom og forlænger tiden til progression. Stabilisering af sygdommen betyder ofte, at patienterne undgår forværring af deres symptomer for en tid. Derfor fremhæver fagudvalget, at det har særlig betydning for patienterne at forblive i en effektiv behandling så længe som muligt. Fagudvalget vurderer derfor, at det er relevant at opgøre PFS som et vigtigt effektmål.

De mindste klinisk relevante forskelle er valgt med udgangspunkt i ESMO-guidelinen "Magnitude of Clinical Benefit Scale" (MCBS). Denne indeholder skemaer, der indikerer, hvordan man kan fastsætte mindste klinisk relevante forskelle afhængigt af patienternes prognose [13]. Ift. mindste klinisk relevante forskelle tager fagudvalget udgangspunkt i ESMOs MCBS-skema, som omhandler behandlinger, der ikke forventes at være kurative, og hvor PFS er det primære endepunkt. Fagudvalget forventer ud fra kendskab til relevant litteratur, at median PFS ved standardbehandling er mere end 6 måneder [15]. Jf. MCBS er den mindste klinisk relevante forskel derfor 3 måneder.

Bivirkninger
Som nævnt er behandlingsmålet at forlænge patienternes liv. Derfor finder fagudvalget, at bivirkninger (adverse reactions, AR) er et vigtigt effektmål, da det belyser, hvor godt patienterne tolererer alpelisib i kombination med fulvestrant sammenlignet med de to komparatorer. Effektmålet er vigtigt, da det er fagudvalgets vurdering, at patienterne er relativt villige til at risikere bivirkninger for at kunne opnå en eventuel forlængelse i overlevelse. Fagudvalget ønsker data på nedenstående måleenheder.

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 [22].

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

Gennemgang af bivirkningsprofil
Fagudvalget ønsker en gennemgang af bivirkningsprofilerne for hhv. alpelisib i kombination med fulvestrant og de to komparatorer med henblik på at vurdere bivirkningernes type, håndterbarhed og reversibilitet. Ansøger bedes derfor levere bivirkningsdata fra både de kliniske studier og produktresuméet for lægemidlerne, så fagudvalget kan vurdere forskelle mellem de forskellige behandlinger.

Grad 3-4 er vægtet mest i den samlede vurdering af effektmålet.

4. Litteratursøgning

Medicinrådets vurdering af lægemidlets værdi vil i udgangspunktet være baseret på data fra fuldtekstartikler publiceret i videnskabelige, fagfællebedømte (peer-reviewed) tidsskrifter og data fra Det Europæiske Lægemiddelagenturs (EMAs) European Public Assessment Reports (EPAR). Herudover kan data fra Food and Drug Administration (FDA) og internationalt anerkendte HTA-agenturer (f.eks. NICE, EUnetHTA, FINOSE og IQWiG) indgå i vurderingen. Hvis disse data er tilstrækkelige til at kunne vurdere lægemidlet, vil Medicinrådet som hovedregel ikke anvende andre data[4]. Data skal derudover stemme overens med protokollens beskrivelser. Hvis ansøger har kendskab til upublicerede data, der kan belyse eventuelle angivne mangler, kan de indgå/indsendes, jf. Medicinrådets principper for anvendelse af upublicerede data.

Klinisk spørgsmål 1
Medicinrådet er i den foreløbige ansøgning blevet orienteret om, at der ikke findes studier, hvor alpelisib i kombination med fulvestrant er sammenlignet direkte med abemaciclib i kombination med fulvestrant. Derfor skal ansøger søge efter studier til en indirekte sammenligning. Søgestrengene fremgår af bilag 1. Derudover skal ansøger konsultere EMAs EPAR for både det aktuelle lægemiddel og dets komparator(er).

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

Klinisk spørgsmål 2
Medicinrådet er i den foreløbige ansøgning blevet orienteret om, at der findes et studie, hvor alpelisib i kombination med fulvestrant er sammenlignet direkte med fulvestrant. Studiet er rapporteret i følgende publikationer:

- SOLAR-1 NCT02437318

Det er ikke tilstrækkeligt datagrundlag til en komplet besvarelse af det kliniske spørgsmål. Dette skyldes, at kun 6 % af patienterne i studiet tidligere havde modtaget behandling med en CDK4/6-hæmmer. Ansøger skal derfor undersøge, om der findes andre studier, som indeholder/beskriver de angivne mangler. Søgestrengene fremgår af bilag 1.

Finder ansøger studier, som tillader direkte eller indirekte analyser for den relevante patientgruppe (dvs. studier, som undersøger effekten af alpelisib hos patienter med *PIK3CA*-mutation, som er progredieret efter behandling med en CDK4/6-hæmmer), skal ansøger benytte disse studier til at besvare det kliniske spørgsmål.

Ansøger skal derudover konsultere EMAs EPAR for både det aktuelle lægemiddel og dets komparatorer.

[4] For yderligere detaljer se Medicinrådets principper for anvendelse af upublicerede data

Kan ansøger ikke finde studier, som tillader direkte eller indirekte analyser for den relevante patientgruppe, kan ansøger besvare det kliniske spørgsmål vha. SOLAR-1-studiet. I så fald skal ansøger argumentere klart for sandsynligheden af, om eventuelle effektforskelle mellem alpelisib i kombination med fulvestrant og fulvestrant alene vil være af samme størrelsesorden for patienter, som tidligere har modtaget behandling med en CDK4/6-hæmmer. Dette skal så vidt muligt understøttes med fagfællebedømte referencer.

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

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

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

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

5. Den endelige ansøgning

Ansøger skal bruge Medicinrådets ansøgningsskema til sin endelige ansøgning. Vær opmærksom på følgende:

Studier og resultater

- Beskriv de inkluderede studier og baselinekarakteristikken af studiepopulationerne.
- Angiv, hvilke studier/referencer der er benyttet til at besvare hvilke kliniske spørgsmål.
- Brug som udgangspunkt ansøgningsskemaet til ekstraktion af al relevant data.
- Krydstjek de ekstraherede data med de resultater, der fremgår af de relevante EPARs.

- Angiv årsager, hvis der er uoverensstemmelser mellem resultaterne fra artikler og EPARs.
- Angiv årsager, hvis der er uoverensstemmelser i forhold til PICO (population, intervention, komparator og effektmål) mellem protokollen og studierne.
- Vurdér, hvordan uoverensstemmelserne påvirker estimaterne.

Statistiske analyser

- Begrund valget af syntesemetode (metaanalyse eller narrativ beskrivelse), og lad specifikke analysevalg fremgå tydeligt.
- Udfør en komparativ analyse for hvert enkelt effektmål på baggrund af de ekstraherede data.
- Hvis data for et effektmål ikke er baseret på alle deltagere i et studie, skal ansøger ikke gøre forsøg på at erstatte manglende data med en meningsfuld værdi.
- Angiv for hvert effektmål og studie, hvilken analysepopulation (f.eks. intention-to-treat (ITT), per-protocol) der er anvendt.
- Angiv en sensitivitetsanalyse baseret på ITT-populationen, hvis den komparative analyse ikke er baseret herpå.
- Angiv for hvert effektmål og studie, hvilken statistisk analysemetode der er anvendt.
- Basér de statistiske analyser for dikotome effektmål på den relative forskel.
- Beregn den absolutte forskel med udgangspunkt i den estimerede relative forskel for et antaget niveau på hændelsesraten i komparatorgruppen (jf. appendiks 5 i Håndbog for Medicinrådets proces og metode vedr. nye lægemidler og indikationsudvidelser).
- Foretag eventuelt en indirekte analyse, hvis der ikke foreligger direkte sammenlignende studier, og hvis intervention og komparator er sammenlignet med samme alternative komparator i separate studier. Anvend eventuelt Buchers metode for indirekte justeret sammenligning.

Metaanalyser

- Foretag en metaanalyse for de effektmål, hvor det er metodemæssigt forsvarligt, hvis der er mere end ét sammenlignende studie.
- Basér metaanalyser vedr. effektmål, hvor forskellige måleinstrumenter er brugt på tværs af de inkluderede studier, på standardized mean difference (SMD). Omregn den estimerede SMD til den foretrukne skala for effektmålet (jf. appendiks 7 i Håndbog for Medicinrådets proces og metode vedr. nye lægemidler og indikationsudvidelser).
- Udfør alene netværksmetaanalyse i de undtagelsesvise situationer, hvor Medicinrådet specifikt beder om det i protokollen. Redegør i disse tilfælde for, i hvilken grad antagelserne om transitivitet og konsistens er opfyldt (gerne ved hjælp af passende statistiske metoder).

- Begrund for alle statistiske analyser valget mellem 'fixed effects'-modeller og 'random effects'-modeller.
- Beskriv den anvendte metode detaljeret.

Narrative analyser

- Begrund valget af syntesemetode (metaanalyse eller narrativ beskrivelse), og lad specifikke analysevalg fremgå tydeligt.
- Syntetisér data narrativt, hvis det ikke er en mulighed at udarbejde komparative analyser baseret på statistiske metoder.
- Beskriv studie- og patientkarakteristika samt resultater fra de inkluderede studier narrativt og i tabelform med angivelse af resultater pr. effektmål for både intervention og komparator(er).
- Beskriv forskelle mellem studier, og vurdér, hvorvidt resultaterne er sammenlignelige.

Særlige forhold i denne protokol
Vær opmærksom på, at Medicinrådets sekretariat forbeholder sig retten til at foretage sensitivitets- og subgruppeanalyser på baggrund af studiernes validitet og relevans, uanset valg af analysemetode.

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

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

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

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

6. Evidensens kvalitet

Medicinrådet anvender GRADE (Grading of Recommendations, Assessments, Development and Evaluation) til at foretage en systematisk og transparent vurdering af kvaliteten af evidensen. Evidensens kvalitet fortæller, i hvor høj grad man kan have tiltro til den evidens, Medicinrådet baserer vurderingen af lægemidlets værdi på.

7. Andre overvejelser

Test for PIK3CA-mutation
I dansk klinisk praksis undersøger man ikke rutinemæssigt patienterne for *PIK3CA*-mutation. Som nævnt i afsnit 2.1 kan undersøgelsen blive indført nationalt med kort varsel.

Medicinrådet ønsker, at ansøger gør rede for, hvilken metode man forventer at anvende i dansk klinisk praksis ved test for PIK3CA-mutation, og om metoden benyttet i det kliniske studie stemmer overens hermed ift. funktionalitet. Endvidere ønsker Medicinrådet, at ansøger gør rede for omkostningerne ved testen og kommer med et estimat for antallet af patienter, der skal testes for at finde én patient med PIK3CA-mutationen. Medicinrådet ønsker, at ansøger redegør for disse forhold, idet omkostninger til implementering af lægemidlet skal indgå som del af den sundhedsøkonomiske analyse.

Indplacering af alpelisib i kombination med fulvestrant i dansk klinisk praksis
Jf. afsnit 4 er fagudvalget opmærksom på, at kun 6 % af patienterne med *PIK3CA*-mutation(er) i SOLAR-1-studiet tidligere havde modtaget behandling med en CDK4/6-hæmmer. Jf. afsnit 2.2 finder fagudvalget dog, at alpelisib bør gives efter behandling med en CDK4/6-hæmmer, selvom studiet ikke belyser alpelisibs effekt på denne patientpopulation.

Supplerende sundhedsøkonomisk analyse
Som nævnt i afsnit 2.3 vil en mindre gruppe af patienter med progression på en CDK4/6-hæmmer i kombination med AI blive tilbudt kemoterapi fremfor fulvestrant. Fagudvalget estimerer, at denne mindre gruppe udgør 5-10 % af patienterne.

Som udgangspunkt vil der i budgetkonsekvensanalysen for klinisk spørgsmål 2 skulle tages kvantitativ højde for dette, men idet der i dansk klinisk praksis anvendes op til flere forskellige kemoterapier, kan det aflede en uhensigtsmæssig kompliceret sundhedsøkonomisk model behæftet med usikkerheder. Medicinrådet ønsker i stedet, at ansøger kvalitativt redegør for retningen af de inkrementelle omkostninger og de afledte budgetkonsekvenser for de 5-10 % af patienterne, som i dansk klinisk praksis modtager kemoterapi.

Medicinrådet ønsker derudover informationer, der kan belyse en vurdering af, hvorvidt og hvordan indførelsen af den ansøgte intervention i dansk klinisk praksis vil påvirke behandlinger i efterfølgende behandlingslinjer hvad angår type, varighed og forventet effekt.

Patienter med visceral krise (eller andre, der ikke kan tages i betragtning til behandling med fulvestrant)
Fagudvalget gør opmærksom på, at fulvestrant ikke er standardbehandling for patienter med visceral krise eller endokrin resistens. Nogle af disse patienter indgår dog i SOLAR-1-studiet, og der er derfor sandsynlighed for, at alpelisib i kombination med fulvestrant også virker for denne patientgruppe. Ansøger bedes redegøre for dette i ansøgningen. Fagudvalget vil kommentere på denne overvejelse i vurderingsrapporten.

8. Relation til behandlingsvejledning

Medicinrådet har udarbejdet en behandlingsvejledning vedr. CDK4/6-hæmmere til ER+/HER2- lokalt fremskreden eller metastatisk brystkræft, men denne omhandler ikke behandling efter en CDK4/6-hæmmer. Der findes således ikke en relevant behandlingsvejledning for klinisk spørgsmål 2.

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10. Sammensætning af fagudvalg og kontaktinformation til Medicinrådet

Medicinrådets fagudvalg vedrørende brystkræft

Sammensætning af fagudvalg	
Formand	**Indstillet af**
Hanne Melgaard Nielsen *Overlæge*	Lægevidenskabelige Selskaber
Medlemmer	**Udpeget af**
Tamás Lörincz *Overlæge*	Region Nordjylland
Julia Kenholm *Overlæge*	Region Midtjylland
Jeanette Dupont Jensen *Overlæge*	Region Syddanmark
Vesna Glavicic *Overlæge*	Region Sjælland
Maja Vestmø Maraldo *Afdelingslæge*	Region Hovedstaden
Philip Hojrizi *Farmaceut*	Dansk Selskab for Sygehusapoteksledelse
Marie Lund *Afdelingslæge*	Dansk Selskab for Klinisk Farmakologi
Iben Kümler *Afdelingslæge*	Danish Breast Cancer Cooperative Group (DBCG)
Susanne Geneser *Patient/patientrepræsentant*	Danske Patienter
Marianne Johansson *Patient/patientrepræsentant*	Danske Patienter
Eva Balslev *Overlæge*	Inviteret af formanden

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11. Versionslog

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

12. Bilag

Bilag 1: Søgestrenge

Klinisk spørgsmål 1 og 2
Da søgningen er relativ afgrænset og der er stort overlap mellem de artikler der forventes at blive identificeret for hhv. klinisk spørgsmål 1 og 2, er der udarbejdet fælles søgestrenge for de to kliniske spørgsmål. Ansøger skal i den endelige ansøgning levere oplysninger vedr. resultater af søgestrategien for hvert af de to kliniske spørgsmål.

Søgestreng til PubMed:

#	Søgestreng	Kommentar
#1	Breast Neoplasms/drug therapy[majr]	
#2	breast[ti] AND (cancer[ti] OR carcinoma[ti] OR adenocarcinoma[ti])	
#3	#1 OR #2	
#4	HR positive[tiab] OR hormone receptor positive[tiab] OR ER positive[tiab] OR estrogen receptor positive[tiab] OR oestrogen receptor positive[tiab] OR Receptors, Estrogen[mh]	Søgning population
#5	metasta*[tw] OR recurren*[tw] OR advanced[tiab] OR relaps*[tiab] OR unresectable[tiab] OR non-resectable[tiab] OR inoperable[tiab]	
#6	#3 AND #4 AND #5	
#7	Fulvestrant[mh] OR fulvestrant[tiab] OR Faslodex*[tiab]	
#8	alpelisib[nm] OR alpelisib[tiab] OR Piqray*[tiab]	
#9	abemaciclib[nm] OR abemaciclib[tiab] OR Verzenio*[tiab]	Søgning intervention/ komparatorer
#10	cdk4-6 inhibit*[tiab] OR cdk-4-6 inhibit*[tiab] OR cyclin-dependent-kinase 4-6 inhibit*[tiab] OR cdk4-6i[tiab] OR palbociclib[tiab] OR ribociclib[tiab]	
#11	#7 AND (#8 OR #9 OR #10)	
#12	#6 AND #11	Kombination, population + behandlinger
#13	Animals[mh] NOT Humans[mh]	
#14	Case Reports[pt] OR Comment[pt] OR Editorial[pt] OR Guideline[pt] OR Letter[pt] OR News[pt] OR Review[pt] OR Systematic Review[pt] OR case report[ti] OR review[ti]	Eksklusion af irrelevante publikationstyper

#15	#12 NOT (#13 OR #14)	
#16	english[la] AND hasabstract	Afgrænsning (engelsk, m. abstracts)
#17	#15 AND #16	Endelig søgning til begge kliniske spørgsmål.

Søgestreng til CENTRAL:

#	Søgestreng	Kommentar
#1	(breast next (neoplasm? or cancer or carcinoma or adenocarcinoma)):ti,kw	Søgning population
#2	((HR or hormone or ER or estrogen or oestrogen) near/1 receptor* or positive):ti,ab,kw	
#3	(metasta* or recurren* or advanced or relaps* or unresectable or non-resectable or inoperable):ti,ab,kw	
#4	#1 and #2 and #3	
#5	(fulvestrant or Faslodex*):ti,ab,kw	Søgning intervention/ komparatorer
#6	(alpelisib or Piqray*):ti,ab,kw	
#7	(abemaciclib or Verzenio*):ti,ab,kw	
#8	((cdk4/6 or cdk next 4/6 or "cyclin dependent kinase 4/6") near/1 inhibit*):ti,ab	
#9	(cdk4/6i or palbociclib OR ribociclib):ti,ab	
#10	#5 and (#6 or #7 or #8 or #9)	
#11	#4 and #10	
#12	(clinicaltrials.gov or trialsearch):so	Eksklusion af irrelevante publikationstyper
#13	NCT*:au	
#14	("conference abstract" or review):ti,pt	
#15	(abstract or conference or meeting or proceeding*):so	
#16	#12 or #13 or #14 or #15	
#17	#11 not #16	Endelig søgning til begge kliniske spørgsmål [afgrænses til Trials]